Personalized Stroke Rehabilitation via Multimodal Data and Model-Guided Neuromodulation

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1 Introduction

Stroke, standing as the world's second-leading cause of death and a major contributor to adult disability, occurs when the blood supply to a part of the brain is interrupted, depriving neural tissue of essential oxygen and nutrients. This sudden disruption, caused either by an ischemic event (arterial blockage) or a hemorrhagic event (vessel rupture), leads to the death of brain cells and widespread neurological damage [1]. As of 2016, approximately 80 million people worldwide had survived a stroke, and the condition remains the second most frequent cause of acquired disability [2, 3].

Among the many functional consequences of stroke (see Figure 1), upper-limb impairment stands out as one of the most critical in shaping survivors' independence, particularly in daily activities such as reaching, grasping, or using tools [3,4]. Between 50 and 80% of stroke survivors experience upper-limb motor deficits, and fewer than 15% regain full functionality [5]. In parallel, cognitive impairments, including deficits in memory, attention, executive function, and language, are also frequently observed and can further complicate the recovery process. These impairments often interfere with patients' ability to participate fully in rehabilitation, limit their autonomy, and significantly impact quality of life and reintegration into daily and professional roles [6,7]. To quantify and monitor these deficits, standardized clinical scores—such as the Fugl-Meyer Assessment (UEFM) and the Action Research Arm Test (ARAT) for motor function, or the MoCA, MMSE, and Clock Drawing Test for cognitive domains—are commonly used in both clinical and research settings [8].

Figure 1: Overview of common neurological deficits post-stroke.

In addition to persistent impairments, stroke survivors face a high risk of recurrence: roughly one in four individuals who have had a stroke will experience another, often more debilitating event [9]. This heightened risk underscores the importance of effective rehabilitation and prevention strategies to support long-term recovery and reduce the burden on patients, families, and healthcare systems.

To address these impairments, a range of treatment options is available, including pharmacological interventions, rehabilitative therapies, and lifestyle modifications. Medications such as antiplatelets, anticoagulants, and statins are commonly prescribed to reduce the risk of recurrent strokes and support vascular health [10]. Simultaneously, rehabilitation programs that focus on specific functional domains (motor, cognitive, speech, behavioral, or occupational) are widely implemented to help patients regain autonomy and improve quality of life [11]. These interventions are often complemented by lifestyle changes, including increased physical activity, nutritional improvements, smoking cessation, and psychological support [12].

In recent years, non-invasive brain stimulation (NIBS) techniques have gained increasing attention as promising adjuncts to conventional therapies. Among these, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are used to modulate cortical excitability and enhance neuroplasticity [13, 14]. When combined with task-specific neurorehabilitative training, these methods have shown greater and more sustained functional improvements than training alone. In particular, repetitive TMS (rTMS) has emerged as the most commonly implemented neuromodulation technique in stroke rehabilitation, supported by mature safety guidelines and the availability of clinical hardware in many hospitals [13].

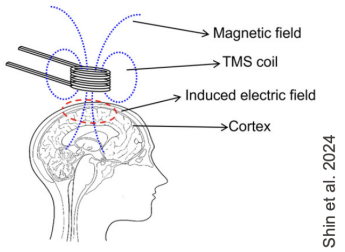
rTMS uses repeated magnetic pulses to modulate brain activity and is commonly applied to restore the interhemispheric balance disrupted by stroke. Its effectiveness depends primarily on stimulation

frequency and cortical target site, which are currently the main parameters adjusted in clinical practice, often based on the patient's stroke severity and lesion profile. For example, Coscia et al. [13] identified three clinically validated rTMS configurations that vary in frequency and stimulation site, each associated with improved outcomes across different levels of impairment. These protocols aim to either suppress maladaptive activity in the contralesional hemisphere or enhance residual function in the ipsilesional hemisphere.

However, applying standardized rTMS protocols across all patients presents important limitations. Failing to account for individual factors such as lesion location, stroke chronicity, residual structural connectivity, and interhemispheric inhibition profiles may result in suboptimal or even counterproductive outcomes [15, 16]. For instance, suppressing the contralesional motor cortex can promote recovery in subcortical strokes but may inadvertently inhibit residual motor areas in cortical lesions [17]. Likewise, individuals with weak transcallosal connections may not benefit from interhemispheric suppression strategies at all [18]. Furthermore, motor thresholds can vary by as much as two-fold across patients, requiring fine-tuned calibration of stimulation intensity [19]. Timing also plays a role: inhibitory rTMS tends to be more effective in the early post-stroke phase (less than 6 months), whereas excitatory ipsilesional stimulation may yield better results in later stages [18].

Lefaucheur et al. 2014

Parameter	Variants
Frequency	1 Hz, 3 Hz, 5Hz, 10 Hz
Target	Contralesional vs Ipsilesional M1, PMv
Intensity	80–120% of resting motor threshold
Pulses	200-1800
Coil type	Tilted, Sham
Sessions	5–20+ sessions, daily or accelerated



Shin et al. 2024

Figure 2: Key adjustable parameters in Repetitive Transcranial Magnetic Stimulation (rTMS)

Figure 2 illustrates the broader range of parameters that define the rTMS configuration space, including stimulation intensity, session duration, and total number of sessions, factors that are not yet routinely personalized but hold significant potential for future optimization of treatment protocols. Ultimately, failing to account for these and other patient-specific factors risks under- or overstimulating large subgroups of stroke survivors, thereby limiting the potential for meaningful functional recovery. To fully harness the brain's capacity for plasticity, stimulation protocols must be tailored to the unique neurobiological and clinical profile of each individual. These considerations underscore the urgent need to move beyond standardized, one-size-fits-all rehabilitation strategies and toward personalized, data-driven approaches capable of optimizing recovery trajectories across a heterogeneous stroke population.

1.1 Recent Trend in research: Prognostic prediction models

A prognosis is a medical estimate of the likely course and outcome of a disease or condition. In the context of stroke, the National Institutes of Health Stroke Scale (NIHSS) is widely used to evaluate the severity of neurological deficits and offers some prognostic value—particularly in predicting 3-month outcomes such as dependency or death, typically measured by the modified Rankin Scale (mRS 3–6), and early case fatality when assessed soon after Emergency Department admission [20]. However, its prognostic utility remains limited, as it primarily reflects initial stroke severity and lacks the granularity needed for truly personalized outcome prediction.

Hence, there has been growing interest in developing models capable of generating more individualized and detailed prognostic predictions. The primary objective of such models is to advance toward more personalized and precise healthcare. In the context of stroke, ongoing research focuses on

collecting detailed patient-specific data and feeding it into statistical or machine learning models to predict recovery trajectories and likely clinical outcomes. These models offer significant value in research settings. They enable more effective patient stratification based on predicted recovery profiles or risk levels, allowing for the design of more targeted clinical trials and more accurate interpretation of results. This, in turn, can improve trial efficiency, reduce costs, and minimize the impact of outcome heterogeneity. Additionally, researchers can use these models to simulate various scenarios, testing hypotheses and exploring how different patient conditions might influence outcomes. Most importantly, these models hold great promise for clinical applications. They are intended to serve as decision-support tools for clinicians—helping to set realistic recovery expectations, personalize therapeutic strategies, and identify the most suitable interventions for each patient.

Over the past decade, numerous prognostic models have been developed to predict post-stroke outcomes at 3, 6, or 12 months, often using diverse input modalities. A common target of these models is the Modified Rankin Scale (mRS), a broad measure of disability and dependence ranging from 0 (no symptoms) to 6 (death). While widely used, the mRS offers limited granularity regarding specific cognitive and motor functions, especially when compared to more specialized assessment tools. Some studies have relied solely on clinical data. For instance, Heo et al. [21] proposed a deep learning model to predict favorable functional outcomes—defined as an mRS ≤ 2 at 90 days—using variables such as patient demographics, initial stroke severity, and stroke subtype. Their model demonstrated strong predictive performance, achieving an area under the curve (AUC) of 0.888

An alternative approach was proposed by Selles et al., who developed a model to predict patient-specific upper limb recovery trajectories by leveraging all serially collected clinical data. The model was trained on recovery profiles from 450 patients who experienced a first-ever ischemic hemispheric stroke, each having undergone at least three assessment sessions between the first week and six months post-stroke. Upper limb function was evaluated using the Action Research Arm Test (ARAT). To handle varying numbers of observations and non-uniform assessment timings, the authors employed mixed-effects models, which enabled them to accurately forecast ARAT recovery trajectories up to six months after stroke onset [22].

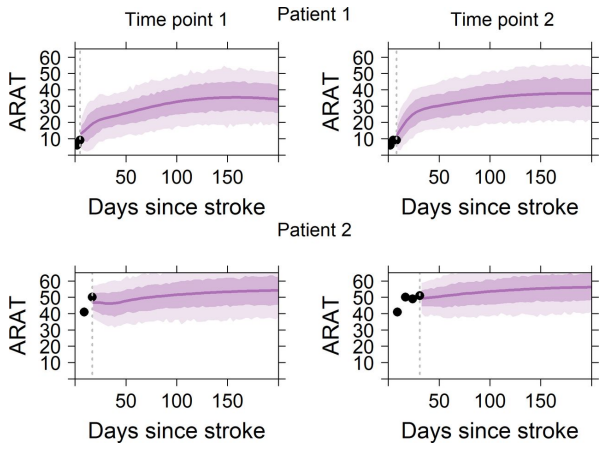


Figure 3: Example of predicted recovery trajectories from [22]

Rehme et al. proposed a more complex approach by using resting-state functional connectivity of the ipsilesional primary motor cortex (M1) as a classifier to assess hand motor impairment [23]. In a cohort of 20 patients, their method achieved a mean classification accuracy of 87.6%, effectively stratifying patients into two functional groups. However, one key limitation of functional imaging approaches lies in their high cost and methodological complexity, which often constrain study sizes and limit broader clinical applicability.

In contrast, Talozzi et al. [24] developed a structurally driven method based on the construction of

a disconnectome morphospace. Using structural MRI (sMRI) rather than diffusion-weighted imaging (DWI), they estimated white matter disconnection patterns by overlaying lesion maps onto a normative diffusion atlas. These disconnection profiles were then embedded into a two-dimensional space using Uniform Manifold Approximation and Projection (UMAP), enabling more intuitive and clinically relevant interpretation. Their model successfully predicted a wide range of 12-month post-stroke outcomes, including motor function, language, visuospatial abilities, verbal memory, and pain—demonstrating the potential of disconnectome-based representations in forecasting multidomain recovery.

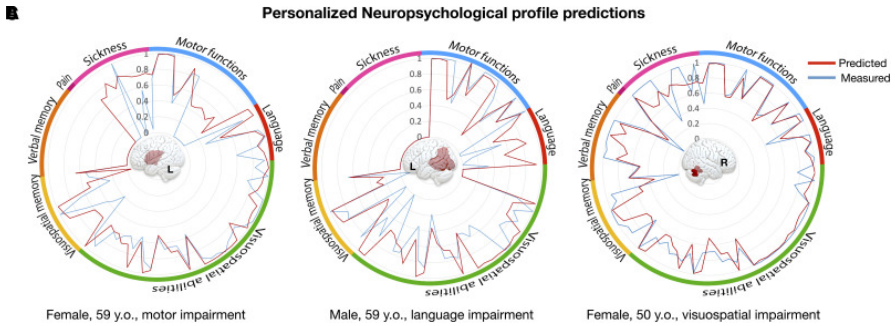


Figure 4: Example of multidomain outcomes from [24]

1.2 Prognostic prediction model Inputs and limitations

Existing prognostic prediction models typically rely on a diverse range of patient data, which can be broadly categorized into three main groups:

- **Biomarkers**: These are quantifiable indicators of a patient's biological state or neural system dynamics. Biomarkers can be derived from electrophysiological and imaging techniques, such as EEG, TMS, fMRI, and MRI, or from biological samples like cerebrospinal fluid. While molecular biomarkers provide insights into cellular damage affecting neurons and glial cells, imaging and electrophysiological biomarkers assess structural brain integrity and functional activity patterns [25].
- **Motor Scores**: These standardized functional assessments evaluate a patient's motor performance and track recovery progress over time. Common tools include the Action Research Arm Test (ARAT) and the Nine-Hole Peg Test, which were notably used in the *TiMeS* project to monitor upper limb function [3].
- **Cognitive Scores**: These tests screen for post-stroke cognitive impairments. For example, the Language Screening Test (LAST) is used to assess a patient's language comprehension and production abilities [26].
- **Complementary Data**: This includes a wide array of categorical and numerical variables that capture patient-specific characteristics or clinical features relevant to stroke recovery. These data are often collected at hospital admission and may include demographic and socioeconomic information, comorbidities, or acute clinical metrics such as blood glucose levels or length of hospitalization [27].

The previously discussed models share several important limitations. With the exception of the Talozzi approach, most produce coarse-grained predictions limited to short-term outcomes—such as whether a patient's modified Rankin Scale (mRS) score exceeds 2 at 90 days post-stroke. While clinically useful, these outputs offer only limited guidance for patients and clinicians seeking a more

detailed understanding of recovery trajectories. Furthermore, these models are typically trained on retrospective stroke datasets originally designed for clinical research, not for predictive modeling. As a result, they often lack key variables—such as fine-grained motor scores or imaging biomarkers—and suffer from restricted generalizability due to exclusion criteria that omit large segments of the stroke population.

This reflects a broader trend in the current landscape of stroke prognostic modeling. Most existing models do not integrate multimodal data streams, instead relying on single data types (e.g., clinical scores, imaging, or demographics) in isolation. Although recent approaches increasingly acknowledge the value of multimodal data integration, significant challenges persist. As highlighted by Shurrab et al. in a recent literature review [28], the main barriers include the scarcity of well-labeled multimodal stroke datasets, heterogeneity in data types and collection protocols, and the computational complexity of training integrated models. The authors also emphasize the need for advanced neural network architectures and multitask learning frameworks capable of jointly predicting multiple recovery outcomes.

To address these limitations, longitudinal and multidomain studies—such as the *TiMeS* initiative—play a critical role. By collecting high-quality, multimodal data over time, they enable the validation of individualized prognostic biomarkers and support the development of models that more accurately reflect the complexity of stroke recovery [3].

Finally, it is worth noting the absence of detailed treatment planning data—such as the specific types of therapies a patient is receiving or the use of neuromodulation techniques. Including this information could provide valuable context and potentially enhance the accuracy of outcome predictions.

2 Proposed solution

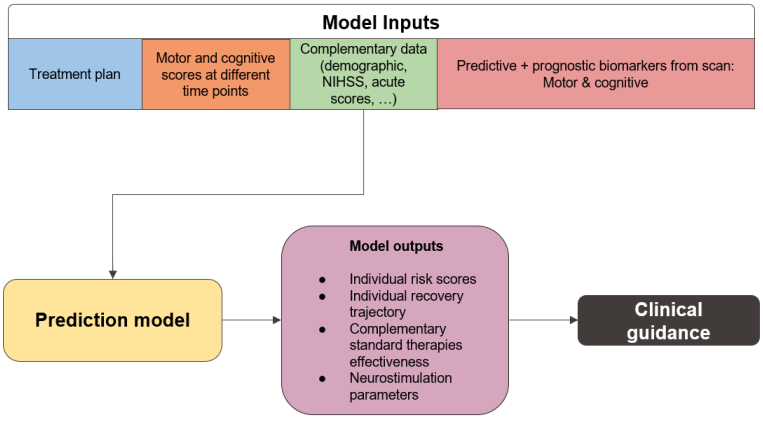


Figure 5: Proposed solution diagrame

To address these limitations, we developed our approach around several key components: the input data, the predictive model, the resulting outputs, and the clinical recommendations derived from them. The goal is to support clinicians in selecting the most appropriate rehabilitation strategy. By integrating these elements, the framework aims to enable personalized rehabilitation plans that account for each patient's distinct neurobiological and clinical profile.

3 Methodology

3.1 Prognostic model inputs

To personalize stroke rehabilitation strategies, we structure our input data into a set of complementary components, each capturing crucial dimensions of patient status and treatment context.

3.1.1 Motor and Cognitive Scores

To evaluate functional impairments, clinical scores offer a standardized and objective way to monitor patient status and track functional progress over time. In the domain of motor function commonly used assessments include the Fugl-Meyer Assessment of the Upper Extremity (UEFM) and the Action Research Arm Test (ARAT). The UEFM evaluates motor functioning, balance, sensation, and joint functioning in patients with post-stroke hemiplegia, while the ARAT focuses on specific tasks that assess grasp, grip, pinch, and gross movement of the upper limb through timed and scored manual activities [8].

For the assessment of cognitive function, several standardized tools are available. The Montreal Cognitive Assessment (MoCA) is commonly used to screen for mild cognitive impairment, evaluating attention, executive functions, memory, language, visuospatial skills, and orientation. The Mini-Mental State Examination (MMSE) is another widely used tool, particularly effective for detecting moderate to severe cognitive deficits. It assesses orientation, short-term memory, attention, calculation, language, and the ability to follow simple commands. Additionally, the Clock Drawing Test is a quick and informative tool used to detect visual neglect and executive dysfunction [8].

By combining these clinical assessments, clinicians can gain a comprehensive understanding of a patient's motor and cognitive function. This multidimensional perspective supports accurate diagnosis, monitors rehabilitation progress, and informs the design of personalized treatment plans. In our work, we selected two standardized and widely recognized clinical assessments:

- *Action Research Arm Test (ARAT)* score for motor function [29].
- *Montreal Cognitive Assessment (MoCA)* for cognitive abilities [3].

Focusing on one validated score per domain reduces assessment time and patient burden while still providing robust, interpretable measures for model input and clinical tracking.

3.1.2 Complementary Clinical and Demographic Data

A broad set of categorical and numerical features is included to capture individual variability relevant to stroke rehabilitation. These include:

- Demographic information (e.g., age, sex, handedness, ethnicity)
- Clinical history (e.g., stroke type, time since onset, comorbidities, NIHSS, lab panel)
- Functional baseline data (e.g., presence of aphasia, apraxia, neglect)

These features enhance model personalization by reflecting stroke-specific characteristics that are often highly predictive of recovery outcomes [30, 31].

3.1.3 Neuroimaging-Based Biomarkers

To enrich prognostic accuracy, we incorporate biomarkers that are known to correlate with both *motor* and *cognitive* recovery outcomes, as well as *response to treatment*. These biomarkers serve as crucial

features in our modeling strategy, guiding both therapeutic decisions and the estimation of patient-specific recovery trajectories.

Predict Motor outcome	Predict Cog. outcome	Predict response to treatment
DWI - CST integrity, full brain connectome **sMRI + DWI -** Full disconnectome **fMRI -** Interhemispheric M1 rsFC **EEG -** BSI-theta, low freq. in ipsilesional hemisphere	**DWI -** Global network efficiency **fMRI -** DMN rsFC, SN rsFC, CEN rsFC **EEG -** Delta to theta ratio, relative theta power, relative delta power, delta to alpha ratio	**DWI -** CST integrity **fMRI -** Interhemispheric M1 rsFC, activation volume **EEG -** theta-alpha ratio **EMG + TMS -** MEPs (network excitability) and short intracortical inhibition

Figure 6: Overview of selected neuroimaging-based biomarkers used for motor and cognitive outcome prediction, as well as treatment response estimation.

As shown in Figure 6, the selected biomarkers span both structural and functional domains, leveraging clinically accessible neuroimaging techniques to characterize patient-specific neurophysiology. From the wide range of options available in the literature, we prioritized those that combine strong predictive value with practical feasibility for routine stroke care.

For **motor recovery prediction**, two structural connectomic features were selected based on their established relevance and accessibility:

- **Corticospinal tract (CST) integrity**, a robust marker of motor function across the stroke continuum. Typically assessed via *diffusion-weighted imaging (DWI)*, CST integrity has also been associated with responsiveness to rTMS-based interventions [32, 33, 34, 35, 36].
- **Full-brain disconnectome**, which captures the lesion's broader disruption of structural connectivity. Derived from *structural MRI (sMRI)* by overlaying lesion masks onto normative diffusion datasets, this biomarker—originally proposed by Talozzi et al. [24]—is particularly valuable due to the widespread availability of sMRI in clinical workflows.

To complement these structural indicators, the **Brain Symmetry Index (BSI)** provides functional insight derived from EEG [37]. By quantifying interhemispheric asymmetry, BSI helps assess contralesional hemisphere involvement and informs individualized rTMS protocol design based on pre-treatment neurophysiological profiles.

For **cognitive outcome prediction**, recent studies have demonstrated that the same disconnectome-based features—particularly measures of global disconnection—are strongly associated with post-stroke cognitive impairments and recovery trajectories [24, 38, 39]. Thus, the full-brain disconnectome serves a dual role in our model, supporting both motor and cognitive prognostic.

In the context of **treatment response**, functional EEG biomarkers have shown promising results, particularly in predicting responsiveness to non-invasive brain stimulation (NIBS) modalities such as rTMS. One such marker is the **theta/alpha ratio (TAR)** in the lesioned hemisphere, where lower baseline values have been linked to greater motor improvement. Furthermore, increases in TAR during rehabilitation correlate with better outcomes, suggesting that TAR may serve as both a predictive and dynamic marker of neuroplasticity [37].

These EEG insights are complemented by TMS-based physiological measures, including **motor evoked potential (MEP) amplitude** and **short intracortical inhibition (SICI)** in the non-lesioned

hemisphere. Both metrics provide additional information on cortical excitability and interhemispheric dynamics relevant to rTMS effectiveness.

By integrating these complementary measures, the model gains a rich, multidimensional view of each patient's neurological profile, enabling both predictive and prognostic insights, and facilitating the development of targeted, personalized rehabilitation strategies.

3.1.4 Treatment Plan

The treatment plan targets patients receiving rTMS in combination with conventional rehabilitation therapies. These conventional interventions—typically including physiotherapy, occupational therapy, and task-specific motor training—are collectively encoded as a categorical variable in the dataset, with associated parameters such as session duration and number of repetitions represented as continuous features. In parallel, the rTMS component is represented through continuous and categorical features that capture key stimulation parameters such as frequency, intensity, target site, and session duration, in alignment with the configuration space outlined in the introduction.

We selected rTMS over tDCS based on its demonstrated superiority in promoting motor recovery. This choice is supported by recent meta-analyses indicating stronger and more sustained effects associated with rTMS protocols. Notably, a network meta-analysis by Ni et al. [40] identified bilateral rTMS as the most effective intervention for improving upper limb function and daily living activities in early stroke patients. Similarly, Ahmed et al. [41] found that high-frequency rTMS was more effective than tDCS in improving upper limb motor function in patients with acute stroke.

3.2 Model outputs

The objective of this prognostic prediction model is to generate a comprehensive and individualized stroke profile to assist clinical decision-making. The output is structured into four main categories, each dynamically updated as new patient data becomes available over time, as described in Section 4.2.

- **Individual Recovery Trajectories**: Drawing on the methodologies of Selles et al. [22] and Talozzi et al. [24], the model predicts the evolution of each patient's recovery over a 12-month period. Forecasts include confidence intervals for key functional domains: general sickness, pain, verbal memory, visuospatial memory, language, and motor function.
- **Risk & Expected Outcome Assessment**: The model provides an interpretable summary of clinical risk, including predictions for functional status, mortality, likelihood of stroke recurrence, and expected motor and cognitive scores. It also includes an evaluation of the patient's suitability for rTMS-based intervention.
- **Complementary Therapy Recommendation**: Based on the patient profile, the model suggests the most beneficial standard rehabilitation therapies—such as Constraint-Induced Movement Therapy (CIMT) or cognitive training programs—along with recommended session frequency.
- **Optimized Neuromodulation Protocol**: The system proposes a personalized rTMS setup, specifying key parameters such as stimulation target, intensity, frequency, duration, number of sessions, and coil type, as illustrated in Figure 2.

3.3 Model Architecture

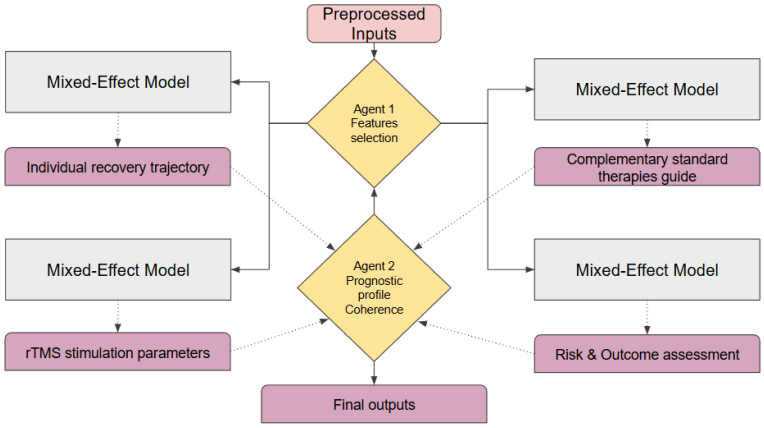


Figure 7: Proposed model architecture

3.4 Model Architecture and Learning Strategy

After collecting the required dataset, appropriate pre-processing steps tailored to each data modality will be applied. For example, EEG data may undergo band-pass filtering and principal component analysis (PCA) for artifact exclusion, while fMRI data will require slice-timing and motion correction. Once pre-processed, the high-dimensional input data will be fed into a **hierarchical deep learning architecture**, designed to handle prediction across multiple output domains.

This architecture consists of **four specialized models**, each dedicated to predicting a specific output category (e.g., recovery trajectory, risk assessment, stimulation parameters, and therapy guidance). To enhance learning efficiency, reduce training costs, and limit overfitting or bias, we propose the integration of **two reinforcement learning (RL) agents** into the system. RL algorithms have shown promise in healthcare applications due to their ability to dynamically adapt to patient-specific variability, distributional shifts, and non-stationary inputs over time [42].

- The **first agent** manages feature allocation across the four specialized models, optimizing which features are sent to which model based on relevance.
- The **second agent** acts as a consistency evaluator. It monitors the coherence of the combined outputs and provides feedback to the first agent. For instance, if one model predicts a promising recovery trajectory while another estimates high mortality risk, the second agent flags this inconsistency and guides feature reassignment to correct the incoherence.

Once the feature sets are finalized by the first agent, each subset of data is processed by one of four models based on **mixed-effect modeling**, a method well-suited for longitudinal and hierarchical clinical data.

Each model integrates both fixed and random effects. **Fixed effects** represent consistent, population-level factors such as age, sex, or stroke type, which are assumed to remain constant throughout the study and exert a uniform influence on the outcome [43]. In contrast, **random effects** capture individual-level variability and unmeasured heterogeneity, accounting for factors such as fluctuations in neuroimaging signals or differences in therapy responses over time.

The choice of mixed-effect models is motivated by the longitudinal structure of the dataset and is supported by evidence from prior studies such as Selles et al. [22], which demonstrated their utility in modeling stroke recovery trajectories.

This hierarchical, task-specific architecture addresses a common issue in machine learning—namely, performance degradation when a single model is tasked with predicting multiple, uncorrelated outcomes. Dividing the learning tasks across models improves interpretability and reduces computational overhead.

Furthermore, the second RL agent ensures consistency across model outputs and enables **direct human oversight**, enhancing transparency and ensuring alignment with clinical reasoning and ethical standards. Its feedback loop allows for continuous improvement and guards against the generation of medically implausible or contradictory recommendations.

4 Implementation

4.1 Data Gathering

Phase 1 of the project focuses on the collection of a high-quality longitudinal dataset, which will form the backbone of the modeling pipeline. Approximately 100 stroke patients will be recruited from multiple international clinical centers, ensuring diversity in stroke presentation, rehabilitation protocols, and healthcare systems. This sample size was chosen to align with previous studies in stroke recovery and personalized neurorehabilitation, such as the TiMeS project [3], which demonstrated that cohorts of this size can support the development of predictive models while remaining feasible for longitudinal follow-up.

Each patient will be monitored over a 12-month period following stroke, with repeated assessments designed to capture the evolving clinical and neurophysiological profile. Data collection will be densest in the early post-stroke phase—when neuroplastic mechanisms are most dynamic—and spaced out as recovery stabilizes. Specifically, motor and cognitive assessments (e.g., UEFM, MoCA), along with imaging-derived biomarkers (e.g., CST integrity, disconnectome maps), will be acquired during the first week, third week, and subsequently at 3, 6, 9, and 12 months post-stroke, following a longitudinal structure inspired by the TiMeS study [3].

In parallel, as detailed in Section 2, comprehensive treatment data will be recorded, encompassing parameters from standard rehabilitation (e.g., type, intensity, and duration of physiotherapy and occupational therapy) as well as rTMS interventions (e.g., frequency, stimulation site, intensity, and protocol type). For ethical reasons, all enrolled patients will receive active treatment in accordance with best clinical practices, rather than being assigned to a control or placebo group. Moreover, although rTMS is not yet universally included in routine rehabilitation protocols, all patients in this study will receive rTMS in addition to standard therapy. This decision is based on the clinical advantages outlined in the introduction, where rTMS is shown to yield stronger and more sustained motor improvements compared to other non-invasive brain stimulation approaches. Any modifications introduced by clinicians, whether due to patient response, tolerance, or logistical factors, will be tracked throughout the rehabilitation process to ensure a faithful representation of real-world treatment dynamics.

Coordinating longitudinal data acquisition across 100 patients and multiple clinical centers presents substantial logistical challenges—particularly with respect to maintaining standardization, ensuring patient adherence over time, and limiting data loss. These anticipated constraints, along with proposed mitigation strategies, will be thoroughly examined in the feasibility assessment (see Section 5).

Despite these challenges, the resulting multi-dimensional, time-resolved dataset will provide a robust foundation for model development. By capturing individualized recovery trajectories, personalized rTMS stimulation parameters, and detailed records of conventional therapy interventions, it will enable the training of predictive models tailored to real-world clinical heterogeneity.

4.2 Model Application

Following model development and training, Phase 2 transitions into clinical application and real-world testing. The proposed workflow is designed to integrate seamlessly into clinical routines.

Upon admission, a stroke patient undergoes a comprehensive baseline assessment including demographic information, medical history, structural and functional imaging, and standardized motor and cognitive evaluations. As discussed, these data serve as input features for the trained model.

The model then produces a set of personalized outputs, as described in Section 3.2, including predicted recovery trajectories, individualized rTMS stimulation parameters, tailored guidance for complementary standard therapies, and a risk & expected outcome assessment of potential adverse outcomes. This personalized plan replaces the standard protocol typically applied to all patients regardless of individual differences.

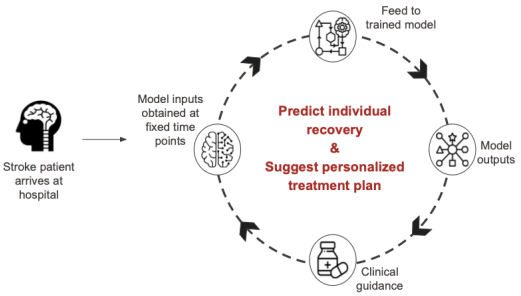


Figure 8: From hospital arrival to recovery: data-driven personalization of post-stroke rehabilitation.

The model remains dynamic throughout the course of rehabilitation. At each follow-up visit, updated patient data, such as new scores, imaging results, or protocol changes, are fed back into the system. This continual updating allows the model to refine its predictions and adjust the proposed therapeutic strategy accordingly, adapting to the patient's actual recovery progression.

This iterative process constitutes the real-world evaluation phase of the model, where its clinical utility, accuracy, and adaptability can be continuously assessed. The loop also allows for ongoing learning and model refinement as more patient data become available, progressively increasing predictive robustness and clinical trustworthiness.

4.3 Personalized rTMS Intervention

As stated in the introduction, among non-invasive brain stimulation techniques, repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising tool to facilitate neuroplasticity and promote upper-limb functional recovery following stroke. rTMS works by delivering repeated magnetic pulses to the cortex, thereby modulating neuronal excitability in a frequency-dependent manner: high-frequency stimulation (> 5 Hz) has excitatory effects, while low-frequency stimulation (≤ 1 Hz) is generally inhibitory [13]. This ability to bidirectionally influence cortical activity is particularly relevant in the context of interhemispheric imbalance, a common phenomenon post-stroke where the contralesional hemisphere becomes hyperactive and exerts excessive inhibitory control over the lesioned motor cortex, thereby impeding motor relearning and functional recovery [44].

To counteract this maladaptive interaction, rTMS can be tailored to the patient's individual neurophysiological status. For instance, patients with preserved corticospinal tract (CST) integrity often benefit from excitatory stimulation of the ipsilesional primary motor cortex (M1), reinforcing residual motor pathways. In contrast, those with severe CST disruption may respond better to inhibitory stimulation of the contralesional M1, helping to reduce pathological interhemispheric inhibition [45]. However, this generalized model does not apply uniformly across all patients: suppressing the contralesional motor cortex, for example, may be beneficial in subcortical strokes but can inadvertently suppress residual motor areas in cortical lesions [17]. Similarly, individuals with weak transcallosal connectivity may not respond to interhemispheric suppression strategies at all [18].

Further personalization must also account for physiological variability: motor thresholds can differ by as much as two-fold across patients, necessitating careful calibration of stimulation intensity to ensure safety and efficacy [19]. Timing is also a key factor; inhibitory rTMS appears to be more

effective during the early post-stroke phase (within 6 months), whereas excitatory stimulation of the ipsilesional cortex may produce better outcomes in the chronic stage of recovery [18].

To address these complexities, our model integrates multimodal data—as presented in Section 3.1.3—to recommend not only whether excitatory or inhibitory rTMS is most appropriate, but also to identify the optimal stimulation site (e.g., ipsilesional M1, contralesional M1, or lesioned premotor cortex such as PMv), and to adapt critical parameters such as frequency, intensity, duration, and number of sessions.

Moreover, the benefits of rTMS are significantly enhanced when combined with motor training interventions—such as constraint-induced movement therapy (CIMT), robot-assisted therapy, or task-oriented occupational therapy. The synergy between neuromodulation and behavioral rehabilitation is essential to drive durable plastic changes and translate stimulation effects into meaningful functional improvements.

5 Discussion & Conclusion

The estimated cost per patient for the complete set of imaging and neurophysiological assessments—including MEG, fMRI, TMS, and EEG—is approximately 1500. For a 100-patient research cohort, as proposed in this study, imaging costs alone could approach $1.2million$, highlighting the considerable financial investment required.

Beyond financial concerns, the project must also address ethical and accessibility challenges. Patients enrolled in the initial data collection phase would not directly benefit from the model's recommendations, as the system would still be under development. Moreover, the reliance on costly or less accessible imaging techniques may limit the model's clinical applicability and increase treatment costs. There is also a risk that clinicians may over-rely on model outputs, particularly if the system operates as a "black box" with limited transparency.

From a regulatory standpoint, the model would likely be classified as a *high-risk AI system* under the EU Artificial Intelligence Act (effective August 1, 2024) due to its medical decision-support role. This designation imposes strict obligations, including rigorous risk assessments, use of high-quality and bias-mitigated datasets, logging for traceability, comprehensive documentation, human oversight, and strong standards for accuracy and cybersecurity [46]. Given its biomedical application, certification by a Notified Body would likely be required, making a fully integrated quality management system essential during development.

The model also faces technical and logistical hurdles. Ensuring demographic diversity is crucial to avoid prediction bias and ensure fairness. Yet, collecting a rich longitudinal dataset with multiple imaging modalities per patient over a year presents major operational challenges. Therefore, the system should be designed to remain robust even when trained on smaller or incomplete datasets.

Although rTMS is generally safe, rare cases of seizure have been reported in post-stroke patients [47]. Consequently, rTMS is still largely restricted to research settings, which may limit the model's near-term clinical deployment.

In summary, our approach integrates multimodal neurophysiological biomarkers, individual impairment profiles, and evidence-based stimulation paradigms to generate personalized rTMS protocols. This strategy directly addresses inter-patient variability and lays the groundwork for an adaptive, precision-guided rehabilitation model tailored to each stroke survivor.

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