

INVITED REVIEW OPEN ACCESS

Harmonized Acquisition of Connectome MRI and Clinical Data for Stroke, Parkinson's Disease and Glioma: Delphi-Derived Protocol Recommendations by the European Academy of Neurology

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Received: 27 April 2026 | **Revised:** 17 June 2026 | **Accepted:** 7 July 2026

Keywords: connectome | data harmonization | data sharing | digital health | network neuroscience

ABSTRACT

Introduction and Aims: The European Academy of Neurology (EAN) joined the Horizon Europe EBRAINS 2.0 research consortium to co-develop recommendations for prospective acquisition and integration of clinical and research core multi-scale human datasets for connectome analysis in stroke, Parkinson's disease (PD), and glioma (GBM).

Methods: Using an online Delphi survey method, expert consensus was sought on 28 statements for each of the following protocols in stroke, PD and GBM: clinical core/research brain MRI, minimum/extended clinical outcomes, minimum/extended cognition assessments, case report forms (CRF). The level of agreement for each statement was predefined as $\geq 80\%$. 536 experts from four EAN Scientific Panels (SP) (SP Neuro-oncology [$n = 70$], SP Movement Disorders [$n = 206$], SP Neuroimaging [$n = 112$], SP Stroke [$n = 148$]) were invited to participate in this Delphi process.

Thomas Berger and Lorenzo Pini share first authorship.

Philippe Ryvlin and Maurizio Corbetta share last authorship.

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Results: Two Delphi voting rounds were conducted to reach the predefined level of agreement ($\geq 80\%$; range: 80.49%–100%) for all items to establish consensus on protocol recommendations for stroke, PD and GBM. Cumulative response rate from SP experts was 25% ($n = 135$ from 30 European countries) for the first, and 32% ($n = 173$ from 35 European countries) for the second Delphi voting round.

Discussion: These consented protocols provide a pragmatic framework for harmonizing multi-scale data acquisition for connectome analyses in stroke, PD, and GBM. Further, these protocols allow future modular extensions for other datasets, e.g., neurophysiological data or non-imaging biomarkers, and serve as a role model for brain network analyses in other neurological disorders.

1 | Introduction

The increasing availability of large-scale, multimodal health data presents valuable opportunities to advance neurological research and improve clinical care in Europe. However, meaningful integration and analysis of such data, i.e., conventional, functional and advanced imaging, clinical measures and their outcomes, require harmonized acquisition protocols and standardized procedures across institutions and countries. Variability in clinical and research practices (particularly in the acquisition, management, and sharing of neurological data) remains a significant barrier to reproducibility, interoperability, and large-scale collaborative research within Europe.

Within this context, the EBRAINS 2.0 consortium partnered with the European Academy of Neurology (EAN) to support a specific EBRAINS 2.0 research task, namely the development of standard operating procedures (SOPs) to standardize acquisition protocols and facilitate harmonization of prospective health data across both routine clinical and research settings, enabling consistent approaches to data collection for connectome analyses for three common neurological conditions: stroke, Parkinson's disease (PD), and glioma, specifically glioblastoma (GBM). These three conditions were predefined by the scope of EBRAINS 2.0 Work Package 2 and were selected as complementary exemplars: stroke and glioma represent two focal disorders of distinct etiology and constitute the pillar of the task, whereas PD serves as a proof-of-concept for neurodegenerative conditions. This design was intended to provide prototype protocols that can subsequently be extended to other neurological and psychiatric diseases.

To ensure that the proposed protocols reflect broad European neurological expert consensus and are feasible across diverse clinical institutions, including research settings, a structured consensus methodology is required. The Delphi method is a well-established technique for systematically eliciting and refining expert opinion through iterative rounds of evaluation and feedback, allowing consensus to emerge among geographically distributed specialists [1, 2].

The resulting consented protocols for clinical core/research brain MRI, minimum/extended clinical outcomes, minimum/extended cognitive assessments, and case report forms are intended to serve as recommended templates for the acquisition, management, and analysis of large-scale, multimodal human datasets. By promoting harmonized data practices, the proposed framework aims to facilitate data acquisition in routine settings, enable collaborative research, enhance reproducibility, and support the development of advanced analytical approaches in European neurology.

While the clinical protocol is intended to provide a feasible acquisition framework (≤ 20 min) suitable for routine clinical settings, ensuring standardized structural imaging and minimum clinical/cognitive assessments across European centers, the research protocol is designed to enable comprehensive connectome reconstruction through advanced multi-modal imaging sequences (≤ 40 min), including resting-state functional brain MRI, multi-shell diffusion-weighted imaging, and perfusion mapping, supporting network-level analyses of brain structure and function in stroke, PD, and GBM.

A central rationale for the development of harmonized research protocols lies in the growing recognition that the brain connectome (i.e., the comprehensive map of structural and functional connections), represents a shared biological substrate underlying diverse neurological diseases (Figure 1). Although stroke, PD and GBM, have fundamentally different etiology, in each of them the analysis of the connectome provides valuable insights into network disruption and reorganization that affect clinical presentation, progression and prognosis [3–6].

In stroke, the brain connectome provides a framework for understanding how focal vascular lesions produce widespread network disruptions far beyond the site of injury. This phenomenon, known as “diaschisis”, manifests as altered functional and structural connectivity between remote, structurally intact brain regions [7, 8]. Critically, the degree of post-stroke functional connectivity normalization has been identified as a key biomarker of recovery, with the emergence of a reorganized “recovery connectome” supporting regained functions rather than a simple restoration of pre-stroke network architecture [8, 9].

In GBM, the connectome perspective has revealed that brain tumors cannot be considered purely focal pathologies but rather diseases of large-scale brain networks. GBM infiltrates and perturbs structural and functional connectivity beyond visible tumor margins, producing remote network disruption analogous to stroke-related diaschisis [3, 5]. Importantly, structural connectivity measures from normative (and harmonized) imaging protocols have demonstrated prognostic value, with white matter tract density at the lesion site significantly predicting overall survival [10–12]. Moreover, experimental evidence has shown that glioma cells form functional synapses with neurons and exploit activity-dependent plasticity mechanisms, positioning the tumor as an active pathological node within the connectome [13].

In neurodegenerative diseases, the connectome is a central feature [4, 14–16], serving as a potential biological substrate for the spread of misfolded proteins and with therapeutic implications [17, 18]. Regarding PD, α -synuclein aggregates,

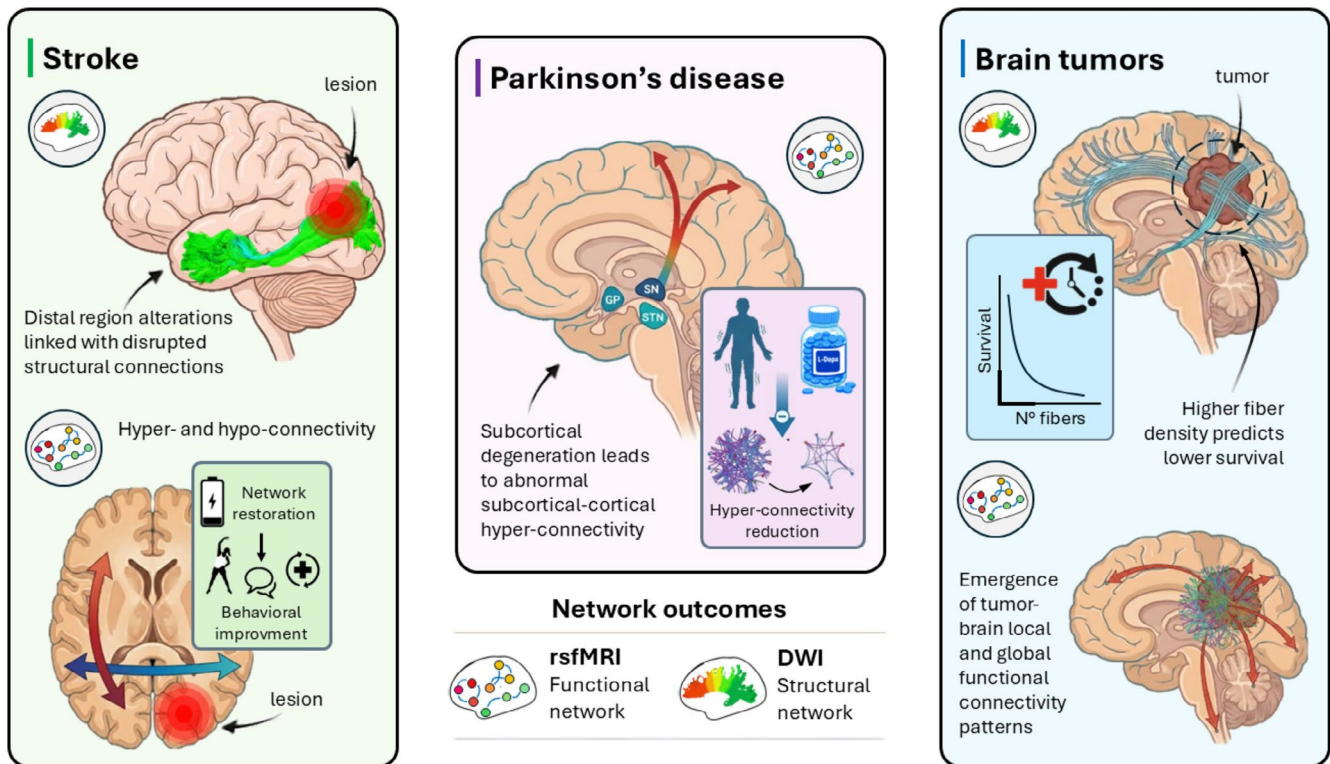


FIGURE 1 | Convergent network-level alterations across neurological diseases. The figure illustrates how distinct brain disorders converge on large-scale network disruption, linking local pathology to system-level dysfunction. Left panel: Stroke lesions induce distal alterations through structural disconnections. These changes are associated with patterns of hypo- and hyper-connectivity across the brain. Network-level normalization may support behavioral recovery. Middle panel: Subcortical alterations in Parkinson's disease are linked with abnormal increases in functional connectivity within the motor cortex. These alterations are associated with clinical phenotype and pharmacological response. Right panel: Tumors affect both local and global functional connectivity patterns. Notably, structural connections interacting with the tumor are associated with overall survival.

the molecular hallmark of this disorder, are hypothesized to propagate along structurally and functionally connected brain networks in a “prion-like” manner, thereby determining the onset and progression of both motor and non-motor symptoms of the disease [19]. Consistent with this, longitudinal analyses suggest that connectivity changes may also precede cognitive symptoms, supporting a model in which connectome disruptions mediate cognitive decline [20]. More recently, emerging evidence links alterations in the so-called somato-cognitive action network with PD pathophysiology, in which hyper-connectivity between disease-affected nuclei and this large-scale circuit correlates with disease severity and treatment response [6].

These findings underscore the need for standardized multi-modal acquisition protocols (both conventional, functional, and advanced imaging for connectome measurements) to enable network-based prognostic and therapeutic approaches in stroke, neuro-oncology, and neurodegenerative conditions.

2 | Methods

Consensus on best-practice protocols for prospective data acquisition was developed using a structured Delphi panel methodology involving iterative rounds of expert evaluation for stroke, PD and GBM combined with three protocol tiers (“Core”,

“Extended”, and “Case Report Form”). The candidate sequences and protocol items were first developed centrally and in a shared manner by the EBRAINS 2.0/WP2 group, constituting a common transdiagnostic framework. From this shared pool, the Delphi voting was subsequently performed separately for each condition by the respective expert panels.

For each neurological condition, a total of seven protocols underwent the Delphi process:

1. Clinical Core MRI Protocol; 2. Research Core MRI Protocol; 3. Minimum Clinical Outcome Protocol; 4. Extended Clinical Outcome Protocol; 5. Minimum Cognition Assessment Protocol; 6. Extended Cognition Assessment Protocol; 7. Case Report Form (CRF).

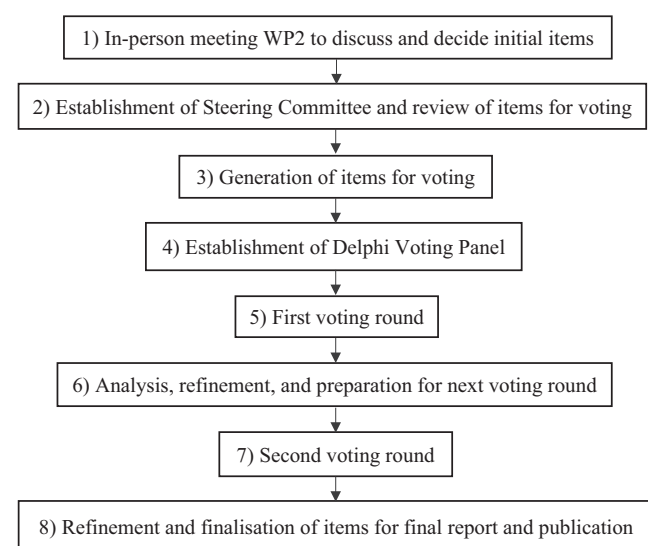
Each item/question of the seven protocols offered five agreement categories (strongly agree/agree/neutral/disagree/strongly disagree) and a feedback/comment text field.

2.1 | Steering Group and Delphi Process Multi-Step Workflow

A Delphi process Steering Group composed by TB (EAN), MC (EBRAINS 2.0, Work Package [WP] 2 lead), LoP (WP2), PR (WP2), RR and AP (co-chairs EAN SP Neuro-oncology),

TABLE 1 | The Delphi technique by implementing a multi-step approach.

1. In-person meeting with WP2 to discuss and decide initial items. WP2 held an in-person meeting in October of 2024. One of the goals of the meeting was to discuss potential items to be subjected to the Delphi process.
2. Establishment of the Steering Committee and review of items for voting. This group prepared and developed the Delphi process, analyzed the voting results, integrated comments/feedback, and wrote the final report.
3. Generation of items for voting. Based on the discussions and feedback at the in-person meeting, the voting items were finalized.
4. Establishment of the Delphi Voting Panel. This group represented the voting participants and comprised the EAN Scientific Panels on Neuroimaging, Neuro-oncology, Stroke, and Movement disorders.
5. 1st voting round. The first voting round took place in February and March 2025.
6. Analysis, refinement, and preparation for the next voting round. The results were analyzed and refined by the Steering Committee, and the Steering Committee prepared them for the next voting round.
7. 2nd voting round. The second voting round took place in June–July 2025.
8. Refinement and finalization of items for publication. The Steering Committee reviewed the voting results and adjusted the items accordingly, producing a final list ready for use and publication.

**FIGURE 2** | The governance and multistep performance of the Delphi process.

CK and AT (co-chairs EAN SP Movement Disorders), AS and TT (co-chairs SP Stroke), MR and RW (co-chairs EAN SP Neuroimaging), LuP, ML and DR (EAN Scientific Department-EAN Head Office), prepared and developed the Delphi survey items, analyzed the voting results, integrated all comments/feedback, and wrote the final analysis of all Delphi survey rounds, the summary of consensus results and the final report.

The steering group pre-defined consensus for every single protocol item/question as $\geq 80\%$ agreement on “strongly agree” and “agree”.

Details of the Delphi multi-step workflow are shown in Table 1 and Figure 2.

2.2 | Design, Content and Procedure of the Survey

To develop the consensus-based protocol criteria, this study followed an iterative, quasi-anonymous, multistage approach with controlled feedback according to the Delphi technique [21–23].

Initial voting items were developed from suggested protocols for clinical core/research MRI, minimum/extended clinical outcomes, minimum/extended cognition assessments, and CRFs received by the WP2 EBRAINS 2.0 partners for the three specified diseases.

Delphi voting questionnaires were set up in Survey Monkey: Online Survey Software.

With the invitation letter, accompanied by a cover sheet outlining Delphi’s aims in the context of this project and a full description of the procedure, the SP experts received the SurveyMonkey link to access the first Delphi voting round. In the second round, a document with detailed feedback on responses from the first Delphi voting round was shared.

Protocol items, which did not reach the predefined $\geq 80\%$ threshold of agreement (cumulative of “strongly agree” and “agree”) in the first voting round, were re-asked, newly phrased, or newly added (based on participants’ comments in the first voting round) by the steering group for the second voting round.

For the second voting round, participants were asked to refrain from voting “neutral” unless they intended to abstain. Thus, following an appropriate and usual methodological approach, for every question in the second voting round, the number of participants who had voted “neutral” was subtracted from the total number of participants for every question. In consequence, voting results for (strong) agreement/(strong) disagreement were recalculated based on the final number of participants (total voters for a particular question minus “neutral voter” for that particular question).

2.3 | Delphi Panel Recruitment and Participants

The expert members of four EAN SP, i.e., Stroke, Movement Disorders, Neuro-Oncology, and Neuroimaging represent broad geographical inclusion of subject-matter expertise from 48 EAN member countries and ensure diverse clinical and research perspectives. All experts from the above-mentioned four EAN SP were, thus, approached with a personalized electronic invitation to participate in this Delphi process. The final

TABLE 2 | Clinical core MRI protocol (to be acquired in ≤ 20 min and typically at 24–48 h post-stroke and post-treatment; for DWI/FLAIR, also pretreatment scans if and where available).

Sequence	Description	Time (minutes)	Goal	Delphi agreement $\geq 80\%$ (given in %)
3D T2-FLAIR (replaceable with 2D T2-FLAIR)	AXI, VS = 1 mm iso (AXI, ST ≤ 3 mm, in-plane resolution 1 mm)	~4' (~3')	WM stroke lesion, segmentation, morphometry	100%
SWI/SWAN	3D GRE, SAG, FA = 12° on 3 T, 20° on 1.5 T, TR shortest or 30 ms on 3 T, shortest or 60 ms on 1.5 T. ST ≤ 1.5 mm	2–4'	Microhemorrhages	100%
SS 2D DWI or SS 3D DWI	SS-EPI, AXI, ST = [2 4] mm, number of directions ≥ 3 , in-plane resolution ≤ 1 mm, TR > 5000 ms, $b = 0$, 1000 s/mm ² if available pre-treatment for definition of the ischemic core: SS-EPI, AXI, number of directions ≥ 30 , 2.5 mm isovoxel, TR > 5000 ms, $b = 0$, 1000 s/mm ²	2' 4'	ADC, diffusion	100%

Abbreviations: ADC, apparent diffusion coefficient; AXI, axial; DWI, diffusion-weighted imaging; FA, flip angle; GRE, gradient recalled echo; SAG, sagittal; SS-EPI, single-shot echo planar imaging; ST, slice thickness; SWAN, susceptibility-weighted angiography; SWI, susceptibility-weighted imaging; TE, echo time; TR, repetition time; VS, voxel size; WM, white matter.

Delphi panel consisted of those SP members who declared no conflicts of interest and were interested to join their disease-specific Delphi survey and to contribute to consensus development through structured, iterative feedback. Members of the SP Neuroimaging were invited to join all disease-specific Delphi voting rounds.

3 | Results

In total, 536 members of the four EAN SPs were invited to participate in this Delphi process. The cumulative response rate across the three disease protocols was 25% ($n = 135$ from 30 European countries; response rates from the respective SP between 16% and 19%) for the first Delphi and 32% ($n = 173$ from 35 European countries; response rates from the respective SP between 22% and 25%) for the second Delphi voting round.

3.1 | Stroke Protocols

260 members of the EAN SPs Stroke ($n = 148$) and Neuroimaging ($n = 112$) were invited to validate the 7 stroke protocols. The results are presented below.

3.1.1 | First Voting Round

The first Delphi voting round included 42 experts (response rate of 16%) representing 22 countries, all with recognized clinical and imaging expertise in stroke. A total of 16 out of 27 items reached the predefined consensus threshold of $\geq 80\%$ agreement and were therefore excluded from the second voting round. In addition, based on participant feedback and

review by the steering group, one item was exchanged for another test (Patient Health Questionnaire should replace the Geriatric depression scale), and three new items were introduced, resulting in a total of fourteen items included in the second voting round (eleven retained from the first round and three newly added).

3.1.2 | Second Voting Round

The second Delphi voting round included 56 experts (response rate of 22%) representing 25 countries, reflecting sustained international engagement across both voting rounds.

In the second voting round, 14 questions were evaluated. After excluding “neutral” responses, a consensus of $\geq 80\%$ agreement was achieved for all remaining questions except one, thereby completing the validation process for the seven stroke protocols.

3.1.3 | Final Validated Protocols

Overall, 30 items were validated through the Delphi consensus process. The final set of validated connectome acquisition protocols for stroke is presented below. The protocols are summarized in Tables 2–8, reflecting the consensus-derived standards agreed upon through the Delphi process.

3.2 | PD Protocols

318 members of the EAN SPs Movement Disorders ($n = 206$) and Neuroimaging ($n = 112$) were invited to validate the 7 PD protocols.

TABLE 3 | Research core MRI protocol for stroke (to be obtained in ≤40 min).

Sequence	Description	Time (minutes)	Goal	Delphi agreement ≥ 80% (given in %)
rsfMRI	2D SS-EPI. TR ≤ 2 s, ST between [2 3] mm. Iso voxels. AP or PA PEP. No slice gap. Additional sequences: 1 SE AP-PEP + 1 SE PA-PEP, same geometry as rsfMRI (max 30'')	Minimum length: 10'	To compute functional connectome (parcel-wise) and voxel-wise connectivity maps (seed-ROI, ICA)	81.82% ^a
DWI multi shell (MB*)	2D SS-EPI, ST = 2 mm. <i>b</i> = 300, 1000, 2000. With approximately 10 b300, 32 b1000, 64 b2000 (directions per shell). Distribution on the unit sphere shared with bvec/bval files. Additional B0 acquired with opposite PEP, minimum 5 volumes (max 30'')	<13'	To compute the structural connectome (probabilistic/deterministic/global tractography) and microstructural parameters (DTI, NODDI, DKI, ...)	80.49%
pCASL/ASL	pCASL or other perfusion sequences	<10'	To assess cerebral perfusion and its relationship with the structural and functional connectome	94.44% ^a
MR Angio-graphy/TOF	Angiography or any other modality providing information on vessels	~5–6'	To evaluate how vascular architecture influences brain connectivity	92.69%

Abbreviations: AP, anterior–posterior; DKI, diffusion kurtosis imaging; DTL, diffusion tensor imaging; DWI, diffusion-weighted imaging; ICA, independent component analysis; MB, multiband; NODDI, Neurite Orientation Dispersion and Density Imaging; PA, posterior–anterior; pCASL/ASL, pseudo continuous/arterial spin labeling; PEP, phase encoding polarity; ROI, region of interest; rsfMRI, resting-state functional MRI; SE, spin echo; ST, slice thickness; TOF, time-of-flight.

^aAfter the second voting round.

TABLE 4 | Minimum clinical outcome protocol for stroke.

Scale	Description	Goal	References	Delphi agreement ≥ 80% (given in %)
NIHSS on admission	0–42 impairment scale	To evaluate impairment of neurological function pre-intervention	D. Schlegel, S. J. Kolb, J. M. Luciano, et al., “Utility of the NIH Stroke Scale as a predictor of hospital disposition,” <i>Stroke</i> 34 (2003): 134–137. T. Rundek, H. Mast, A. Hartmann, et al., “Predictors of resource use after acute hospitalization: the Northern Manhattan Stroke Study,” <i>Neurology</i> 24 (2000): 1180–1187.	100%
NIHSS at 24–48 h	0–42 impairment scale	To evaluate impairment of neurological function post-intervention or spontaneous recovery	V. Chalos, N. A. M. van der Ende, H. F. Lingsma, et al., “National Institutes of Health Stroke Scale: An alternative primary outcome measure for trials of acute treatment for ischemic stroke,” <i>Stroke</i> 51 (2020): 282–290. S.E. Kasner, “Clinical interpretation and use of stroke scales,” <i>Lancet Neurology</i> 5 (2006): 603–612.	95.12%
mRS (at 3 months)	0–6 disability scale most used in clinical trials	To evaluate disability at 3 months. 3 months is a time point where most recovery has occurred	P. W. Duncan, “Outcome measures in stroke rehabilitation,” <i>Handbook of Clinical Neurology</i> 110 (2013): 105–111.	97.56%

Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale.

TABLE 5 | Extended clinical outcome protocol for stroke.

Scale	Description	Goal	References	Delphi agreement ≥ 80% (given in %)
SIS at 6–12 months, also by phone interview	A self-report questionnaire that evaluates disability and health-related quality of life after a stroke	To evaluate disability and quality of life at 6–12 months post-stroke stroke	M. Muldler, R. Nijland, “Stroke Impact Scale,” <i>Journal of Physiotherapy</i> 2 (2016): 117.	100% ^a
PHQ	A self-report instrument used to screen for and measure the severity of depressive and other common mental health symptoms in primary care and research settings	To provide a brief, standardized assessment that supports case identification, symptom monitoring, and evaluation of treatment response	K. Kroenke, R. L. Spitzer, J. B. Williams, “The PHQ-9: validity of a brief depression severity measure,” <i>Journal of General Internal Medicine</i> 16 (2001): 606–613.	94.44% ^a
EQ-5D	A standardized questionnaire that measures health-related quality of life across five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression	To provide a simple, comparable index of overall health status for clinical assessment, outcome evaluation, and health-economic analyses	R Rabin, F. de Charro, “EQ-5D: a measure of health status from the EuroQoL group,” <i>Annals of Medicine</i> 33 (2001): 337–343.	93.10% ^a
HDS	A clinician-rated scale used to assess the severity of depressive symptoms	To quantify depression at baseline and track changes over time, especially in response to treatment	M. Hamilton, “A rating scale for depression,” <i>Journal of Neurology, Neurosurgery, and Psychiatry</i> 23 (1960): 56–62.	90.91% ^a

Abbreviations: EQ-5D, Health-Related Quality of Life Questionnaire; HDS, Hamilton Depression Scale; PHQ, Patient Health Questionnaire; SIS, Stroke Impact Scale.

^aAfter the second voting round.

TABLE 6 | Minimum cognitive assessment protocol for stroke.

Cognition assessment	Description	Goal	Reference	Delphi agreement $\geq 80\%$ (given in %)
MoCA	30-point scale assessing cognition in multiple domains: visuospatial/ executive, language, attention, memory, orientation	A well-established scale to evaluate cognition in patients who suffer primarily from memory, attention, and executive deficits	Z. S. Nasreddine, N. A. Phillips, V. Bedirian, et al., "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment," <i>Journal of the American Geriatrics Society</i> 53 (2005): 695–699.	95.12%

Abbreviation: MoCA, Montreal Cognitive Assessment.

3.2.1 | First Voting Round

The first Delphi voting round included 62 experts (response rate of 19%) representing 27 countries, all with recognized clinical and imaging expertise in movement disorders, specifically PD. A total of 17 out of 25 items reached the predefined consensus threshold of $\geq 80\%$ agreement and were therefore excluded from the second voting round. In addition, based on participant feedback and the steering group's review, no new items were introduced, resulting in a total of 8 items included in the second voting round.

3.2.2 | Second Voting Round

The second Delphi voting round included 80 experts (response rate of 25%) representing 31 countries, reflecting sustained international engagement across both voting rounds.

In the second voting round, eight questions were evaluated. After excluding "neutral" responses, consensus above the predefined threshold of $\geq 80\%$ agreement was achieved for five questions. Further, for one question, $\geq 80\%$ agreement was achieved for the question to be deleted from the protocol. For two items, the predefined agreement threshold was not reached.

3.2.3 | Final Validated Protocols

The final set of validated connectome acquisition protocols for PD is presented below. The protocols are summarized in Tables 9–15, reflecting the consensus-derived standards agreed upon through the Delphi process.

3.3 | GBM Protocols

182 members of the EAN SPs Neuro-Oncology ($n = 70$) and Neuroimaging ($n = 112$) were invited to validate the seven protocols for GBM.

3.3.1 | First Voting Round

The first Delphi voting round included 32 experts (response rate of 27%) representing 14 countries, all with recognized clinical and imaging expertise in Neuro-Oncology, specifically in glioma. A total of 22 out of 28 items reached the predefined consensus threshold of $\geq 80\%$ agreement and were therefore excluded from the second voting round. In addition, based on participant feedback and the steering group's review, two new items were introduced, bringing the total to eight in the second voting round (six retained from the first round and two newly added).

3.3.2 | Second Voting Round

The second Delphi voting round included 41 experts (response rate of 35%) representing 19 countries, reflecting sustained international engagement across both voting rounds.

TABLE 7 | Extended cognitive assessment protocol for stroke. Assessments were selected because of validation and availability in different languages.

Cognitive assessment	Description	Goal	References	Delphi agreement ≥ 80% (given in %)
OCS		To assess different cognitive functions: language, attention, memory, praxis and executive function	N. Demeyere, M. J. Riddoch, E. D. Slavkova, et al., "The Oxford Cognitive Screen: validation of a stroke-specific short cognitive screening tool," <i>Journal of Neurology</i> 263 (2016): 306–315.	92.59% ^a
ROCF	The test consists of an immediate copying task of a complex figure and a delayed memory recall of the figure	To assess the visuo-constructional ability and visual memory	X. Zhang, L. Lv, G. Min, et al., "Overview of the Complex Figure Test and its clinical application in neuropsychiatric disorders, including copying and recall," <i>Frontiers in Neurology</i> 12 (2021): 680474.	92% ^a
TMT A-B	Form A: to connect a set of 25 numbers as quickly as possible Form B: to connect a set of 13 numbers and 13 letters in an alternating numerical and alphabetical order	To assess selective attention and task switching	L. A. Rabin, W. B. Barr, L. A. Burton, "Assessment practices of clinical neuropsychologists in the United States and Canada: a survey of INS, NAN, and APA Division 40 members," <i>Archives of Clinical Neuropsychology</i> 20 (2005): 33–65.	100% ^a
Phonemic Fluency	In this test, the patient is asked to produce as many words as possible beginning with a specific letter, in 60 s	To assess verbal fluency and mental flexibility	J. M. Biesbroek, M. J. van Zandvoort, L. J. Kappelle, et al., "Shared and distinct anatomical correlates of semantic and phonemic fluency revealed by lesion-symptom mapping in patients with ischemic stroke," <i>Brain Structure and Function</i> 221 (2016): 2123–2134.	96.86% ^a
Digit Span	In this test, the patient is asked to repeat series of digits of increasing length	To assess short term verbal memory	S. Geva, T. Truneh, M. L. Seghier, et al., "Lesions that do or do not impair digit span: a study of 816 stroke survivors," <i>Brain Communications</i> 3 (2021): fcab031.	100% ^a
Stroop test	In the test, participants are shown a series of color words that are printed in different colors of ink. The task is to name the color of the ink, rather than reading the word itself	To assess the response inhibition	F. Scarpina, S. Tagini, "The Stroop Color and Word Test," <i>Frontiers Psychology</i> 8 (2017): 557.	96.56% ^a
Token test	In this test, the patient is asked to perform verbal instructions of increasing complexity	To assess verbal comprehension	M. Paci, C. Lorenzini, E. Fioravanti, et al., "Reliability of the 36-item version of the Token Test in patients with poststroke aphasia," <i>Topics in Stroke Rehabilitation</i> 22 (2015): 374–376.	92.31% ^a

Abbreviations: OCS, Oxford Cognitive Screen; ROCF, Rey-Osterrieth Complex Figure; TMT, Trail Making Test.

^a After the second voting round.

TABLE 8 | Case report form for stroke.

Item	Description	Delphi agreement ≥ 80% (given in %)
Age of person	Expressed in years from the execution of the MRI	97.56%
Sex of person	The dichotomous variable for biological sex at birth	97.56%
Disease onset	Expressed in years at the time of the event related to the collected data	97.56%
Family history	(i) Family history of stroke (presence of stroke in first-degree relatives); (ii) prevalence of risk factors (diet, smoking, obesity, sleep habits, depression and anxiety); (iii) race and ethnic group; (iv) socio-economic background (education level, income level, occupational status, living conditions, access to healthcare, social support and networking, geographic mobility)	82.93%
Co-morbidities	Hypertension, diabetes, hyperlipidemia, atrial fibrillation, heart disease, carotid artery disease, atherosclerosis, chronic kidney disease, chronic obstructive pulmonary disease	95.12%
Current medication(s)	List of all medications currently in use	87.80%
Acute treatment (thrombolysis, mechanical intervention/thrombectomy)	Intravenous thrombolysis: Yes/No Mechanical thrombectomy: Yes/No	100% ^a

^aAfter the second voting round.

In the second voting round, eight questions were evaluated. After excluding “neutral” responses, a consensus of ≥ 80% agreement was achieved across all remaining 8 questions, thereby completing the validation process for the seven glioma protocols.

3.3.3 | Final Validated Protocols

Overall, 30 items were validated through the Delphi consensus process. The final set of validated connectome acquisition protocols for GBM is presented below. The protocols are summarized in Tables 16–22, reflecting the consensus-derived standards agreed upon through the Delphi process.

4 | Discussion

Consensus on core and extended protocol recommendations for stroke, PD, and GBM was achieved through a structured Delphi process involving brain MRI parameters, clinical outcomes, cognitive assessments, and CRF items. The resulting recommendations reflect broad expert agreement from a total of 35 European countries and define standardized data elements suitable for implementation across clinical and research settings in Europe.

These consensus-based protocols provide a pragmatic framework for harmonized multi-scale data acquisition to support neuroimaging, clinical, and neuropsychological analyses in routine clinical practice and in research applications across three major neurological diseases. The following sections discuss how

the specific protocol components align with current evidence on both clinical features and network-level mechanisms for each condition.

4.1 | Clinical Core Protocols

The Core MRI protocols were designed to characterize key lesion features, including location and volume (in stroke and GBM), as well as associated pathological changes such as perilesional edema and blood–brain barrier disruption (GBM).

In PD, the core protocol has the main purpose of ruling out any underlying cause of symptomatic parkinsonism (e.g., vascular, traumatic, space-occupying or toxic brain injury, hydrocephalus) and to support the identification of imaging markers of atypical Parkinsonism (e.g., the *hummingbird sign*, *hot-cross bun sign* and putaminal atrophy) and early indicators of dementia, such as medial temporal lobe atrophy. Importantly, the core MRI protocol also provides the basis for *indirect connectome analyses*, obtained by embedding lesions (stroke, GBM) or regions of atrophy (PD) into normative structural and functional atlases derived from healthy populations [24–26]. These analyses allow identification of structurally and functionally disconnected brain regions and networks. Disconnection mapping can then be used for behavioral correlations both cross-sectionally by identifying which disrupted networks best explain specific clinical or cognitive impairments, or longitudinally by predicting outcomes such as functional recovery after stroke, survival in GBM, or the onset of dementia in PD. We note, however, that the indirect lesion network mapping approach has recently been subject to important methodological

TABLE 9 | Clinical core MRI protocol for PD (to be obtained ≤ 20 min).

Sequence	Description	Time (minutes)	Goal	Delphi agreement $\geq 80\%$ (given in %)
3D T1 MP	SAG, VS = 1 mm iso. Magnetization prepared. In case of contrast, same parameters pre and post. FA = [10 15]°. FOV = 256 mm	5–10'	Normalization and morphometry	90.32%
3D T2-FLAIR (replaceable with 2D T2-FLAIR)	AXI, VS = 1 mm iso. (AXI, ST ≤ 3 mm, in-plane resolution 1 mm)	~4' (~3')	WM lesion, segmentation, morphometry	88.70%
SWI/SWAN	3D GRE, SAG, FA = 12° on 3 T, 20° on 1.5 T, TR shortest or 30 ms on 3 T, shortest or 60 ms on 1.5 T. ST ≤ 1.5 mm. Additional high res. Substantia Nigra slice suggested	2–4'	Microhemorrhages, nigrosomes	81.97%
SS 2D DWI or SS 3D DWI	SS-EPI, AXI, ST = [2 4]mm, number of directions ≥ 3 , in-plane resolution ≤ 1 mm, TR > 5000 ms, $b = 0$, 1000 s/mm ² SS-EPI, AXI, number of directions ≥ 30 , 2.5 mm isovoxel, TR > 5000 ms, $b = 0$, 1000 s/mm ²	2' 4'	Diffusion, ADC	70.59% ^a

Abbreviations: ADC: apparent diffusion coefficient; AXI, axial; DWI, diffusion-weighted imaging; FA, flip angle; FOV, field of view; GRE, gradient recalled echo; MP, multiparametric; SAG, sagittal; SS-EPI, single-shot echo planar imaging; ST, slice thickness; SWAN, susceptibility-weighted angiography; SWI, susceptibility-weighted imaging; TR, repetition time; VS, voxel size; WM, white matter.

^aAfter the second voting round.

TABLE 10 | Research core MRI protocol for PD (to be obtained in ≤ 40 min).

Sequence	Description	Time (minutes)	Goal	Delphi agreement $\geq 80\%$ (given in %)
rsfMRI	2D SS-EPI. TR ≤ 2 s, ST between [2 3] mm. Iso voxels. AP or PA PEp. No slice gap. Additional sequences: 1 SE AP-PEp + 1 SE PA-PEp, same geometry as rsfMRI (max 30")	Minimum length: 10'	Functional connectome (parcel-wise) and voxel-wise connectivity maps (seed-ROI, ICA)	93.02% ^a
DWI multi shell (MB*)	2D SS-EPI, ST = 2 mm. $b = 300, 1000, 2000$. With approximately 10 b300, 32 b1000, 64 b2000 (directions per shell). Distribution on the unit sphere shared with bvec/bval files. Additional B0 acquired with opposite PEp, minimum 5 volumes (max 30")	< 13'	Structural connectome (probabilistic/deterministic/global tractography) and microstructural parameters (DTI, NODDI, DKI...)	95.45% ^a
3D T2	VS = 1 mm iso, matched to T1, T2-FLAIR	~5–6'	To improve structural analysis and machine learning algorithm for segmentation	95.74% ^a

Abbreviations: AP, anterior–posterior; DKI, diffusion kurtosis imaging; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; ICA, independent component analysis; MB, multiband; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NODDI, Neurite Orientation Dispersion and Density Imaging; PA, posterior–anterior; PEp, phase encoding polarity; ROI, region of interest; rsfMRI, resting-state functional MRI; SE, spin echo; SS-EPI, single-shot echo planar imaging; ST, slice thickness; TR, repetition time; VS, voxel size.

^aAfter the second voting round.

and biological criticisms [27, 28]. This limitation further underscores the value of the patient-specific connectome measurements enabled by the research protocols proposed here. A key strength of the core clinical MRI protocol is its efficiency: all sequences can be acquired in less than 20 min, enabling seamless integration into routine clinical workflows. Moreover, all sequences are standard on the most widely used MRI platforms, facilitating broad implementation across centers. It was beyond the scope of these recommendations to provide specific parameter recommendations (i.e., repetition time, echo time, inversion time or flip angle prescriptions), since MR protocol parameters vary across scanners and vendors as well as during hardware innovation cycles. Rather, our intention was to enable vendor agnostic and robust protocol recommendations to create a pre-specified and balanced reading environment, as well as to facilitate automated and large-scale quantitative image analysis across Europe. Our recommendations target harmonization at the point of acquisition (prospective harmonization). This is complementary to well-established post hoc statistical (e.g., ComBat) or more recent deep-learning harmonization methods [29], which aim to remove residual scanner- and site-related variance after data collection. Prospective standardization reduces the non-biological variability that such methods must subsequently model, an advantage that is particularly relevant for pathological datasets.

4.2 | Research Connectome Core and Acquisition Principles

The research MRI protocol for each pathology was designed to enable direct physiological and structural assessment of disease effects on brain networks through resting-state fMRI (for functional connectivity) and multi-shell diffusion-weighted imaging (for structural connectivity and microstructural white-matter features). The central diffusion recommendation is the principle of acquiring multi-shell, multi-directional data, rather than any specific set of b -values. These principles are shared across all three diseases. Multiple diffusion shells enable advanced non-Gaussian diffusion models beyond the basic tensor (e.g., NODDI, DKI) and distributed gradient directions improve crossing fibers identification for robust tractography. The scheme reported here ($b = 300/1000/2000$ s/mm², with approximately 10/32/64 directions per shell) is provided as one feasible example that balances modeling flexibility against a clinically realistic acquisition time. The precise shell and direction values may be adapted to the local scanner and research question without compromising harmonization. A similar general principle applies to fMRI, where a minimum duration is recommended for stable connectivity estimation. In both diffusion and functional imaging, isotropic voxels (equal size along all axes) are preferable to avoid

TABLE 11 | Minimum clinical outcome protocol for PD.

Scale	Description	Goal	References	Delphi agreement ≥ 80% (given in %)
MDS-UPDRS	The UPDRS is composed of: • Part I: evaluation of mentation, behavior, and mood • Part II: self-evaluation of the activities of daily life (ADLs) including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, and cutting food • Part III: clinician-scored monitored motor evaluation • Part IV: complications of therapy • Part V: Hoehn and Yahr staging of severity of Parkinson's disease • Part VI: Schwab and England ADL scale	The Unified Parkinson's Disease Rating Scale (UPDRS) is used to follow the longitudinal course of PD	Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, "The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations," <i>Movement Disorders</i> 18 (2003): 738–750.	96.78%
RBDIQ	A screening question for dream enactment with a simple yes/no response	To assess the most prominent clinical features of RBD	K. Stiasny-Kolster, G. Mayer, S. Schaefer, et al., "The REM sleep behavior disorder screening questionnaire – a new diagnostic instrument," <i>Movement Disorders</i> 22 (2007): 2386–2393.	78% ^a
PDQ8	The 8-item version is a shortened version of the 39-item Parkinson's Disease Questionnaire	To assess quality of life in Parkinson's disease patients	V. Peto, C. Jenkinson, R. Fitzpatrick, "PDQ-39: a review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures," <i>Journal of Neurology</i> 245 (1998): S10–14.	80.65%

Abbreviations: MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; PDQ8, Parkinson's Disease Questionnaire 8 item; RBDIQ, REM (Rapid Eye Movement) Sleep Behavior Disorder Questionnaire.
^aAfter the second voting round.

TABLE 12 | Extended clinical outcome protocol for PD.

Scale	Description	Goal	References	Delphi agreement ≥ 80% (given in %)
SCOPA-AUT	The scale is self-completed by patients and consists of 25 items assessing the following domains: gastrointestinal (7), urinary (6), cardiovascular (3), thermoregulatory (4), pupillomotor (1), and sexual (2) items for men and 2 items for women)	The SCOPA-AUT was developed to evaluate autonomic symptoms in patients with Parkinson's disease as well as patients with multiple system atrophy	M. Visser, J. marinus, A. M. Stiggelbout, J. J. Van Hilten, "Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT," <i>Movement Disorders</i> 19 (2004): 1306–1312.	88.71%
IRBD-SSS (instead of RBDSQ)	A clinical severity scale designed to quantify the frequency, intensity, and consequences of REM sleep behavior disorder symptoms, with patient and bedpartner versions	To provide a standardized measure of RBD severity for clinical assessment, symptom monitoring, and therapeutic trials	M. L. Fantini, R. B. Postuma, M. Puligheddu, et al., "Validation of the International REM Sleep Behavior Disorder Study Group Symptoms Severity Scale (IRBD-SSS): a new tool to assess RBD clinical severity," <i>Journal of Neurology</i> 271 (2024): 7264–7271.	78.05% ^a

Abbreviations: IRBD-SSS, International REM (Rapid Eye Movement) Sleep Behavior Disorder Study Group Symptom Severity Scale; SCOPA-AUT, Scales for Outcomes in Parkinson's disease Autonomic Function.

^a After the second voting round.

TABLE 13 | Minimum cognitive assessment protocol for PD.

Cognitive assessment	Description	Goal	Reference	Delphi agreement ≥ 80% (given in %)
MoCA	30-point scale assessing cognition in multiple domains: visuospatial/executive, language, attention, memory, orientation	A widely recognized global cognitive scale, originally developed as a screening tool for MCI in the general population and has been identified as one of the fully 'recommended' screening toll for clinical practice and research in PD. MoCA effectively evaluates all PD-relevant cognitive domains, including executive functioning, making it a robust and comprehensive measure	Z. S. Nasreddine, N. A. Phillips, V. Bedirian, et al., "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment," <i>Journal of the American Geriatrics Society</i> 53 (2005): 695–699. E. Fiorenzato, S. Cauzzo, L. Weis, et al., "Optimal MMSE and MoCA cutoffs for cognitive diagnoses in Parkinson's disease: A data-driven decision tree model," <i>Journal of Neurological Sciences</i> 466 (2024): 123283.	98.39%

Abbreviations: MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment.

TABLE 14 | Extended cognitive assessment protocol for PD. Assessments were selected because of validation and availability in different languages.

Cognitive assessment	Description	Goal	References	Delphi agreement $\geq 80\%$ (given in %)
ROCF	The test consists of an immediate copying task of a complex figure and a delayed memory recall of the figure	To assess the visuo-constructional ability and visual memory. In PD, ROCF has been identified as the most suitable visuo-cognitive test to differentiate PD-MCI vs. PD with dementia (PDD)	X. Zhang, L. Lv, G. Min, et al., "Overview of the Complex Figure Test and its clinical application in neuropsychiatric disorders, including copying and recall," <i>Frontiers in Neurology</i> 12 (2021): 680474. H. Liebermann-Jordanidis, M. Roheger, L. Boosfeld, et al., "Which test is the best to assess visuo-cognitive impairment in patients with Parkinson's Disease with mild cognitive impairment and dementia? A systematic review and meta-analysis," <i>Journal of Parkinson's Disease</i> 12 (2022): 1749–1782.	90.24% ^a
TMT A-B	Form A: to connect a set of 25 numbers as quickly as possible Form B: to connect a set of 13 numbers and 13 letters in an alternating numerical and alphabetical order	To provide estimates of visual search, visual attention, speed of processing and mental flexibility. TMT (A-B) can reliably differentiate PD from controls, as well as between different PD-cognitive statuses (PD with normal cognition vs. PD-MCI vs. PDD)	L. A. Rabin, W. B. Barr, L. A. Burton, "Assessment practices of clinical neuropsychologists in the United States and Canada: a survey of INS, NAN, and APA Division 40 members," <i>Archives of Clinical Neuropsychology</i> 20 (2005): 33–65. G. Santangelo, C. Vitale, M. Picillo, et al., "Mild Cognitive Impairment in newly diagnosed Parkinson's disease: A longitudinal prospective study," <i>Parkinsonism and Related Disorders</i> 21 (2015): 1219–1226.	80.65%
Phonemic Fluency	In this test the patient is asked to produce as many words as possible beginning with a specific letter, in 60 s	To assess self-monitoring, processing speed and attention, working memory, and language processing including the retrieval of appropriate responses from the mental lexicon, by drawing on phonological word knowledge	Obeso, E. Casabona, M. L. Bringas, et al., "Semantic and phonemic verbal fluency in Parkinson's disease: Influence of clinical and demographic variables," <i>Behavioral Neurology</i> 25 (2012): 111–118.	88.71%

(Continues)

TABLE 14 | (Continued)

Cognitive assessment	Description	Goal	References	Delphi agreement ≥ 80% (given in %)
Digit Span	In this test the patient is asked to repeat series of digits of increasing length in forward and backward order	To evaluate attention, concentration and working-memory abilities. In PD, particularly the Digit Span Backward has been used in PD research, demonstrating to be sensitive to change with aging and PD-MCI	C. Warden, J. Hwang, A. Marshall, et al., "The effects of dopamine on digit span in Parkinson's disease," <i>Journal of Clinical Movement Disorders</i> 3 (2016): 5. J. P. Grogan, L. E. Knight, L. Smith L, et al., "Effects of Parkinson's disease and dopamine on digit span measures of working memory," <i>Psychopharmacology</i> 235 (2018): 3443–3450.	87.09%
Stroop test	In the test, participants are shown a series of color words that are printed in different colors of ink. The task is to name the color of the ink, rather than reading the word itself	To assess the ability to inhibit cognitive interference, primarily involving selective attention, cognitive flexibility, and sensitivity to interference – functions closely linked to the frontal lobe. Stroop test is particularly valuable in PD, as a poor performance is a good predictor of cognitive decline, including progression from normal cognition to PD-MCI and PDD	F. Scarpina, S. Tagini, "The Stroop Color and Word Test," <i>Frontiers Psychology</i> 8 (2017): 557. C. C. Janvin, D. Aarsland, J. P. Larsen, "Cognitive predictors of dementia in Parkinson's disease: a community-based, 4-year longitudinal study," <i>Journal of Geriatric Psychiatry and Neurology</i> 18 (2005): 149–154.	80.64%

Abbreviations: MCI, mild cognitive impairment; ROCF, Rey-Osterrieth Complex Figure; TMT, Trail Making Test.
a After the second voting round.

TABLE 15 | Case report form for PD.

Item	Description	Delphi agreement $\geq 80\%$ (given in %)
Age of person	Age at the time of MRI scan	98.39%
Sex of person	The dichotomous variable for biological sex at birth	95.16%
Disease onset	Date of first symptom(s) at onset Date of diagnosis	98.39%
Family history	Significant hereditary neurological conditions	93.55%
Co-morbidities	Other significant co-existent clinical conditions	90.32%
Current medication(s)	Medication the patient was assuming at the time of diagnosis	88.70%

orientation-dependent biases in tractography and provide uniform spatial resolution for functional connectivity, respectively. Where appropriate, perfusion imaging further provides complementary metabolic information. These advanced measures are expected to become increasingly important as machine learning based-approaches, such as foundation models, explainable AI, and deep learning (especially convolutional and graph neural networks increasingly used for imaging), are integrated into classification and diagnostic pipelines, as they offer a substantially richer set of discriminative features. As with the clinical protocol, all sequences included in the research protocol are available on the major scanner platforms and can be acquired within a feasible time window (< 40 min). The 10-min minimum for resting-state fMRI reflects a consensus-derived suggestion rather than a fixed threshold. This range offer a reasonable reliability trade-off, while longer acquisitions are more reliable and enable more nuanced analyses. Clinical and cognitive protocols were designed to provide standardized characterization of neurological impairment and its longitudinal evolution across pathologies, as well as their impact on cognition, functional status, and disability. Impairment, function, and disability represent the three core axes of the World Health Organization's International Classification of Functioning framework and are all recognized as critical outcome domains for evaluating the effectiveness of emerging therapies.

4.3 | Disease-Specific Considerations

For stroke, the research protocol is designed to capture the connectome signatures that have been shown to drive both acute impairment and long-term recovery. The inclusion of resting-state functional MRI and multi-shell diffusion imaging enables the computation of both functional and structural connectomes. Current evidence demonstrates that stroke-related behavioral deficits are strongly shaped by alterations in large-scale brain networks rather than by lesion volume alone, and that the degree of functional connectivity normalization at follow-up represents a meaningful biomarker of recovery potential [9, 30–32]. Furthermore, a recent longitudinal study has revealed that structural connectivity undergoes widespread degeneration in the months following stroke, while functional recovery appears to depend on synaptic

reweighting of residual structural connections, a finding that underscores the complementary value of both diffusion and functional MRI sequences included in these protocols [33]. The addition of non-contrast imaging (pCASL/ASL) and MR angiography in the stroke research protocol further enables the assessment of cerebrovascular architecture and its relationship with the structural and functional connectome, providing a multi-modal characterization of the post-stroke brain. Clinical outcome measures, including the NIHSS at admission and at 24–48 h and the mRS at 3 months, align with the time points at which informative connectivity changes have been documented [34], facilitating the development of predictive models linking acute network disruption to functional recovery trajectories.

For GBM, these protocols address the growing recognition that brain tumors produce a “disconnectome-like” condition in which network-level alterations critically shape clinical outcomes [3, 5]. The inclusion of multi-shell diffusion imaging and resting-state functional MRI enables the computation of both structural and functional connectivity measures that have demonstrated significant prognostic value. Notably, structural disconnection derived from white matter tract density at the lesion site has been shown to outperform conventional clinical predictors of overall survival, including lesion volume, degree of surgical resection, and genetic markers [10]. In contrast, indirect functional connectivity measures derived from normative datasets appear to have limited clinical predictive value in GBM [35], reinforcing the importance of patient-specific, direct connectome assessments as enabled by the present protocols. Furthermore, the DSC T2* perfusion sequence included in the clinical core protocol provides information on cerebral blood volume that complements the connectomic assessment. The extended cognitive assessment battery (MoCA, ROCF, TMT, phonemic fluency, digit span) captures the cognitive domains most affected by network disruption in GBM patients, while the CRF items on genetic markers (IDH, MGMT) and WHO classification enable the integration of molecular and network-level data for comprehensive prognostic modeling. The homogenized protocol will further enable the incorporation of automated and longitudinal lesion segmentation at larger scale and prepare for successful federated learning initiatives across Europe, as previously demonstrated in international network cooperations [36, 37].

TABLE 16 | Clinical core MRI protocol for GBM (to be obtained ≤ 20 min).

Sequence	Description	Time (minutes)	Goal	Delphi agreement ≥ 80% (given in %)
3D T1 SE pre-contrast (replaceable with 3D T1 IRP)	SAG, VS = 1 mm iso. Magnetization prepared. In case of contrast, same parameters pre and post. FA = [10 15]°. FOV = 256 mm. Eventually use contrast enhancement if time allows	2–4'	Normalization and morphometry	96.88%
3D T2-FLAIR (replaceable with 2D T2-FLAIR)	AXI, VS = 1 mm iso. (AXI, ST ≤ 3 mm, in-plane resolution 1 mm)	~4' (~3')	Tumor lesion, segmentation, morphometry	100%
SS 2D DWI or SS 3D DWI	SS-EPI, AXI, ST = [2 4]mm, number of directions ≥ 3, in-plane resolution ≤ 1 mm, TR > 5000 ms, b = 0, 1000 s/mm ² SS-EPI, AXI, number of directions ≥ 30, 2.5 mm isovoxel, TR > 5000 ms, b = 0, 1000 s/mm ²	2' 4'	Diffusion, increased cellularity	100%
Contrast injection	0.1 mmol/kg dose injection with a gadolinium-chelated contrast agent*. Use of a power injector is desirable at an injection rate of 3–5 cc/s	10'	* or equivalent	100%
DSC T2* perfusion	GRE-EPI, TE = short as possible. Slice thickness 3–5 mm. Temporal coverage = 120 time points. Eventually use SE-EPI. TR = 1.0/1.5 s with TE = 40–45 ms	~2'	CBV (CBF, MTT)* * based on software availability	87.51%
3D T1 SE post-contrast, exactly as pre-contrast (replaceable with 3D T1 IRP)	SAG, VS = 1 mm iso. Magnetization prepared. In case of contrast, same parameters pre and post. FA = [10 15]°. FOV = 256 mm. Eventually use contrast enhancement if time allows	2–4'	Normalization and morphometry. Tumor lesion, segmentation, morphometry, blood brain barrier breakdown	96.88%

Abbreviations: AXI, axial; CBF, cerebral blood flow; CBV, cerebral blood volume; DSC, dynamic susceptibility contrast; DWI, diffusion-weighted imaging; FA, flip angle; FOV, field of view; GRE, gradient recalled echo; IRP, inversion pulse-prepped; MTT, mean transit time; PEp, phase encoding polarity; SAG, sagittal; SE, spin echo; SS-EPI, single-shot echo planar imaging; ST, slice thickness; TE, echo time; TR, repetition time; VS, voxel size.

TABLE 17 | Research core MRI protocol for GBM (to be obtained in ≤40 min).

Sequence	Description	Time (minutes)	Goal	Delphi agreement ≥ 80% (given in %)
rsfMRI	2D SS-EPI. TR ≤ 2 s, ST between [2 3] mm. Iso voxels. AP or PA PEp. No slice gap. Additional sequences: 1 SE AP-PEp + 1 SE PA-PEp, same geometry as rsfMRI (max 30'')	Minimum length: 10'	Functional connectome (parcel-wise) and voxel-wise connectivity maps (seed-ROI, ICA)	81.48% ^a
DWI multi shell (MB*)	2D SS-EPI, ST = 2 mm. <i>b</i> = 300, 1000, 2000. With approximately 10 b300, 32 b1000, 64 b2000 (directions per shell). Distribution on the unit sphere shared with bvec/bval files. Additional B0 acquired with opposite PEp, minimum 5 volumes (max 30'')	<13'	Structural connectome (probabilistic/deterministic/global tractography) and microstructural parameters (DTI, NODDI, DKI, ...)	90.32% ^a
3D T2	VS = 1 mm iso, matched to T1, T2-FLAIR	~5–6'	Improving structural analysis and machine learning algorithm for segmentation	94.29%
MRS	Proton single-voxel spectroscopy (¹ H-MRS, SVS), most commonly with PRESS localization on 3 T scanners. A standard protocol is TE = 30–35 ms, TR = ~2000 ms, voxel size = 15–20 mm per side; 64 averages for a 20 mm voxel or 128 averages for a 15 mm voxel at 3 T; other protocols: STEAM or semi-LASER	~5' for a single voxel at 3 T; multi-voxel/CSI or MRSI ~10–15' min	To characterize tumor metabolism beyond conventional MRI. In practice, it is used to assess metabolites such as Cho, Cr, NAA, lactate, lipids, and sometimes myoinositol; this helps with tumor characterization and grading, distinguishing glioma from metastasis, identifying more aggressive regions for biopsy targeting, and helping differentiate tumor progression/recurrence from treatment effect or radiation necrosis	81.25% ^a

Abbreviations: Cho, choline; Cr, creatine; DKI, diffusion kurtosis imaging; DTI, diffusion tensor imaging; ICA, independent component analysis; MB, multiband; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; NODDI, Neurite Orientation Dispersion and Density Imaging; PEp, phase encoding polarity; ROI, region of interest; rsfMRI, resting-state functional MRI; SE, spin echo; SS-EPI, single-shot echo planar imaging; ST, slice thickness; TE, echo time; TR, repetition time; VS, voxel size.
^aAfter the second voting round.

TABLE 18 | Minimum clinical outcome protocol for GBM.

Scale	Description	Goal	References	Delphi agreement $\geq 80\%$ (given in %)
OS	Time (months) from the first surgery to the death resulting from any cause	Main outcome in clinical trials and evaluation of treatment	R. Stupp, W. P. Mason, M. J. van den Bent, et al., "Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma," <i>New England Journal of Medicine</i> 352 (2005): 987–996.	96.88%
PFS	Time (months) from the first surgery to disease progression according to RANO criteria	Second most common outcome in clinical trials and evaluation of treatment	P. Y. Wen, M. van den Bent, G. Youssef, et al., "RANO 2.0: Update to the response assessment in neuro-oncology criteria for high- and low-grade gliomas in adults," <i>Journal of Clinical Oncology</i> 41 (2023): 5187–5199.	90.63%
ECOG KPS	Describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability	Common scales to quantify cancer patients' general well-being and activities of daily living	M. M. Oken, R. H. Creech, D. C. Tormey, et al., "Toxicity and response criteria of the Eastern Cooperative Oncology Group," <i>American Journal of Clinical Oncology</i> 5 (1982): 649–655. C. C. Schag, R. L. Heinrich, P. A. Ganz, "Karnofsky performance status revisited: reliability, validity, and guidelines," <i>Journal of Clinical Oncology</i> 2 (1984): 187–193.	93.75%

Abbreviations: ECOG, Eastern Cooperative Group Score; KPS, Karnofsky Performance Score; OS, Overall Survival; PFS, Progression Free Interval; RANO, Response Assessment in Neuro-Oncology.

TABLE 19 | Extended clinical outcome protocol for GBM.

Scale	Description	Goal	References	Delphi agreement $\geq 80\%$ (given in %)
NANO-Scale	An objective and quantifiable metric of neurologic function evaluable during a routine office examination	To provide an overall assessment of outcome for neuro-oncology patients in clinical trials and in daily practice	L. Nayak, L. M. DeAngelis, A. A. Brandes, et al., "The Neurologic Assessment in Neuro-Oncology (NANO) scale: a tool to assess neurologic function for integration into the Response Assessment in Neuro-Oncology (RANO) criteria," <i>Neuro-Oncology</i> 19 (2017): 625–635.	87.51%
QLQ-C30	A standardized questionnaire on quality-of-life of oncological patients exploring several domains	One of the most widely used patients reported outcome instrument to assess health-related quality of life in cancer patients	N. K. Aaronson, S. Ahmedzai, B. Bergman, et al., "The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology," <i>Journal of the National Cancer Institute</i> 85 (1993): 365–376.	87.50%
QLQ-BN20	A brain-specific module that contains 20 items grouped into four domains (future uncertainty: four items; visual disorder, motor dysfunction, communication deficit: each three items) as well as seven single items (headaches, seizures, drowsiness, hair loss, itchy skin, weakness of legs, bladder control)	One of the most widely used patients reported outcome to assess health-related quality of life in brain cancer patients (complementary to QLQ-C30)	D. Steinmann, Y. Paelecke-Habermann, H. Geinitz, et al., "Prospective evaluation of quality-of-life effects in patients undergoing palliative radiotherapy for brain metastases," <i>BMC Cancer</i> 12 (2012): 283.	87.51%

Abbreviations: EORTC, European Organization of Research and Treatment of Cancer; NANO, Neurologic Assessment in Neuro-Oncology; QLQ-BN20, Quality of Life Questionnaire Brain Cancer Module 20; QLQ-C30, Quality of Life Questionnaire Core 30.

TABLE 20 | Minimum cognitive assessment protocol for GBM.

Cognitive assessment	Description	Goal	Reference	Delphi agreement $\geq 80\%$ (given in %)
MoCA	30-point scale assessing cognition in multiple domains: visuospatial/executive, language, attention, memory, orientation	A well-established scale to evaluate cognition in glioma patients who suffer primarily of memory, attention, and executive deficits	V. Jammula, J. L. Rogers, E. Vera, et al., "The Montreal Cognitive Assessment (MoCA) in neuro-oncology: A pilot study of feasibility and utility in telehealth and in-person clinical assessments," <i>Neurooncological Practice</i> 9 (2022): 429–440.	96.88%

Abbreviation: MoCA, Montreal Cognitive Assessment.

For PD, the protocols are designed to capture the progressive network degeneration that characterizes this neurodegenerative condition. The resting-state fMRI sequence in the research protocol enables the assessment of functional connectivity disruptions that have been consistently reported in PD [38], including altered connectivity between frontal and posterior cortical regions and disrupted integration within the default mode and sensorimotor networks [39–41]. The multi-shell diffusion imaging protocol allows for the computation of structural connectomes and microstructural parameters that can reveal the axonal pathways along which α -synuclein pathology may propagate [19, 42]. The SWI/SWAN sequence included in the clinical core protocol provides additional information through visualization of the nigrosome-1 signal, which has demonstrated high sensitivity and specificity in the diagnosis of PD, making it a reliable imaging biomarker for distinguishing affected patients from healthy individuals. Finally, the clinical outcome scales (UPDRS, PDQ-8) and extended assessments (SCOPA-AUT) are well-suited for tracking the motor and some non-motor manifestations of network dysfunction across disease stages. In addition to the MoCA test, widely recognized as a comprehensive screening tool for cognitive impairment in patients with PD, the extended cognitive battery, including the ROCF, the Stroop Test, and the TMT, captures visuoconstructional ability, visual memory, and executive function deficits. These domains have been closely linked to connectivity alterations in PD and may serve as potential early predictors of cognitive decline and progression to dementia [43].

4.4 | Cross-Disease Design and Harmonization

A key strength of the present framework lies in its cross-disease design. By adopting harmonized acquisition protocols across stroke, GBM, and PD, these recommendations enable direct comparisons of connectome alterations across conditions with fundamentally different etiologies. This approach is supported by accumulating evidence that these diseases share common patterns of network dysfunction, including the characteristic trajectory from initial hyperconnectivity to progressive network failure [44]. The shared MRI sequences (3D T1, T2-FLAIR, resting-state fMRI, multi-shell DWI) across all three disease protocols allow for the extraction of comparable brain features, facilitating cross-disease analyses. Crucially, resting-state fMRI, for capturing the functional connectome, and multi-shell DWI, for the structural connectome, represent the connectome core common to all three conditions. Furthermore, the use of MoCA as a minimum cognitive assessment provides a standardized cognitive endpoint that can be related to network measures across disease boundaries. This cross-disease analytical capability is particularly relevant for identifying shared vulnerability patterns, such as the preferential involvement of network hubs and rich-club connections observed across neurological disorders, and for developing transdiagnostic network-based biomarkers that may inform therapeutic strategies applicable across multiple conditions.

Importantly, the framework is designed to remain adaptable, allowing modular extensions to incorporate additional data domains such as neurophysiological measures or non-imaging biomarkers. Beyond the diseases addressed here, this approach

TABLE 21 | Extended cognitive assessment protocol for GBM. Assessments were selected because of validation and availability in different languages.

Cognitive assessment	Description	Goal	References	Delphi agreement ≥ 80% (given in %)
ROCF	The test consists of an immediate copying task of a complex figure and a delayed memory recall of the figure	To assess the visuo-constructional ability and visual memory	X. Zhang, L. Lv, G. Min, et al., "Overview of the Complex Figure Test and its clinical application in neuropsychiatric disorders, including copying and recall," <i>Frontiers in Neurology</i> 12 (2021): 680474.	100% ^a
TMT A-B	Form A: to connect a set of 25 numbers as quickly as possible Form B: to connect a set of 13 numbers and 13 letters in an alternating numerical and alphabetical order	To assess selective attention and task switching	L. A. Rabin, W. B. Barr, L. A. Burton, "Assessment practices of clinical neuropsychologists in the United States and Canada: a survey of INS, NAN, and APA Division 40 members," <i>Archives of Clinical Neuropsychology</i> 20 (2005): 33–65.	81.26%
Phonemic Fluency	In this test, the patient is asked to produce as many words as possible beginning with a specific letter, in 60 s	To assess verbal fluency and mental flexibility	T. N. Tombaugh, J. Kozak, L. Rees, "Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming," <i>Archives of Clinical Neuropsychology</i> 14 (1999): 167–177.	100%
Digit Span	In this test, the patient is asked to repeat series of digits of increasing length	To assess short term verbal memory	F. Campanella, F. del Missier, T. Shallice, M. Skrap, "Localizing memory functions in brain tumor patients: anatomical hotspots over 260 patients," <i>World Neurosurgery</i> 120 (2018): e690–e709.	100%

Abbreviations: ROCF, Rey-Osterrieth Complex Figure; TMT, Trail Making Test.

^aAfter the second voting round.

TABLE 22 | Case report form for GBM.

Item	Description	Delphi agreement $\geq 80\%$ (given in %)
Age of person	Age at the time of MRI scan	100%
Sex of person	The dichotomous variable for biological sex at birth	100%
Disease onset	Date of first symptom(s) at onset Date of diagnosis	100%
Family history	Significant hereditary oncological or neurological conditions	81.26%
Co-morbidities	Other significant co-existents clinical conditions	90.63%
Current medication(s)	Medication the patients was assuming at the time of diagnosis	87.51%
Genetic testing: IDH, MGMT promoter methylation, others	IDH: Are essential enzymes that participate in several major metabolic processes with a significant biological, prognostic, and therapeutic role in gliomas. Specify if mutated or wild type and in case of mutation specify the mutated isoform (IDH1/2/) MGMT promoter methylation: when the methylation is present, it is associated with a better response to alkylating agents (e.g., Temozolomide) representing a predictive factor. Specify if the methylation is present or not. Others: report if any other molecular test were performed (e.g., TP53, PTEN, EGFR, NF1, BRAF, FGFR, NTRK)	81.25%
2021 WHO classification	Indicate diagnosis according to WHO classification	100%
Seizures at onset	Yes/No	100% ^a

Abbreviations: IDH, isocitrate dehydrogenase; MGMT, O⁶-methylguanine-DNA methyltransferase; WHO, World Health Organization.

^aAfter the second voting round.

may serve as a model for developing network-oriented study frameworks for other neurological disorders.

These protocols will provide European neurologists with robust procedures for operating and securely sharing sensitive health data, while also strengthening data owners' confidence in their validity for both research and clinical applications. The broader vision is to enable not only major hub hospitals in tertiary medical centers, but also smaller spoke hospitals across Europe to actively participate in clinical research through GDPR-compliant platforms for sensitive data sharing. By contributing to large-scale AI models, Europe can leverage the unique strengths of its national health systems to play a leading global role in medical artificial intelligence and advanced health analytics.

4.5 | Limitations

Several limitations should be acknowledged. First, although 536 experts from four EAN Scientific Panels were invited, the cumulative response rate was modest. This attrition may introduce self-selection bias, with responders potentially differing from non-responders (e.g., greater interest or expertise in connectomics), and participation may have been unevenly distributed

across countries and panels despite representation from around thirty countries; future iterations may benefit from broader consultation. Second, some imaging metrics (e.g., diffusion-based) should be interpreted with caution in pathological brains, as lesions, oedema, or tumor infiltration can increase measurement uncertainty, so structural connectome estimates require careful interpretation. Finally, the protocols were not benchmarked against existing large-scale imaging initiatives (e.g., the Human Connectome Project); however, within EBRAINS 2.0 a multi-modal connectome in healthy controls is being prospectively acquired and will provide a physiological reference against which disease-related connectome alterations can be calibrated in future work.

4.6 | Conclusions

In conclusion, by enabling standardized, multi-modal data acquisition across European centers, the present framework facilitates the transition from traditional lesion-based or region-specific analyses to a network-based understanding of neurological disease. This paradigm shift, from studying isolated brain regions to investigating large-scale network dynamics, has the potential to reveal shared mechanisms of vulnerability and resilience across neurological conditions and to support the

development of personalized, connectivity-informed therapeutic interventions. The EBRAINS 2.0 research infrastructure, with its capacity for large-scale data integration, multi-center collaboration, and advanced computational modeling, provides the ideal platform for realizing this connectome-based vision of European neurology.

Author Contributions

Thomas Berger: conceptualization, investigation, writing – original draft, writing – review and editing, funding acquisition, methodology, validation, project administration, data curation, supervision. **Lorenzo Pini:** visualization, writing – original draft, writing – review and editing, data curation, conceptualization, methodology, investigation, validation. **Alessandro Salvalaggio:** investigation, methodology, validation, writing – review and editing. **Simone Cauzzo:** investigation, methodology, validation, writing – review and editing. **Christine Klein:** conceptualization, investigation, validation, writing – review and editing. **Maria Lolich:** conceptualization, investigation, funding acquisition, methodology, project administration, resources, writing – original draft. **Alberto Picca:** conceptualization, investigation, validation, writing – review and editing. **Dauren Ramankulov:** conceptualization, investigation, funding acquisition, writing – original draft, methodology, project administration, resources. **Maria A. Rocca:** conceptualization, investigation, validation, writing – review and editing. **Roberta Rudà:** conceptualization, investigation, validation, writing – review and editing. **Alessandro Soderò:** conceptualization, investigation, validation, writing – review and editing. **Alessandro Tessitore:** conceptualization, investigation, validation, writing – review and editing. **Thomas Truelsen:** conceptualization, investigation, validation, writing – review and editing. **Roland Wiest:** conceptualization, investigation, validation, writing – review and editing. **Gereon R. Fink:** conceptualization, investigation, validation, writing – review and editing, resources. **Elena Moro:** conceptualization, investigation, funding acquisition, validation, writing – review and editing, resources. **Philippe Ryvlin:** conceptualization, investigation, funding acquisition, methodology, validation, writing – review and editing, supervision, resources. **Maurizio Corbetta:** conceptualization, investigation, funding acquisition, methodology, validation, writing – review and editing, supervision, resources.

Funding

This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No 101147319 (EBRAINS 2.0).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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