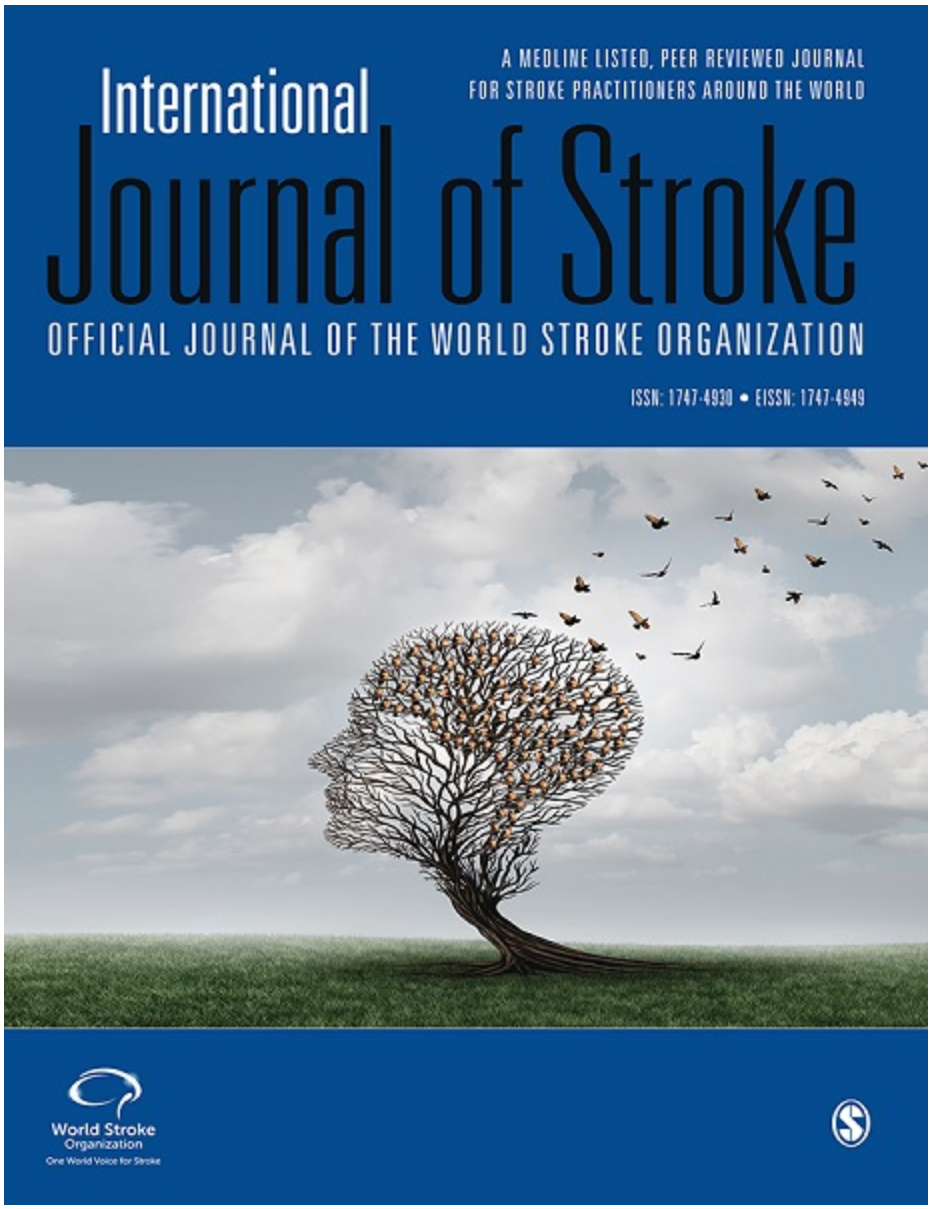

International Stroke Genetics Consortium Recommendations for Studies of Genetics of Stroke Outcome and Recovery

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International Stroke Genetics Consortium Recommendations for Studies of Genetics of Stroke Outcome and RecoveryStandardized data collection in prospective genetic studies of ischemic stroke evolution and recovery

Cover title: Genetics and stroke recovery

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Abstract

Numerous biological mechanisms contribute to outcome after stroke, including brain injury, inflammation, and repair mechanisms. ~~While this has been studied in animal models,~~ ~~e~~Clinical genetic studies have the potential to discover biological mechanisms affecting stroke recovery in humans and identify intervention targets ~~for intervention~~. Large sample sizes are needed to detect commonly occurring genetic variations related to stroke brain injury and recovery. However, this usually requires combining data from multiple studies where consistent terminology, methodology, and data collection timelines are essential. Our group of expert stroke and rehabilitation clinicians and researchers with knowledge in genetics of stroke recovery ~~– including persons identified through the International Stroke Genetics Consortium and the Stroke Recovery and Rehabilitation Roundtable networks~~ here present recommendations for harmonizing phenotype data with focus on measures suitable for multicenter genetic studies of ischemic stroke brain injury and recovery. Our recommendations have been endorsed by the International Stroke Genetics Consortium.

Introduction

~~Stroke is a major global health problem and a major cause of adult disability, leaving millions of patients with deficits every year.~~ Genetic studies can potentially ~~yield~~ discover~~ies of~~ biological mechanisms affecting stroke recovery with treatment implications. However, they ~~rely upon~~need large sample sizes ~~that in general can~~ only ~~be~~ achiev~~able~~~~ed~~ by combining data from multiple studies, where harmonized terminology, methodology, and data collection timelines are essential.

The terms *stroke outcome* and *stroke recovery* differ in ~~their~~ meaning. Stroke *outcome* describes the degree of function at specific time points ~~post-stroke~~; stroke *recovery* encompasses the degree of improvement (or deterioration) over time and better captures ~~the~~ dynamic biological processes ~~after stroke~~. Stroke recovery evaluation requires ~~information about~~ initial stroke severity data; without which~~if this is not collected,~~ only stroke outcome is~~can be~~ measur~~able~~~~ed~~. It is also important to distinguish restitution/~~(sometimes called~~ "true" recovery~~)~~ from behavioral compensation. For example, "true" motor recovery suggests restoration of pre-stroke movement patterns[1] whereas "compensation," implies ~~that~~ new (~~and~~ possibly dysfunctional) movement patterns ~~are used to~~ for accomplish~~ing~~ functional tasks.[2]

The dynamics of stroke recovery depend on ~~multiple~~ intrinsic and extrinsic factors.[3] Each patient's recovery pattern uniquely reflects the combined influences of lesion size and location, biological mechanisms of brain repair, comorbidities, pre-morbid health status and post-stroke factors including acute recanalization ~~treatment~~, rehabilitation, psychosocial factors and environmental influences. Consequently, the degree of stroke recovery varies considerably between individuals, and even skilled clinicians have difficulty making accurate recovery predictions.[4]

The need for improved predictive models of stroke recovery has ~~now~~ become a major research focus~~.~~[5,6] and recent studies suggest that genetic variations influence recovery after stroke.[7-9] Despite multiple studies, findings remain heterogeneous, due to differences in populations ~~studied~~, recovery metrics, assessment time points, and study designs. Most studies using global assessments incorporate the modified Rankin Scale (mRS)[10] while some use more detailed modality-specific functions, e.g. upper extremity motor (UE) function, language or cognitive function[3], or patient-reported outcome measures (PROMs). Few studies

use repeated measures, leading to knowledge gaps on ~~the time course of~~ stroke recovery time course. To standardize timing and metric choices across studies, the Stroke Recovery and Rehabilitation Roundtable task force (SRRR) in 2017 recommended core outcomes for trials and standardized measurement time points to reduce heterogeneity.[11]

~~Several recent reports suggest that genetic variations influence recovery after stroke.[9-11] However, these studies only assessed mRS at one time and were heterogeneous regarding other metrics and time points, emphasizing the importance of collecting harmonized data.~~

Here~~In this report~~, we focus specifically on design of prospective genetic studies of ischemic stroke (IS) recovery, aiming~~with an overarching goal~~ to ascertain the underlying genetic influences on stroke recovery biology. Our recommendations complement existing recommendations for standardizing phenotype data[12] and biological sample collection[13] for ~~clinical studies on~~ stroke risk and ~~stroke~~ recovery studies[11,14] by providing ~~comprehensive~~ recommendations for pre-specified harmonized data sets suitable for large, high-~~-~~quality, multi-center collaborations in prospective stroke genetic recovery studies. ~~Studies examining common genetic variations generally require thousands of participants and a set of~~ We propose measures comprehensive enough to provide both stroke- and domain-specific data, but simple enough to allow collection of large sample sizes across numerous and diverse enrollment sites. This will allow ~~increased~~ opportunities to discover genetic factors influencing hitherto unknown biological pathways affecting the dynamics of IS~~ischemic stroke~~ recovery. We do not here consider~~Recovery mechanisms after~~ intracerebral hemorrhage (ICH) given ICH recovery mechanisms differ from IS~~ischemic stroke and this manuscript does not include recommendations for ICH~~.

Methods

Methods for reaching a consensus on these recommendations are described in the Supplement.

~~The authors of this manuscript are stroke and rehabilitation clinicians and researchers with knowledge in genetics of stroke recovery. They were identified and contacted through the International Stroke Genetics Consortium (ISGC) networks, working groups and initiatives focusing on stroke recovery including Genetics of Ischaemic Stroke Functional Outcome (GISCOME), Global Alliance for ISGC Acute and Long-term Outcome studies, Genomic Platform for Acute Stroke Drug Discovery (GPAS); and SRRR. A formal Delphi process for reaching consensus was not used. Instead aAn agreement on the recommendations ispresented here was obtained after extensive in-person meetings, telephone conferences and e-mail correspondence between 2017 and 2020. The final recommendations have been endorsed by the ISGC.~~

Results

Overview of phenotypic variables

We ~~grouped~~ prioritized phenotypic variables into ~~three priority~~ categories: (1) *minimum variables ~~set~~* - mandatory for all studies; (2) *preferred variables ~~set~~* - recommended but may ~~sometimes~~ be precluded by practical limitations; and (3) *optional variables ~~set~~* - ~~suggested by multiple authors as~~ interesting for multi-center projects. ~~We grouped the variables depending on their type.~~ The Table shows the minimum (mandatory) variable set. Supplemental Table I lists a ~~more~~ detailed comprehensive set. S~~and S~~upplemental Table II suggests variable formats to facilitate ~~future~~ compilation of joint data ~~sets~~. RA ~~r~~egularly updated versions ~~(and older versions) of Supplemental Table II~~ will be kept at the Global Alliance for ISGC Acute and Long-term Outcome studies (https://genestroke.wixsite.com/alliesinstroke).

Timing of recovery assessment

~~The biological processes of~~S ~~s~~troke recovery starts immediately at symptom onset and continues for years thereafter (Figure 1). B~~Concentrations of b~~lood biomarkers~~, for instance plasma proteins and RNA levels~~, and ~~findings on~~ other biomarker evaluations, e.g. MRI ~~examinations~~, often vary across ~~different~~ time points ~~(Figure 2)~~. To provide simplification ~~avoid too many different time points~~, we recommend the time course for assessment of evolution and recovery into three phases post-stroke (~~where~~ day 0 is ~~the~~ day of stroke onset): ~~(1)~~ 0 to 24-48 hours; ~~(2) at~~ 7 days; and ~~(3)~~ approximately day 90 after stroke onset and when possible ~~at~~ 1 year and later. When appropriate, ~~This does not preclude that some~~ studies may choose ~~to use~~ additional precisely-defined time periods.

~~For~~ S~~s~~tudies ~~evaluating~~ of hyperacute recovery and ~~revascularization~~ therapy~~, baseline~~ should perform evaluations ~~should be~~ within 6h (when possible) or at least within 24h after stroke onset and before ~~the~~ revascularization therapy, followed by a new ~~recommended~~ evaluation at 24h post stroke[15] or 24h after recanalization therapy (~~please~~ see below).

Seven~~Though 7~~ days post-stroke is often recommended for evaluation.~~,~~[1] However, because many ~~stroke~~ patients leave ~~the~~ hospital ~~before 7 days~~earlier, w~~. As a practical matter, w~~e ~~therefore~~ recommend evaluation either at 7 days or discharge ~~from hospital~~, whichever occurs earlier.

ISschemic stroke treatment studies often evaluate conclude evaluations atpatients after 3 months., assuming that recovery mostly occurs during the first 90 days post-stroke,[16,17] and that functional status at longer intervals is increasingly related to other medical problems. However, continued improvement is likely tomay occur at 6-12 months and possibly beyond.[18] Recovery is not linear, and- time frames recovery in language and other cognitive functions may occur over different time frames may vary by different domains e.g. cognitive vs. compared to recovery of other deficits such as motor function.[19] To evaluate 3-month recovery independently of earlyier acute phases, sometimes influenced by acute treatments such ase.g. revascularization, we recommend measuring recovery as functional change between day 7 (, or discharge if earlier), and 3 months. If possible, additional evaluations at 1 and 3 years are strongly recommended to evaluate longer-term recovery.

Recommended phenotypic variables

1. Pre-stroke variables, and demographic data

Pre-stroke functional status has a large eaffects on stroke outcome and should be measured as mRS, ideally specifying whether due to a stroke preceding the index stroke (as originally intended in the mRS) versus other conditions. We also recommend recording the Charlson Comorbidity Index (CCI),[20] with information about pere-existing key medical conditions including hypertension, myocardial infarction, stroke, dementia, and diabetes mellitus. Further For further ddetails, see about recommended pre-stroke variables including stroke risk factors and medications, are provided in the Table and Supplemental Table I. Pre-stroke physical activity has also been related to outcome after stroke so information about this is of value.

All studies should provide demographics information: age at time of stroke onset,, sex, and race/ethnicity,; type of residential area type (urban/rural), educational status, living situation (type of housing type), and available social support measured as (living alone/ or with someonsomeone).e[21].

2. Baseline clinical and imaging information

Baseline characteristics of current IS~~ischemic stroke~~ should include initial NIH stroke scale (NIHSS) total and individual component scores and Trial of ORG 10172 in Acute Stroke Treatment (TOAST)[22] and/or Causative Classification of Stroke (CCS) subtype.[23] Specific "other determined" stroke etiologies (e.g. cervical artery dissection~~, recreational drug use, genetic disorders~~) could be detailed. Laboratory parameters and Glasgow coma scale may be recorded.

We recommend baseline ~~imaging~~ registration of ~~with non-contrast~~ head CT/MR, and CT/MR angiography and ~~CT/MR~~ perfusion, because e.g. ~~in part measurementsCollateral blood flow, measured either by vascular imaging (e.g. digital subtraction angiography or multi-phase CTA) or perfusion imaging estimates, may be related to~~dynamic blood flow changes may be related to genetic influences ~~on collateral vessel formation or dynamic changes in response to acute ischemia~~.[24]

3. Stroke treatment and neuroimaging at 0-48 hours and ~~at~~ 7 days/hospital discharge

Treatment with thrombolysis and thrombectomy should be noted. Final expanded TICI (eTICI) score[25] indicating degree of revascularization achieved should be mandated in l~~Any study that is especially focused on Large~~ arge v~~V~~essel ~~O~~clusionocclusion ~~(LVO)~~ stroke studies. Additional treatments ~~that may~~possibly affecting recovery ~~should be recorded,~~ includ~~eing~~ carotid endarterectomy~~/ or~~ stenting, and pharmacologic interventions for blood pressure, ~~dyslipidema~~dyslipidemia, or atrial fibrillation.

Follow~~-~~-up imaging at 24 hours after recanalization therapy with CT~~/ or~~ MR is valuable to evaluate location and extent of the acute ischemic lesion(s). Whene ~~recommend that when~~ possible, MR with FLAIR, DWI, MRA, and GRE/T2* is recommended~~should be performed~~ within 24 hours (or within 3 days at the latest) after stroke onset. ~~However,~~ MR performed later might also have value. ~~Given their effect on recovery~~I~~,~~ ~~i~~maging measures of ~~cerebrovascular conditions such as~~ leukoaraiosis, ~~number and spatial distribution of~~ microhemorrhages~~,~~ ~~and~~ prior infarcts, and arterial stenoses could be considered. ~~Extent of~~I ~~i~~njury extent to specific neural structures, such as corticospinal tract, may be useful for some hypotheses.

Neuroimaging biomarkers ~~for secondary brain injury following AIS~~ can serve as endophenotypes. F~~.F~~or example~~s~~, please see Supplement. ~~hemorrhagic transformation can be described as either categorical variables (HT1, HT2, PH1, or PH2) or a continuous variable (hemorrhage volume).[15] Likewise, serial CT scans can define cerebral edema with quantitative biomarkers for edema formation as change in CSF volume over time,[26] or change in lesion water uptake.[27] Automated methods could assess thousands of images required for GWAS.[28]~~

4. Clinical measures at 0-48 hours and ~~at~~ 7 days/hospital discharge

In the first days after stroke, neurological deficits can be highly unstable, with ~~some~~ patients rapidly improv~~inge~~, or ~~while others rapidly~~ deteriorat~~inge~~. Serial NIHSS scores,[26] often ~~used~~ standard of care in ~~the setting of~~ acute stroke ~~as standard of care~~, capture~~s~~ these changes. A change in NIHSS between baseline (<6 h~~ours~~ from ~~stroke~~ onset) and 24 h~~ours~~ ($\Delta NIHSS_{6\text{-}24h}$) is related to~~has a strong influence on~~ 90-day outcome~~,~~ independent of baseline NIHSS[27] with GWAS of $\Delta NIHSS_{6\text{-}24h}$ having revealed genes potentially involved in ischemic brain injury (data not shown). We therefore recommend NIHSS (including subitems) at baseline <6h or at least within 24h after stroke onset, and short-term follow-up at 24h after stroke onset/ ~~or 24h~~ after recanalization therapy, noting ~~the~~ number of hours since stroke onset.
Recovery during the initial days after stroke onset is difficult to measure, and w~~. W~~e recommend evaluations including NIHSS (with subitems) either at 7 days or discharge from hospital, whichever occurs earlier.

The Shoulder Abduction Finger Extension ~~(SAFE)~~ score ~~conducted specifically~~ during the first 3 days after stroke predicts upper limb motor outcome.[28] This complements the NIHSS and is useful as an early marker, easier to assess than~~where~~ more complex motor assessments such as the Fugl-Meyer (FM) or Action Research Arm Test (ARAT) ~~may be difficult to perform~~.

Gait performance measured as walking speed ~~is a valuable~~ predict~~sor of~~ walking recovery and falls risk. Gait is ~~of high value because it is~~also linked with quality of life and participation level, and ~~gait~~ testing does not require much time. On day 7 we recommend recording the ability to walk 10 meters independently (yes/no), and for those able, a 10-meter walk test. This may be repeated at later time points (see~~as suggested~~ below).

Early complications such as infections and recurrent stroke may also influence recovery and should be considered.

5. Considerations and treatment information up to 3 months and beyond

Stroke recurrence, with a 30-40%~~with~~ cumulative risk among first stroke survivors ~~of approximately 30% - 40%~~, is ~~expected to be~~ a common cause of worsening disability and requires tracking.[29,30] Secondary prevention measures, ~~and~~ complications (e.g.~~such as~~ depression, infections, seizures, fractures after falls), level of physical activity, and socioeconomic factors may substantially affect outcome and recovery~~, as may level of physical activity and socioeconomic factors~~. At the designing stage, ~~each~~ studiesy~~s~~ should define ~~if~~ which of these variables ~~will be~~to collect~~ed~~ as confounding factors ~~for adjustment~~, exclusion criteria, or endpoint/dependent variables.

Rehabilitation treatment is ~~very~~ heterogeneous across ~~the globe~~centers and difficult to uniformly register. We suggest registering how often the treatment is administered per week or month and ~~the~~ duration of rehabilitation in days. The starting day after stroke onset and treatment dose (minutes per day) may be recorded.

Treatment with antidepressants and other psychotropic medication[31] should be noted as should ~~any~~ other rehabilitation adjuncts, whether pharmacologic or device-based (e.g. transcranial magnetic stimulation).

6. Evaluation at 3 months and beyond

~~Genetic and other~~F ~~f~~actors, influencing long-term recovery (improvement/~~ or~~ deterioration) may differ from those important in earlier time periods. As mentioned above, we recommend evaluation at day 7, or discharge, if earlier as a new baseline for long-term recovery at 3 months.

Stroke variably ~~Due to the variation in~~ affect~~s~~ed different functional domains ~~after stroke.~~,[32] W~~w~~e recommend that specific domains are considered separately and only in more detail where appropriate. For example, if a motor deficit ~~in motor function~~ is detected on the NIHSS, more in-depth motor testing can be performed (Figure ~~3~~ 2 and Supplemental Table

1). In this way the NIHSS subitems ~~can~~ provide screening for ~~deficits and only the affected domains are chosen for~~ requiring more detailed evaluation, saving time and resources.

Evaluation of specific recovery domains:

Motor function

Motor deficits are seen in >~~-~~80% of IS~~acute stroke patients~~.[33] and can be screened by NIHSS items 5 and 6 ~~provide screening tools for motor deficits~~. A more detailed assessment ~~of change~~ of motor deficit~~s~~ changes over time is of great importance to evaluate recovery. The ~~Fugl-Meyer upper extremity (~~FM-UE~~)~~ motor scale[34] is well known and recommended ~~to capture arm motor impairment~~ but requires trained personnel.[35] The F~~Mugl-Meyer~~ lower extremity motor scale may be considered,[34] but limited~~has less~~ reproducibility~~, than FM-UE and may add little value because~~ a high concordance with ~~proportion of those with~~ UE weakness, and ~~also have LE weakness and~~ overlapping recovery mechanisms may limit its value~~likely overlap~~. UE ~~pper limb~~ motor function is best captured with ARAT but this requires equipment.[11]

Gait velocity (see~~as described~~ above), is also useful for long-term motor function evaluation.

Sensory function

The F~~Mugl-Meyer~~ Sensory exam or the Nottingham Sensory Scale could be considered.

Cognitive function

Combining the four NIHSS items Orientation (~~item~~ 1b), Executive function (~~item~~ 1c), Language (~~item~~ 9) and Inattention (~~item~~ 911) has similar value as the Mini-Mental State Examination in detecting severe cognitive impairment.[36] A more elaborate cognitive evaluation with the Montreal Cognitive Assessment Scale~~-~~[37] is recommended when possible. When even more detailed or longitudinal understanding of specific cognitive domains is needed, an in-depth neuropsychological assessment ~~corresponding to age and pre-morbid status~~ may ~~be considered,~~ encompass~~ing~~ multiple cognitive domains, especially verbal episodic memory, executive function, and processing speed. Pre-stroke cognitive assessment with tools such as the IQCODE[38] is important, as pre-stroke cognitive impairment is frequent

and associated with post-stroke dementia.[39] TDetails of the genetics of post-stroke cognitive impairment is are not covered herein this manuscript, but addressed in the imaging and cognitiveseparate working groups of the ISGC (www.strokegenetics.org) and the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium.

Speech function

NIHSS item 9 provides a screening tool for aphasia. Aphasia evaluations are hampered by language differences between populations. We found it difficult to recommend one evaluation tool for aphasia over another, but favor the Western Aphasia Battery-Revised version bedside screening test, which takes 10-15 minutes and is well-accepted by researchers.[40] It is also possible to useL language evaluation items in cognitive tests are also a possibility.

Neglect

NIHSS item 11 provides a screening tool for neglect and hemi-inattention. Of Among the many available bedside assessments, the Star cancellation test is recommended.

Mood

The Hospital Anxiety and Depression Scale[41] (HADS) had most consensus in our group for utility across different time points in recovery. Alternatives haveThe PHQ-9 can also be used and has been recommended by others.[42]

Other specific domains

Post-stroke visual field loss, eye movement abnormalities of extraocular movement, dysphagia, balance disorders, fatigue, frailty, and urinary incontinence are all important aspects of post-stroke recovery for which there are several different measurement tools available. We agreed that no specific recommendations can be made for these domains at this time, buttime but provide some suggestions in the supplementSupplemental tables.

Global assessment

The 3-month mRS ~~at 3 months has been~~is used in ~~a majority of~~most stroke trials and should be performed in ~~prospective~~ studies ~~on genetics~~ of stroke recovery genetics ~~as it~~to facilitate~~s~~ comparison across cohorts. Evaluation of mRS at other time points (e.g. ~~such as~~ 6 months, 12 months, and yearly thereafter) may ~~also~~ be useful. The mRS offers ~~the~~ advantages of ease of administration, ~~and~~ good inter-observer reproducibility, certification, and available phone-based evaluation.[10,43] ~~Investigators should be mRS-certified; phone evaluation is acceptable~~. The mRS score has been analyzed both as a continuous and ~~as~~ an ordinal variable,~~,~~[44,45] but d~~D~~ichotomization may ~~cause reduction of~~lose information and statistical power.

Other functional scales such as Barthel Index and the Nottingham extended ADL, have limitations such as ceiling effects or rarer~~are less widely~~ usage~~d~~.

Patient-reported outcome measures (PROMs)

O~~The o~~utcome~~s~~ and recovery evaluations ~~considered~~ important ~~by~~ to clinicians are not always congruent with those of~~relevant to~~ patients. When possible, PROMs should be included in ~~studies of stroke~~ recovery studies to~~;~~ ~~they~~ support the validity of other measures and ~~in~~ reflect~~ing~~ meaningful stroke outcomes and recovery. PROMs can assess disability, ~~as well as~~ mood, ~~global~~ cognitive function, pain, mobility, and fatigue. The Patient-Reported Outcome Measurement Information System (PROMIS), 36-Item Short Form Survey (SF-36), EQ5D, and Stroke Impact Scale are ~~examples of~~ frequently ~~-~~used PROMs.[46]

Combining dynamic changes from different domains

Genetic correlates of recovery mechanisms may ~~have general impact on neural systems with~~ influence ~~on more than one~~several functional domains. Combined measurements across domains can be obtained by quantification of the domain with greatest impairment in individual subjects (defined as the system with the worst baseline sub-score from the baseline NIHSS), and computing the percentage of the maximum possible score for this domain followed by comparing these measures on Day 7 and Day 90. Recovery is ~~and~~ calculate~~ding recovery in terms of~~ as the remaining deficit (% recovery = 100*(1-(ScoreMax-$Score_{d90}$)/(ScoreMax-$Score_{d7}$))) for each subject.[47]

Neuroimaging

Neuroimaging ~~in the follow-up~~ after stroke can detect new infarcts, hemorrhages, and small vessel disease including white matter changes and brain atrophy. For these purposes, MRI including FLAIR and GRE/T2*/ ~~(or~~ SWI~~)~~ sequences could be considered at 3 months, 1 year and later.

Several other forms of neuroimaging and associated methods have been examined in relation to genetic variation, for examples - please see Supplement.

Discussion

We here ~~for the first time~~ recommend a specific set of phenotype outcome variables, timeframes, and ~~important~~ covariates for prospective genetic studies of recovery after IS~~ischemic stroke including various timeframes~~. ~~The evolution of symptoms after ischemic stroke is variable and the dynamic change of individual variables may differ during different time periods.~~ To detect ~~changes~~changes in the patient-specific evolution of symptoms ~~it is important that~~ the same variables ~~are~~ should, when possible, be measured at the different time points.

Our suggested time points for evaluations and the ~~our recommendations for~~ assessments categorized as~~to be considered~~ minimum, preferred, or optional can be useful tools for individual studies, comparative, and multi-center studies on stroke recovery genetics~~, facilitated comparisons across studies, and multicenter joint analyses~~. Of the ~~There are a~~ large number of available potential evaluation tools available for assessment of IS ~~ischemic stroke~~ recovery, ~~.~~ we~~Not all of these are suitable for large-scale genetic studies. The~~ suggested~~selected~~ tools that should be simple and accessible ~~but also sufficiently~~while detailed enough to capture dynamic changes in the designated domains~~, contributing to stroke recovery~~.

Physical follow-up examinations after the acute phase of stroke, are labor intensive ~~making this difficult to perform at many centers~~. Patient telephone interviews may be an alternative. ~~There are strengths and weaknesses of both day-90 approaches.~~ Live exams permit detailed determination of many neurological features but come at a higher price such as cost and travel. Phone and video-based exams are ~~easier and~~ less expensive, but more limited in the data that can be reliably measured. Given the focus of the current recommendations, ~~this group~~we advise~~s~~ live exams for studies focusing on recovery at 90 days and beyond to be performed whenever resources permit.

We stress the use of NIHSS, including its subscores, for screening because it is already widely ~~known and used~~utilized~~.~~ ~~The NIHSS evaluates 11 specific components, allows professionals to reproduce initial screening data at later stages, and is widely used~~ in clinical routine, clinical trials, ~~epidemiological,~~ and recovery ~~and demographic~~ studies. More elaborate evaluations focusing on specific domains can be complementary, as can combined measures

such as the PREP2 algorithm evaluating clinical function, MRI and ~~TMS~~ surrogate parameters to predict 3-month UE motor function.[28] Other clinical evaluations to predict recovery such as sitting balance for independent walking, and ability to comprehend and repeat spoken language are uncommonly standardized and systematically investigated and may currently have less value for genetic studies of stroke recovery. Increasing importance is being placed on PROMs to ~~help~~ ensure that recovery measured using tools based on neurological impairment is meaningful from the patient's perspective, although the role of PROMs in stroke genetics research has not been established.

Training, certification, and recertification is essential to reduce error and ~~as well as~~ inter-rater variance. A plan for training, certification, and recertification for each behavioral scale should be ~~provided as~~ a part of every stroke recovery study or trial.

Statistical considerations are important. Many scales ~~for assessment, definition and tracking of recovery~~ are ordinal and non-linear. An improvement in the NIHSS ~~scale~~ of 10 points, for instance, may signify different degrees of improvement when a patient improves from 20 to 10 versus from 10 to 0. Additional concerns regarding repeated measurements include regression to the mean and management of missing data. A~~Furthermore, a~~nalyses must consider collinearity when employing the same variable to calculate both the independent and the dependent variables to avoid misinterpretation of paired observations when comparing baseline scores with follow-up results.[48] Analyses combining different domains may be considered for detecting genetic influence on general stroke recovery.

Conclusions

T~~With t~~he rapid progress of genetic research methodologies ~~in medicine there is now~~provides ~~an~~ excellent opportunities~~y~~ to discover new factors ~~that~~ influencinge stroke recovery. However, to obtain optimal efficiency, ~~it is important to use~~ harmonized and well-accepted phenotyping instruments across studies are required. We suggest selected evaluations of stroke recovery ~~with ability~~ to measure important recovery domains. Harmonization of these evaluations between studies will ~~provide increased capacity to~~allow performance of large prospective studies of genetic influence on ~~the~~ recovery dynamics ~~of recovery~~ in the early and later phases after stroke.

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Please see Supplement.

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Table. Recommended *minimum* variable sets for genetic studies of ischemic stroke recovery,

Evaluation time	Clinical	Stroke clinical	Stroke imaging	Treatment	Functional
Stroke onset-2 days	Pre-stroke/demographics[a] ●Pre-stroke mRS ●Charlson Comorbidity Index[EP] ●Age at time of stroke onset ●Sex ●Race Risk factors at stroke onset[a] ●Hypertension ●Atrial fibrillation ●Coronary Heart Disease ●Diabetes Mellitus ●Smoking ●Hypercholesterolemia ●Previous stroke	●Main stroke type[b] ●TOAST/CCS subtype ●Survival[LP] ●Time from stroke to death[LP]	●Initial CT/MR examination performed ●Time to initial CT/MR scan[LO] ●CT at 24h[LO] ●Time to CT 24h scan[LO] ●Hemorrhagic transformation on 24h CT scan[LO]	●Thrombolysis ●Thrombectomy	●Initial stroke severity: NIHSS[C] within 6h[d] after hospital presentation (when possible) or just before recanalization therapy ●Time from stroke onset to initial NIHSS[LP] ●NIHSS[C] 24h after recanalization therapy / 24h after baseline NIHSS,if no recanalization therapy[LO] ●Time from stroke onset to 24h NIHSS[LO]
7 days/ discharge	As above	●Survival ●Time from stroke to death[LP]			●NIHSS[c] at 7days or at discharge, if earlier[EP] ●Time from stroke onset to NIHSS at 7 days/ discharge[EP]
3 months	●Time of evaluation[EO] ●Survival[EO] ●Recurrent stroke[EO]				●NIHSS[c,EO] ●mRS[EO]
12 months, yearly thereafter	●Time of evaluation[EO] ●Survival[EO] ●Recurrent stroke[EO]				●NIHSS[c,EO] ●mRS[EO]

Listed variables are recommended as *minimum* for Early Phase Studies (with focus on 0-48h and 7 days/hospital discharge) and Later Phase Studies (with focus on 3 months and beyond), unless otherwise specified.

A comprehensive outline of all suggested *minimum*, *preferred*, and *optional* variables are shown in Supplemental Table I.

Time of evaluation after stroke onset (hours for up to 72h; days thereafter) should be registered.

mRS, modified Rankin scale; IS, ischemic stroke; ICH, intracerebral haemorrhage; CTA, CT angiography; h, hour; NIHSS, NIH Stroke Scale.

[a]can often be collected somewhat later; [b]only IS in this manuscript; [c]including individual subitems; [d]for Later phase studies: NIHSS within 6h=*preferred*, NIHSS within 24h=*minimum*; [EP]Early Phase Studies, *preferred*; [LP]Later Phase Studies, *preferred*; [EO]Early Phase Studies, *optional*; [LO]Later Phase Studies, *optional*.

Figure 1.

Framework showing time points post stroke related to current known biology of stroke recovery. Time post stroke should always be included in data acquisition ~~(see text)~~. Adapted from Bernhardt et al[~~2~~1] to represent ischemic stroke only.

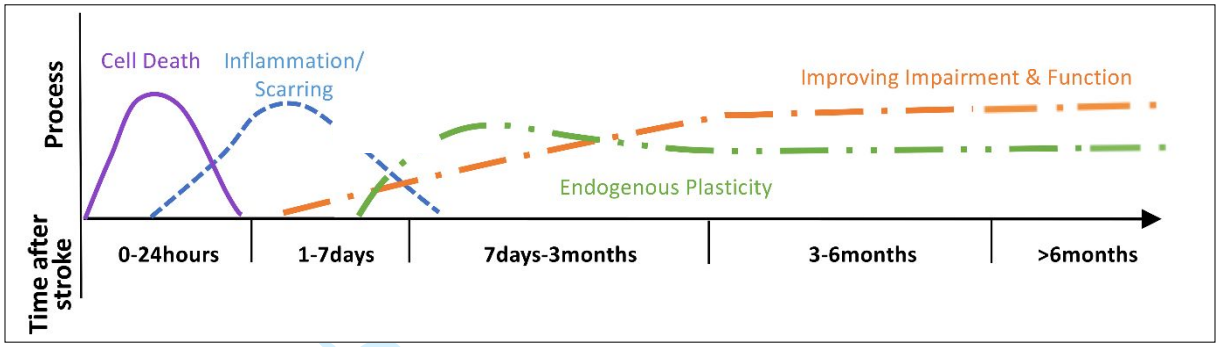
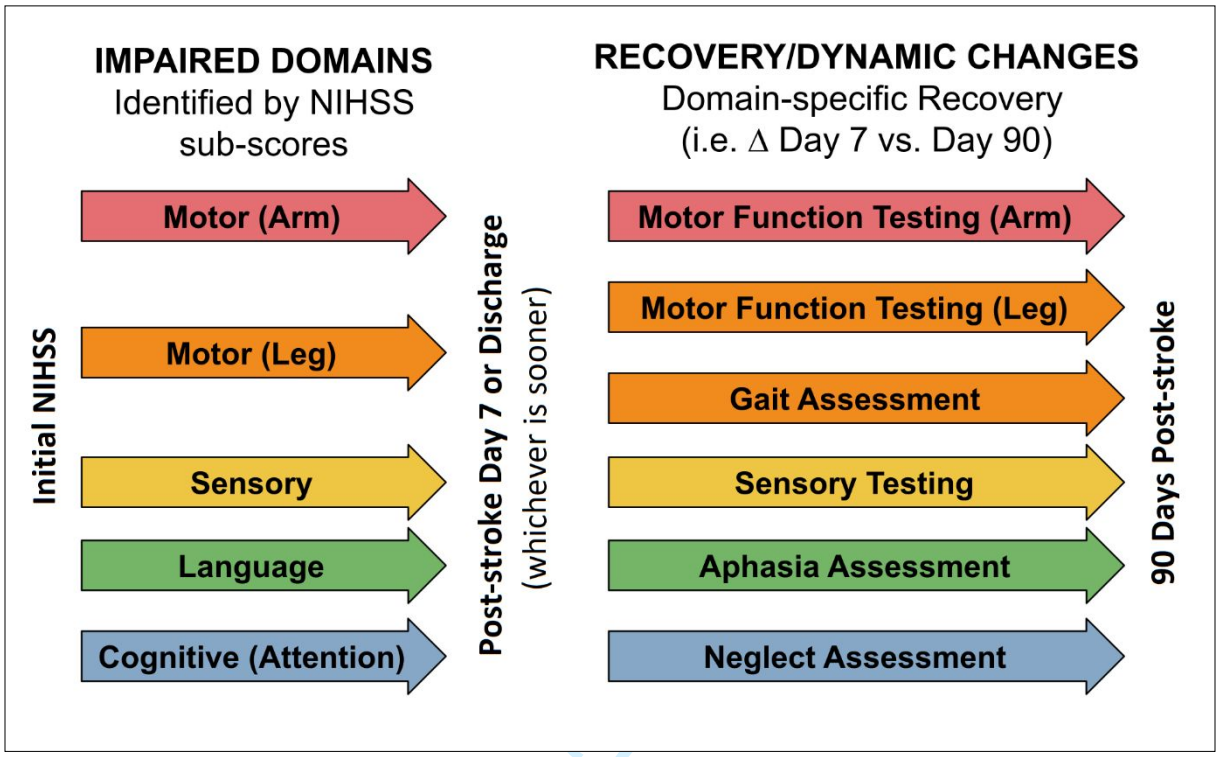


Figure 2~~3~~.

Suggested domain-specific screening by using NIHSS. Detected deficits are assessed with more detailed evaluations.



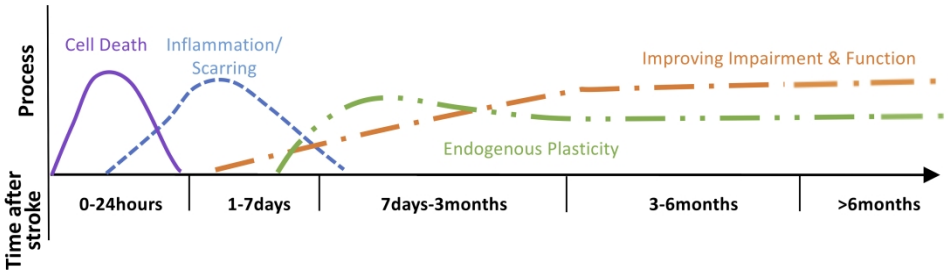


Figure 1. Framework showing time points post stroke related to current known biology of stroke recovery. Time post stroke should always be included in data acquisition. Adapted from Bernhardt et al[1] to represent ischemic stroke only.

757x211mm (144 x 144 DPI)

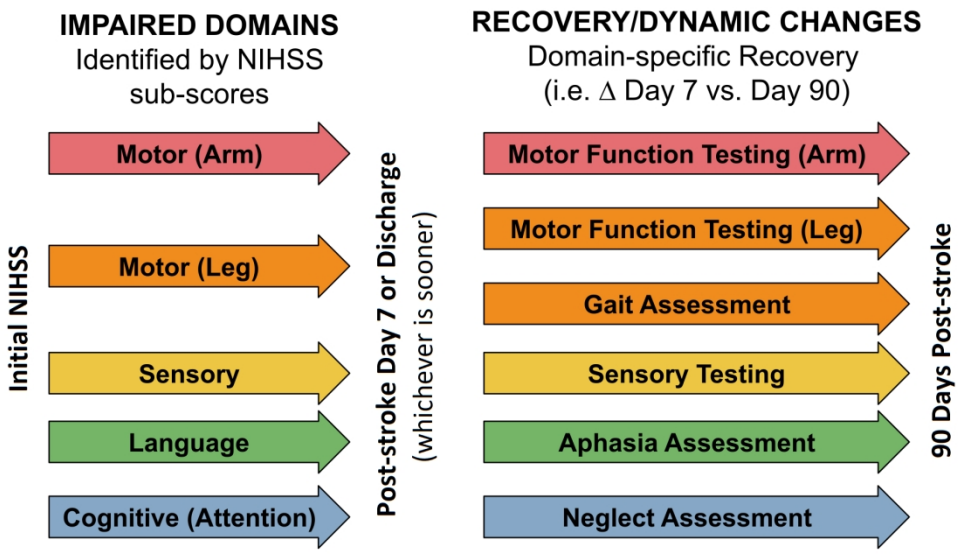


Figure 2. Suggested domain-specific screening by using NIHSS. Detected deficits are assessed with more detailed evaluations.

343x211mm (144 x 144 DPI)