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# Longitudinal evaluation of the mechanisms supporting post-stroke motor recovery using TMS-EEG coupling

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par

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## Abstract (EN) :

Stroke is the main source of long-lasting disability, affecting dominantly motor functions. The extent and course of recovery are highly heterogeneous between patients, with a minority of patients fully recovering from their initial impairments, leaving 85% persisting deficits. The pathophysiological mechanisms underlying inter-patients heterogeneity are still not fully understood. Most motor recovery is taking place during the first months after a stroke, with limited improvement after that time, emphasizing the importance of this early period. These first months after a stroke are characterized by dynamic modulations of excitatory and inhibitory processes in the brain. Most notably, modulation of intracortical inhibition is thought to promote both neuronal protection from further damage in the hyperacute phase and functional reorganization to compensate for the lesioned brain regions in the following phases. Previous research in animal models and stroke patients has highlighted specifically the importance of the GABAergic system, the main actor of inhibition in the brain. However, the specific functional role and the time course of changes of GABAergic inhibition in the course of recovery are only partially understood. To better characterize the spatial and temporal properties of the inhibiting mechanisms occurring after a stroke and their association with motor recovery, we investigated the neurophysiological changes of 66 stroke patients longitudinally from the first week to 3 months post stroke. Cortical excitability and inhibition were determined by transcranial magnetic stimulation (TMS) coupled with electroencephalography (EEG).

The present results revealed two disinhibition phases with distinct regionality and timing patterns. In Study I, a local ipsilesional disinhibition, expressed by larger evoked activity, in the acute phase was related with better motor recovery at 3 months post stroke. Patients recovering the most showed a return to normal excitatory/inhibitory balance between the acute and early chronic stage. In Study II, global excitatory and inhibitory activity were evaluated through a data-driven analysis of TMS-induced brain oscillatory modes. The late alpha-oscillations, a proxy of GABAergic activity, displayed a small increase in the acute stage followed by a large decrease between the subacute and early chronic stage. This global disinhibition was correlated with greater recovery of fine upper-limb motor function.

This thesis underlines the importance of GABAergic disinhibition, both locally and globally, for motor recovery after a stroke and determined its specific time courses. The acquired knowledge will provide the basis to pave the way to electrophysiological biomarkers for individual phenotyping of patients. Personalized interventional strategies targeting changes in cortical excitability have to potential to maximize functional recovery in each individual patient.

## Résumé (FR) :

L'accident vasculaire cérébral (AVC) est la principale source de handicap de longue durée, affectant principalement les fonctions motrices. L'étendue de la récupération ainsi que son évolution dans le temps sont très hétérogènes d'un patient à l'autre. Tandis qu'une minorité de patients récupèrent entièrement de leurs déficits initiaux, 85% gardent un handicap moteur. Les mécanismes pathophysiologiques qui sous-tendent l'hétérogénéité entre patients ne sont pas encore pleinement connus. La majeure partie de la récupération motrice a lieu au cours des premiers mois suivant l'AVC, avec des gains limités une fois cette période passée, ce qui souligne l'importance de cette première phase post-AVC. Ces premiers mois après un AVC sont caractérisés par des modulations dynamiques des processus excitateurs et inhibiteurs dans le cerveau. Plus précisément, la modulation de l'inhibition intra-corticale favorise à la fois la protection neuronale contre de nouvelles pertes cellulaires dans la phase hyperaigüe et la réorganisation fonctionnelle pour compenser les régions cérébrales lésées dans les phases suivantes. Des recherches antérieures menées sur des modèles animaux et chez des patients victimes d'un AVC ont mis en évidence l'importance du système GABAergique, principal acteur de l'inhibition dans le cerveau. Cependant, le rôle fonctionnel spécifique et l'évolution temporelle de médiateur de l'inhibition au cours de la récupération ne sont que partiellement connues.

Afin de mieux caractériser les propriétés spatiales et temporelles des mécanismes d'inhibition survenant après un AVC et leur association avec la récupération motrice, nous avons étudié les changements neurophysiologiques de 66 patients de manière longitudinale, de la première semaine à 3 mois après l'AVC. L'excitabilité et l'inhibition corticale ont été déterminées par stimulation magnétique transcrânienne (SMT) couplée à l'électroencéphalographie (EEG).

Les résultats de ces travaux ont révélé deux phases de désinhibition avec une régionalité et une évolution temporelle distincts. Dans l'étude I, une désinhibition locale ipsilésionnelle, exprimée par une plus grande activité évoquée par la stimulation, dans la phase aiguë était liée à une meilleure récupération motrice 3 mois après l'AVC. Les patients ayant le mieux récupéré présentaient un retour à un équilibre excitation/inhibition normal entre la phase aiguë et le début de la phase chronique. Dans l'étude II, les mécanismes globaux excitateurs et inhibiteurs ont été évalués par une analyse des modes oscillatoires cérébraux induits par SMT. Les oscillations alpha, un indicateur de l'activité GABAergique, ont montré une légère augmentation dans la phase aiguë suivie d'une forte diminution entre la phase subaiguë et la phase chronique précoce. Cette désinhibition globale était corrélée à une meilleure récupération de la fonction motrice fine des membres supérieurs.

Cette thèse souligne l'importance de la désinhibition GABAergique, à la fois locale et globale, pour la récupération motrice après un AVC et a déterminé son évolution

temporelle spécifique. Les connaissances acquises serviront de socle pour ouvrir la voie à l’élaboration de biomarqueurs électrophysiologiques servant au phénotypage individuel des patients. La mise en place de stratégies d'intervention personnalisées, ciblant les changements de l'excitabilité corticale, pourraient ainsi permettre de maximiser le niveau de récupération fonctionnelle chez chaque patient.

**Keywords**
Stroke, motor recovery, TMS, EEG, SICI, PARAFAC, disinhibition, GABA, evoked-activity, induced-activity

**Mots-clés**
Accident vasculaire cérébral (AVC), récupération motrice, stimulation magnétique transcrânienne (SMT), EEG, SICI, PARAFAC, désinhibition, GABA, activité évoquée, activité induite

# Table of contents

# List of figures



# List of tables

# 1. GENERAL INTRODUCTION

## 1.1 Stroke

This chapter will provide an introduction in the field of stroke recovery. It will present the long-term impact of stroke on the patient's quality of life and on society. The pathophysiology of stroke will be broached, with an emphasis on the excitation/inhibition (E/I) balance time course at each stage. Finally, we will discuss the natural recovery and the current strategies to enhance restauration of motor function.

### 1.1.1 The burden of stroke on human societies

With more than 15 million strokes worldwide and 20,000 in Switzerland per year, stroke is the 2nd source of death worldwide and the first source of long-lasting impairments (WHO 2017; Swiss Federal Statistical Office 2020). Furthermore, with the ageing population, the absolute number of stroke is rising, with a 70% increase worldwide from 1990 to 2019 (Feigin et al. 2021) and the current projection indicates that between 2015 and 2035, there will be a 34% increase in total number of stroke events in the EU, from 613,148 to 819,771 (Stevens et al. 2017). The behavioural deficits caused by a stroke are various and can persist for life (Ramsey et al. 2017). Motor deficits are one of the most frequent impairments after stroke, have a significant impact on daily life and are a hindrance to the return to a working life. Deficits of the upper extremity, especially hand function, are the main responsible and key impediment on the way back to a normal life. Even though a lot has been done to improve the prognosis in the acute phase (e.g., development of stroke units, thrombolysis or recanalization) and later on with rehabilitation therapies, complete motor recovery from stroke only occurs in approximately 15% of the patients. It results in many patients unable to return to work, needing extensive therapies and medical monitoring. Apart from the major impact on the patient's independence and quality of life, stroke leads to a significant burden to the patient's surroundings and to the society itself, with a total cost of 51 billion CHF attributed to stroke in Europe (Stevens et al. 2017)

To improve treatment strategies, enhance stroke recovery and reduce the negative impact of stroke on each patient and the society, there is a strong need to improve current clinical strategies, develop novel and innovative ideas and especially personalize the treatments to the needs of each individual patient. To do so, better knowledge of the mechanisms occurring after stroke and of the processes sustaining recovery is needed.

### 1.1.2 Types of strokes and current hyperacute treatments

A stroke occurs when part of the brain cannot be supplied with blood, leading to brain cell death. There are two main types of stroke: ischemic (87% of cases) and haemorrhagic (13%) (Virani et al. 2021). Their diagnosis is based on evidence of permanent brain injury through Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans.
Clinically, an ischemic stroke causes an episode of neurological dysfunctions, such as paresis of the arm and/or leg or the inability to comprehend or produce speech. Also called a central nervous system (CNS) infarction, it is usually caused by a clot or a plaque causing respectively an embolic or thrombotic blockage, which deprives the supplied areas of oxygen (**Figure 1.1A**) (Sacco et al. 2013). The stroke lesion consists of the infarct core, composed of irreversibly damaged tissue, and the brain tissue surrounding the central necrotic core, called the penumbra. The latter corresponds to tissues with limited cerebral blood flow that can still survive if perfused on time. Restoration of blood flow is made possible by dissolving the blood clot (thrombolysis) or mechanically removing the thrombus (thrombectomy). If the blood flow is restored within a few hours, the cells within the penumbra might survive, whereas the longer we wait, the more likely the cells will die, resulting in a worse clinical outcome (Sacco et al. 2013).

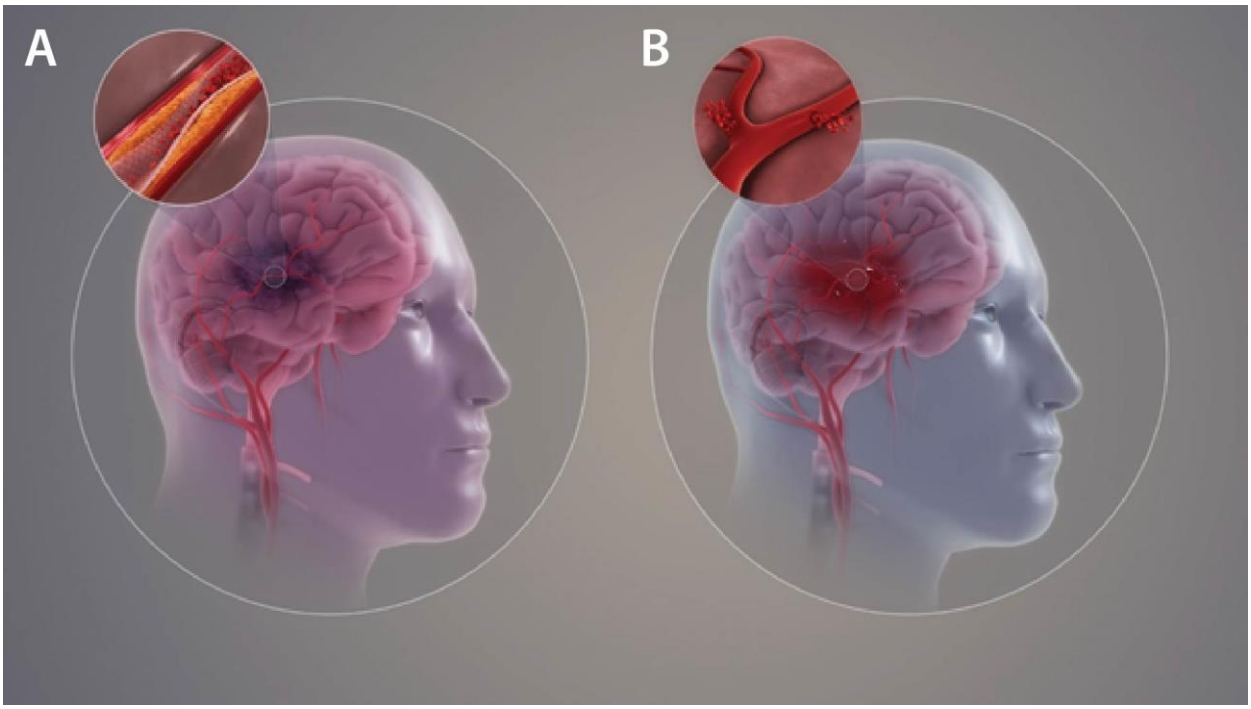


**Figure 1.1 Types of strokes. Left**: Ischemic stroke, where a blood clot or a plaque is obstructing an artery in the brain causing the downstream areas to be deprived of oxygen. **Right**: Hemorrhagic stroke, where a blood vessel ruptures and causes a focal collection of blood within the brain tissue or ventricular system. Image under Creative Commons, taken from https://www.scientificanimations.com/wiki-images/, consulted on 22.10.2022.

In the case of a haemorrhagic stroke, clinical signs include neurological dysfunction and/or headache due to the accumulation of blood in the extravascular space and increased pressure to the adjacent tissues (Sacco et al. 2013). A haemorrhagic stroke is caused by the rupture of a weakened vessel that is not caused by trauma (**Figure 1.1B**). Morbidity and mortality are higher in haemorrhagic than ischemic stroke patients, emphasizing the need of prompt diagnosis and treatment to reduce the intracranial pressure (Chen et al., 2014). Possible treatments include blood pressure control, osmotherapy, and surgical interventions.

With a count of 1.9 million neurons dying each minute until treatment, it is apparent that "time is brain", meaning that patients should be taken care of as soon as possible, with each minute counting (Saver 2006). Despite the proven potency of the developed treatment, only a small proportion of stroke cases are eligible for thrombectomy and thrombolysis, leading to a greater pressure on the following rehabilitation therapies to minimize the long-lasting impact of strokes.

Overall, an ischemic and a haemorrhagic stroke require opposite treatment, with the former needing the restoration of blood flow and the latter the halting of further bleeding. Early diagnosis of the type of stroke is thus crucial for adequate treatment. However, both types of stroke lead to functional impairments, such as motor or cognitive deficits which will be further elaborated in the next section.

### 1.1.3 Stroke related deficits

Although progress has been made in risk factor awareness and acute patient management, stroke remains one of the main causes of lasting impairment (Katan & Luft, 2018).

Stroke related deficits can be very diverse, with motor deficits being the most common (80-85% of stroke related impairments) followed by somatosensory (40-50%), attention (25-30%), language (20-25%), memory (15-25%) and visual deficits (15-20%) (Appelros et al. 2002; Buxbaum et al. 2004; Lawrence et al. 2001; Nys et al. 2007; Ramsey et al. 2017; Rathore et al. 2002). However, deficits are often not restricted to one domain and combinations can slow down recovery, leading to impairments that can last for long after discharge. Impairments resulting from a stroke are thus numerous. Indeed, only 15% of patients with paralysis fully recover from their initial deficits (Hendricks et al. 2002). Thus, motor deficits, especially in the upper body, might then hinder the patient's independence in every-day task and greatly reduce his/her quality of life.

Despite having different pathophysiology, ischemic and haemorrhagic strokes might lead to similar functional and clinical status at discharge, possibly reflecting common physiological process occurring after both types of infarct (Salvadori et al. 2020; Perna et Temple 2015; Stinear et al. 2020).

### 1.1.4 Pathophysiology

Different physiological mechanisms are taking place after a stroke, as direct consequences of the infarct and to later permit both neuronal protection and plasticity. These events occur with a specific chronology and involve excitatory and inhibitory phenomena. However, whether theses mechanisms support recovery or if they correspond to maladaptive processes resulting from the infarct is still largely unknown. To understand what is responsible for motor deficits and what supports recovery, it is thus critical to look at the temporal dynamics of stroke-induced processes.

#### 1.1.4.1 Post stroke stages

Despite advances in the understanding of the mechanisms occurring after a stroke, the exact cascade of cellular and molecular events that sustains recovery is still not known (Stinear et al. 2020). It appears that the ischaemic cascade is a complex process involving multiple interconnected pathways and cell types with sequential and parallel dynamics (Fisher et Savitz 2022; Xing et al. 2012). Time after stroke can be divided in four distinct phases: the hyperacute (0-24 hours post stroke), acute (1$^{st}$ week), subacute (1$^{st}$ week to 3$^{rd}$ month) and chronic (>3$^{rd}$ months) stages.

##### Hyperacute

In the first minutes after the stroke, the reduction of blood flow causes a diminution of the Adenosine Triphosphate (ATP) generation which creates a breakdown of the ionic gradient (Arai et al. 2011). Glutamate reuptake processes are impaired and its accumulation stimulates N-Methyl-D-aspartic acid (NMDA) receptors and induces calcium influx through ionotropic receptors. Death-signalling proteins are then activated by these receptors to trigger a cascade of signals leading to progressive neuronal cell death (Lai, Zhang, et Wang 2014; Joy et Carmichael 2021). It is worth noting that even though different cells – including astrocytes, microglia and pericytes – are affected by the ischemic event, neurons are likely to be the most vulnerable and their death is probably the most important contributor to clinical deficits in stroke (Fisher et Savitz 2022; Savitz et al. 2019). To counter the excitotoxic effect of this excessive release of glutamate, neurons in the peri-infarct cortex exhibit an hyperpolarisation mediated by an increased in Gamma-Aminobutyric Acid (GABA) current (Carmichael 2012). As nearby astrocytes show a reduced GABA uptake, GABA accumulates in the extracellular space and stimulates GABA-receptors (GABAR), which increases the tonic GABA current and lowers the neuronal excitability.

### Acute

While this early cytoprotective mechanism of tonic inhibition seems to be beneficial for recovery in the first hours to days following a stroke, animal studies have demonstrated that relieving this tonic inhibition 3 days after stroke promotes behavioural recovery (Clarkson et al. 2010), leaving one to think that a shift in the acute stage towards elevated excitation is beneficial for recovery. In that sense, electrophysiological recordings in both patients (P. Manganotti et al. 2002) and rats (Schiene et al. 1996) have demonstrated either an increase in excitation or a decrease of inhibition in, respectively, the ipsilesional hemisphere and perilesional area a few days after stroke. This increase of excitation, or disinhibition, might create an environment favourable to the reopening of a plasticity period similar to that seen during critical development (Moskowitz, Lo, et Iadecola 2010; Hill et al. 2012; Gherardini, Gennaro, et Pizzorusso 2015). This sensitive period is also promoted by cholinergic signalling (Yaeger, Ringach, et Trachtenberg 2019; Conner, Chiba, et Tuszynski 2005). Increased neuronal activity is thought to be at the origin of neurogenesis, as well as of an increase in growth factors such as brain-derived neurotropic factor (BDNF) (Felling et Song 2015). Furthermore, decreased inhibition has also been linked in rodents to expanded receptive fields (Alia et al. 2016a; Winship et Murphy 2008), increased LTP (Hagemann et al. 1998) and sensorimotor functions remapping in the ipsi- and contralesional hemispheres (Que et al. 1999; Takatsuru et al. 2009). All these processes are thought to support post-stroke recovery. Hence, it is believed that a change in balance between GABA- and glutamatergic signalling in the first weeks post stroke could be a pivotal event at the origin of neural plasticity (Liuzzi et al. 2014; Ward 2017).

### Subacute

The subacute phase, which lasts in the rodent for approximately 1 month and in humans for up to 3 months after stroke, is marked by reduced inflammatory responses and maximal plasticity (Bernhardt et al. 2017; Corbett et al. 2017). This phase exhibits enhanced dendritic spine turnover in mice (Brown et al. 2007; Brown, Wong, et Murphy 2008; Brown et al. 2009; Mostany et al. 2010), providing a substrate for the synaptic termination of new connections. However, the window of plasticity diminishes as the stroke progresses from the subacute phase to the chronic phase, in which there is a limited potential to induce recovery. In this sensitive period after stroke, cortical recovery start to be inhibited by an increased GABAergic tone through extrasynaptic GABA signalling (Clarkson et al. 2010; Lake et al. 2015; Hiu et al. 2016) and increase in neurite growth inhibiting factors (e.g., NOGO-A). NOGO-A limits brain plasticity after stroke and blocking NOGO-A signalling enhances functional plasticity and stroke recovery (Sozmen et al. 2016; Papadopoulos et al. 2002; Markus et al. 2005; Lindau et al. 2014). While one could thus think that the return of the balance toward less excitation is invariably hindering

recovery, Clarkson et al. also showed that, conversely, increasing cortical excitability too much or reducing phasic inhibition negatively impact functional recovery (Clarkson et al. 2010).

#### Chronic

The chronic phase of stroke begins 3 months after stroke onset in humans and is characterized by an absence of spontaneous recovery (Bernhardt et al. 2017; Corbett et al. 2017). Recovery is still possible at this stage but requires intensive neurorehabilitation therapy and substantial focus by the patient (Ward, Brander, et Kelly 2019). Even with these practices, the amount of recovery in the chronic phase, as measured through scales of neurological impairment, appears to be roughly 10% of the recovery seen in the subacute phase (Lo et al. 2010; P W Duncan et al. 1992; Pamela W Duncan, Min Lai, et Keighley 2000; Wolf et al. 2010).

Of note, these phases seem to be induced after each stroke, as it is illustrated in an experiment by (Zeiler et al. 2016) in mice, through the induction of a second stroke, in the same hemisphere 7 days after the first. Combined with training starting the following day, the mice were able to fully recover from both events while not having completely recover from the first event before. This shows that there might be a short period of time in which function can be regained when training is combined with a favourable biological environment, which is engendered by a stroke.

In summary, there is a changing balance between excitation and inhibition throughout the post-stroke phases. In the very first phase, an overinhibition aims at reducing the initial excitotoxicity. In a second phase, a disinhibition opens a restricted time window of neuroplasticity called “window of opportunity” (Biernaskie 2004; Zeiler et al. 2016) or “sensitive period” (Dromerick et al. 2015; Kraft et al. 2018). This phase shares similarities with the concept of heightened plasticity during development. It corresponds to a time associated with robust spontaneous plasticity, during which the greatest functional gains are possible when associated with training (Biernaskie 2004; Zeiler et al. 2016). Finally, the balance returns to an equilibrium, similar to what can be found in healthy subjects (Kim et al. 2014).While this stroke-related plasticity is responsible for spontaneous recovery, not all patients show the same evolution.

### 1.1.4.2 Post-stroke recovery and rehabilitation

#### Natural recovery

A majority of the patients exhibit spontaneous recovery to some extent, defined as the improvement in body function and activity exclusively driven by time (Kwakkel et al. 2003; Cassidy et Cramer 2017). It has been suggested that this natural recovery corresponds to around 70% of the patient’s initial impairment. In other words, following a stroke, one is expected to recover around 70% of the difference between his/her initial motor

assessment score (usually the Fugl-Meyer of the upper extremity, FM-UE) and the maximum score on this assessment. Hence, severely affected patients are expected to show a larger absolute recovery than mildly impaired ones. While first demonstrated for the upper limb, the same has shown to be true for other domains such as the lower limb (Smith et al. 2017; Veerbeek et al. 2018), visual spatial neglect (Marchi et al. 2017; Winters et al. 2017), aphasia (Lazar et al. 2010; Marchi et al. 2017) and other cognitive domains (Ramsey et al. 2017)

However, criticism has been voiced regarding this model of recovery. The main limitation arises from heavily inflated effect sizes (Bonkhoff et al. 2020) due to ceiling effects, mathematical coupling between the initial impairment and recovery and the assumption that outcomes are largely independent of training (Hawe, Scott, et Dukelow 2019; Hope et al. 2019; Goldsmith et al. 2022). Nonetheless, if appropriate statistical methods are applied, this model can still be seen as good model, given it performed better than several other models used for recovery prediction (Goldsmith et al. 2022). This model has also shown that around a third of the severely affected patients do not recover to the extent that was predicted (**Figure 1.2A**). This finding was proved not to be artifactual and was then consolidated by other models and empirical studies (Bonkhoff et Grefkes 2022; van der Vliet et al. 2020; Koch et al. 2021; Goldsmith et al. 2022). The incomplete understanding of the limited recovery for 'non-fitters' has puzzled the field in the last couple of years and underlines the heterogeneity and unpredictability associated to stroke recovery (Stinear 2017; Ward 2017). Indeed, despite the observed 70% recovery of most of patients, motor recovery can greatly vary between individuals, with very different improvements for similar initial deficits (**Figure 1.2B**). Therefore, the understanding and prediction of post-stroke recovery and outcome, in particular the non-recovery of a sub-group of patients, remain a challenge and should be further addressed in the future, ideally to predict outcomes and target specific physiological mechanisms for individual patients in order to allow for a better personalization of treatments.

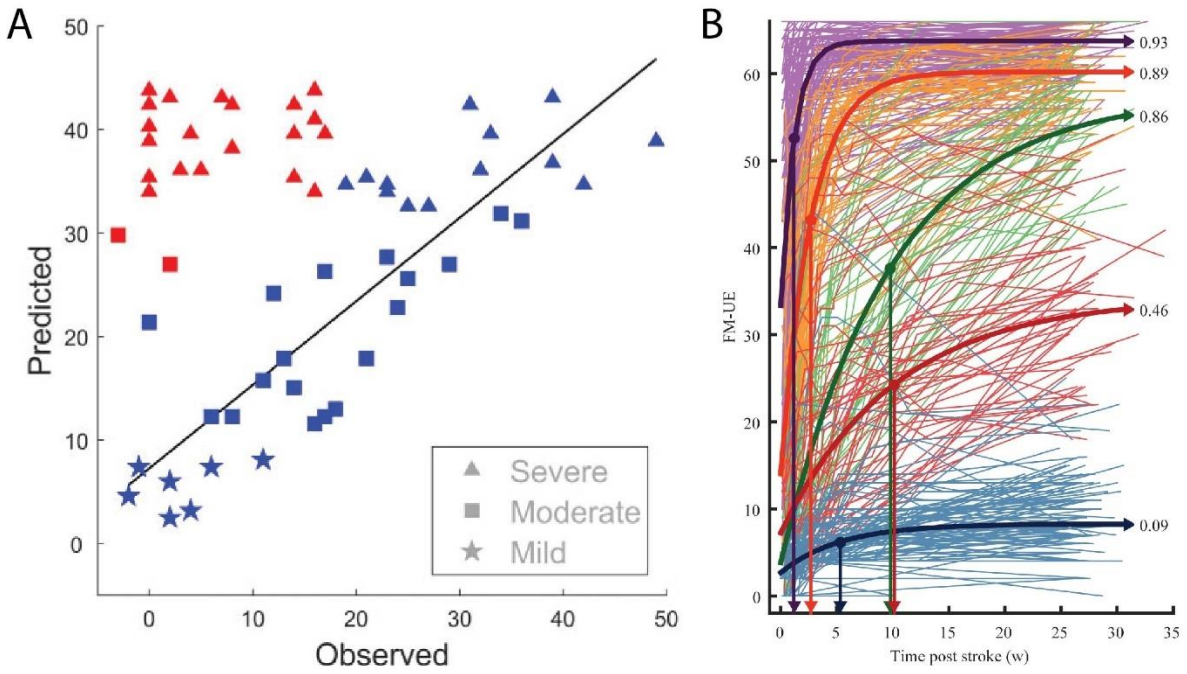


**Figure 1.2 Proportional motor recovery in the upper limb. A.** Predicted change in a behavioral score based on proportional recovery model vs. observed change. Patients in blue show proportional recovery, whereas patients in red recover poorly. Adapted from Koch (2021). **B.** FM-UE recovery data of 412 ischemic stroke patients in their data set. Individual patients are color-coded according to the subgroup they were assigned to most by the longitudinal mixture model of FM-UE recovery. The numbers next to the recovery graphs represent the proportional recovery coefficient rK, which denotes how much of the potential recovery has been achieved based on the FM-UE score. The downward arrows indicate the time constants τk in weeks, i.e., how fast patients recovered. Adapted from van der Vliet et al. (2020).

### Therapy-induced recovery

We have just seen that different states of excitability exist depending on time after stroke. The timing in which therapies are applied can thus have critical effect on their efficiency. Indeed, the work of Zeiler et al. showed that the timing of therapy is of utmost importance for motor recovery (Zeiler et al. 2016). Mice recovered from their initial motor deficits only when physical training started the day after the infarct and not when a 7-day delay was applied. Because of the release of inhibition and the instauration of a milieu favourable to plasticity occurring after the initial phase of protective hyper-inhibition, it appears that rehabilitation therapies would achieve maximum efficiency when applied during this plastic phase. Rehabilitation therapies aspire thus to support the spontaneous recovery in order to achieve maximal improvement.

Depending on the deficits, current therapies can take the form of classical physical, occupational, language training or more innovative treatments, such as functional electrical stimulation (FES) or robot-assisted therapies (Veerbeek et al. 2017; Eraifej et

al. 2017; Cassidy et Cramer 2017). Regarding motor rehabilitation, while usual therapies have proven to be efficient in the majority of cases (Stinear et al. 2020; Winstein et al. 2016), the effect of such training during the acute phase on spontaneous recovery is still under debate (Stinear 2017). The limitation of all current therapies can be inherent to their application in a “one-fits-all” approach and the lack of personalization to a specific patient’s profile and his/her needs.

The development of new ways of delivering therapies is thus essential to tackle the large heterogeneity of recovery. However, despite numerous clinical trials, including physical training, as well as technological and pharmacological interventions, their effects are often indiscernible from their control condition (Cassidy et Cramer 2017; Stinear et al. 2020). These inconclusive trials can be explained by several limitations (Stinear et al. 2020), some of which will be discussed next.

First, patients’ characteristics are not always reported and important differences can occur between intervention and control groups. The selection of patients based on prognostic biomarkers might improve the matching of groups, especially with the aim to balance the degree of improvement that is likely to result from spontaneous biological recovery processes. Indeed, if groups differ in terms of timing of spontaneous recovery, the effects of the intervention cannot be untangled from the effect of the endogenous biological recovery process. Secondly, the stage of recovery is also important in terms of expected effect size. We have seen earlier that the acute and subacute stages are the periods when interventions might have the greatest effect. However, the majority of clinical trials on stroke rehabilitation have focused on the chronic stage (Lohse et al. 2016). Whereas recruiting chronic stroke patients enable us to better disentangle the specific effect of the intervention from the spontaneous recovery, numerous trials might have been inconclusive due to the reduced plasticity in that stage. Finally, standardised and blinded rehabilitation therapies are a complex task to achieve (Bamman et al. 2018). Indeed, concealment of group allocation for training protocols is challenging due to the physical nature of the interventions.

Partly in order to tackle these limitations and to target more specifically the physiological processes detailed above, non-invasive neuromodulation therapies have been introduced. By using, for instance, transcranial magnetic stimulation (TMS) or transcranial direct-current stimulation (tDCS), it is possible to inflect on neural plasticity in a personalized fashion (Lefaucheur et al. 2020; Grefkes et Fink 2020; Stagg et Johansen-Berg 2013; Rothwell 2016) and to benefit from validated sham paradigms (Gandiga, Hummel, et Cohen 2006; Mansur et al. 2005). However, underpowered studies and heterogeneity in subject’s responses to stimulation lead to relatively small effect sizes and hinder their implementation in clinical practice (Cassidy et Cramer 2017; O’Brien et al. 2018; Raffin et Hummel 2018; Hussain et Cohen 2017).

### Heterogeneous role and timing of the E/I balance

In order to achieve maximum efficiency in post-stroke treatment, more knowledge is necessary to understand which physiological processes to target and when. The difficulty for such s task lies in the diverse profiles of patients who can have impairments in multiple motor and cognitive domains and different courses of recovery. We described earlier how electrophysiological studies have shown that the excitation/inhibition (E/I) balance plays a major role in recovery. Modulation of the E/I balance is responsible for neuronal protection, plasticity and stabilization of the recovered function. In particular, the GABAergic signaling appears to be a major actor of this modulation. However, the exact role and dynamic of this activity is not fully understood: a beneficial change in this balance at a given post-stroke stage could turn out to be detrimental at another stage (Carmichael 2012).

Indeed, Transcranial Magnetic Stimulation (TMS) studies have shown that intracortical inhibition is reduced after a stroke, both in the acute (J Liepert et al. 2000; P. Manganotti et al. 2002; 2008) and chronic stages (Joachim Liepert 2006; P. Manganotti et al. 2008; Ferreiro de Andrade et Conforto 2018). A meta-analysis also revealed that Short-interval Intracortical Inhibition (SICI) is reduced (i.e., more disinhibition) in the affected hemisphere compared to both the unaffected and controls, in the early post-stroke phase but not in the chronic phase (McDonnell et Stinear 2017). Similarly, magnetic resonance spectroscopy (MRS) studies showed decreased GABA levels from the acute to chronic stages (Blicher et al. 2015; Głodzik-Sobańska et al. 2004). However, it appears that - at least for the unaffected hemisphere - the time course of the disinhibition is different between patients and is related to the functional recovery (P. Manganotti et al. 2008). For the ipsilesional hemisphere, the link between disinhibition at rest and recovery remains unclear with no changes in intracortical inhibition over time in several TMS and MRS studies (P. Manganotti et al. 2008; Cirillo et al. 2020; Takechi et al. 2014; Blicher et al. 2009; Huynh et al. 2016) but significant correlation in other (Fujiwara et al. 2015). There is thus still much to know regarding the role and time course of the disinhibition levels at rest, especially in the ipsilesional hemisphere.
Moreover, when looking at functional changes in GABA, it was found that chronic stroke patients present a persistent local inhibition in the premovement phase (Hummel et al. 2009) while exhibiting an higher disinhibition than controls during movement (Ding et al. 2019). This functional modulation of inhibition is also thought to be crucial for recovery as a greater movement-related disinhibition in the acute phase is related with better recovery (Liuzzi et al. 2014). It shows the existence of different mechanisms involving GABAergic signalling with possibly reduced resting levels of inhibition in chronic patients associated with a less flexible mechanism of inhibition release (Johnstone et al. 2018).

We are thus currently in need for more knowledge about the physiological mechanisms sustaining motor recovery, especially regarding the role of the disinhibition processes. It would permit the identification of predictive biomarkers for a better allocation of patients in clinical trials, the discovery of new targets for therapies (in particular pharmacological and neuromodulation interventions), and a better characterization of the physiological status, allowing better therapy personalization. This would for instance permit promoting inhibition with Non-Invasive Brain Stimulation (NIBS) in the most beneficial time frame for a given patient. In that view, large and longitudinal studies including patients presenting heterogenous stroke type and deficits need to be realized (Guggisberg et al. 2019). Furthermore, studies should provide mechanistic comprehension of the neuronal changes involved in motor deficits and recovery. As the dynamic of the GABAergic-mediated inhibition can change rapidly, it is essential to be able to capture these rapid changes. Observing how these processes are evolving with time post stroke and their relationship with motor recovery could help identify specific inhibitory mechanisms, i.e., resting tonic or phasic inhibition, to target future interventions. Finally, combining different modalities is necessary to inspect the factors responsible for the E/I evolution from complementary angles. Multimodal electrophysiological recordings, by informing on the fast interaction between excitatory and inhibitory activities, can bring such information at each stage of the recovery.

## 1.2 Assessing and quantifying motor recovery through electrophysiological recordings

Knowing the electrophysiological factors associated with recovery is essential. But to draw any conclusion on the significance of a factor, it is necessary to relate its properties with clinical and behavioral assessments, i.e., with better or worse motor recovery.

### 1.2.1 Clinical evaluation of motor impairment and residual motor functions after a stroke

#### 1.2.1.1 Fugl-Meyer assessment

In order to follow the recovery in terms of motor function and activity, the use of standardised assessments is crucial. In this regard, different motor scores are used to evaluate motor functions and the related motor deficits (Stinear et al. 2020).
It is common practice to start by evaluating specific anatomical movements or muscle activation and to what extent they can be achieved compared to a normal activity. The most frequently used evaluations is the Fugl-Meyer assessment (FM), but other tests are also often encountered such as the Action Research Arm Test (ARAT) or the Wolf Motor Function Test (WMFT) (Stinear et al. 2020). Each test involves different compounds

related to the specific movements that can be done, scored from null (not able to perform at all) to several points for normal performance. In our specific framework, we focused on the Fugl-Meyer of the upper extremity. The Fugl-Meyer assessme is a multi-items scale initially developed to provide a comprehensive and quantitative measure of recovery from hemiplegic stroke (Fugl-Meyer et al. 1975). This scale was designed to integrate assessments of the neuromuscular capacity notably through the evaluation of movement synergies (Fugl-Meyer 1980) and is currently considered as one of the gold-standards to assess post-stroke sensorimotor recovery (Gladstone, Danells, et Black 2002; Santisteban et al. 2016).

The FM assesses both upper and lower limbs and includes 5 general sections: motor function, sensation, balance, joint range of motion and joint pain. However, sections are often administered separately to test a specific construct. The upper-limb assessment (FMA-UL) used in this thesis focuses on upper-limb motor impairment and includes reflexes activity, upper extremity, wrist, hand and coordination/speed. Each item is visually assessed by the rater and scored on a 3-point ordinal scale (0 = cannot perform, 1 = performs partially, 2 = performs fully). The total score for the FMA-UE ranges from 0 (complete hemiplegia) to 66 (normal motor performance).

Despite its excellent psychometric properties and its large use in the field of stroke research, the FMA still measures gross limb movements only and could be associated with a non-negligible ceiling effect (Lin et al. 2009; Thompson-Butel et al. 2015). Therefore, it might be completed by other measures of specific upper-limb motor function aspects to quantify impairment, i.e., hand strength, and fine and gross manual dexterity (Santisteban et al. 2016).

#### 1.2.1.2 Complementary motor assessments

In this thesis, we also used the pinch and grip (P&G) force, the 9 Hole Peg Test (9HP) and the Box and Block test (BnB). The Pinch & Grip test allows to assess the maximum voluntary and isometric hand strength in multiple types of grasp (Mathiowetz et al. 1984). Hand strength represents a highly reliable and valid measurement (Mathiowetz et al. 1984) and can be used to reflect changes in time (see Bobos et al. 2020, for a review). Furthermore, this parameter objectively reflects the functional status of the upper extremity and the impairment level, notably in the stroke population (Bertrand et al. 2015; Boissy et al. 1999). The hand strength is evaluated using a dynamometer with an adjustable handle for the fist and fingers grips. Three different grips are assessed using standard testing positions: the fist grip with the full hand gripping the handle, the pinch grip where the patient only uses the thumb and index finger to apply force and key grip with the device positioned between the middle phalanges of the index finger and the thumb. Averaged performances in kilograms for each grip and each hand represent the final scores. Unaffected hand performances can be compared to the unaffected hand

performances with the assumption that pre-stroke performances were similar for both hands.

The Nine-Hole Peg Test (9HP) was developed to assess fine manual dexterity. It is particularly useful in combination with other upper limb scales to estimate fine motor function more precisely (Santisteban et al. 2016). The apparatus of the test is a rectangle board which contains 9 pegs, placed in a shallow round dish on one the side on the board. On the other side of the board are nine holes for the pegs to fit in to. The patient is instructed to place all pegs (one-by-one) in the holes and then to remove and replace them back in the container (one-by-one) as quickly as possible. The time to complete each trial is recorded is seconds from the moment the patient touches the first peg until the moment the last peg hits the container. The shorter time for each hand represents the final score of the test, with a maximum time of 180 seconds.

The Box and Block test (BnB) was originally developed to assess unilateral gross manual dexterity (Cromwell 1960; Mathiowetz, Volland, et al. 1985). The patient sits in front of a wooden box divided into two compartments of equal size by a vertical panel. The box is placed lengthwise and the compartment close to the hand being assessed contains 150 small blocks. The patient is instructed to move one-by-one the maximum number of blocks from one compartment to the other, within 60 seconds. Fingertips must cross the partition before releasing the blocks, and patients do not have to pick up the blocks that fell outside on the box. The unaffected hand is assessed first. The final scores are the numbers of blocks transferred for each hand, and higher scores indicate higher gross manual dexterity.

Combined, these motor assessments provide a complete and reliable picture of hand motor performances and can assess motor recovery over time. To investigate the neuronal correlates of the motor assessments, TMS-EEG presents the advantage of characterizing both the affected motor cortex that is locally stimulated, as well as the distributed brain networks that are connected to it.

### 1.2.2 TMS-EEG coupling as a tool to investigate motor recovery

#### 1.2.2.1Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation (TMS) was first introduced in 1985 by Barker and colleagues (Barker, Jalinous, et Freeston 1985) and has been widely used since to explore motor cortex (Siebner et al. 2022) and other brain areas function (Railo et Hurme 2021), as well as for developing innovative treatments through the modulation of cortical excitability (Iglesias 2020; Burke, Fried, et Pascual-Leone 2019). TMS consists in applying a strong time-varying electromagnetic field on the brain by using a stimulation coil placed tangentially on the scalp. Thanks to the phenomenon of electromagnetic induction, the magnetic field produced by the coil will then induce a phasic electric current

on the cortical surface that will depolarize excitable neurons located below the coil. Due to the limited penetration depth of the induced electric field, the primarily stimulated areas will be the gyral crowns, lips and rims (Siebner et al. 2022). Inside these regions, excitable cells with long projection in the direction of the currents will most likely be activated. Thus, myelinated axons terminals of pyramidal cells are the most low-threshold targets. They are however not the only cells easily activated by TMS. Aberra et al. 2020 used a morphologically realistic model to study the activation threshold by TMS of several cortical cells. They found that pyramidal cells in lamina 5 had the lowest threshold compared to large, nested and small basket cells in laminae 2-6 and to neurogliaform cells.

### Single pulse paradigms

When applied over the motor cortex, the induced electrical field will predominantly activate longitudinally oriented pyramidal cells (Siebner et al. 2022) which will generate an action potential travelling down the corticospinal tract to the spinal cord (**Figure 1.3A**). There, motoneurons will be recruited and will in turn activate their target muscles, according to the precise location of the stimulated area on the somatotopic map of the motor cortex. Using electromyography (EMG), one can record the electrical potentials generated by the muscle fibers due to the contraction of these muscles, commonly called motor evoked potentials (MEPs). In most studies using TMS, the intensities are set according to the excitability of the motor cortex. The primary target, or “hotspot”, corresponds to the functional cortical representation of a target muscle, e.g., the first dorsal interosseous muscle. By varying the intensity one can find the minimal value necessary to evoke a MEP. This threshold is called the resting motor threshold (RMT) and can provide information on the excitability and integrity of the corticospinal tract at a given time or in a specific condition (Klöppel et al. 2008). This value is then used as reference for the stimulation of other cortical regions which don’t evoke MEPs. Hotspot and RMT hunting constitute the gold standard procedure for the normalization of the target region and intensities used across subjects and TMS studies. Action potentials also propagate through the excitatory and inhibitory circuits in the target regions and in interconnected cortical and subcortical regions (Siebner et al. 2022).

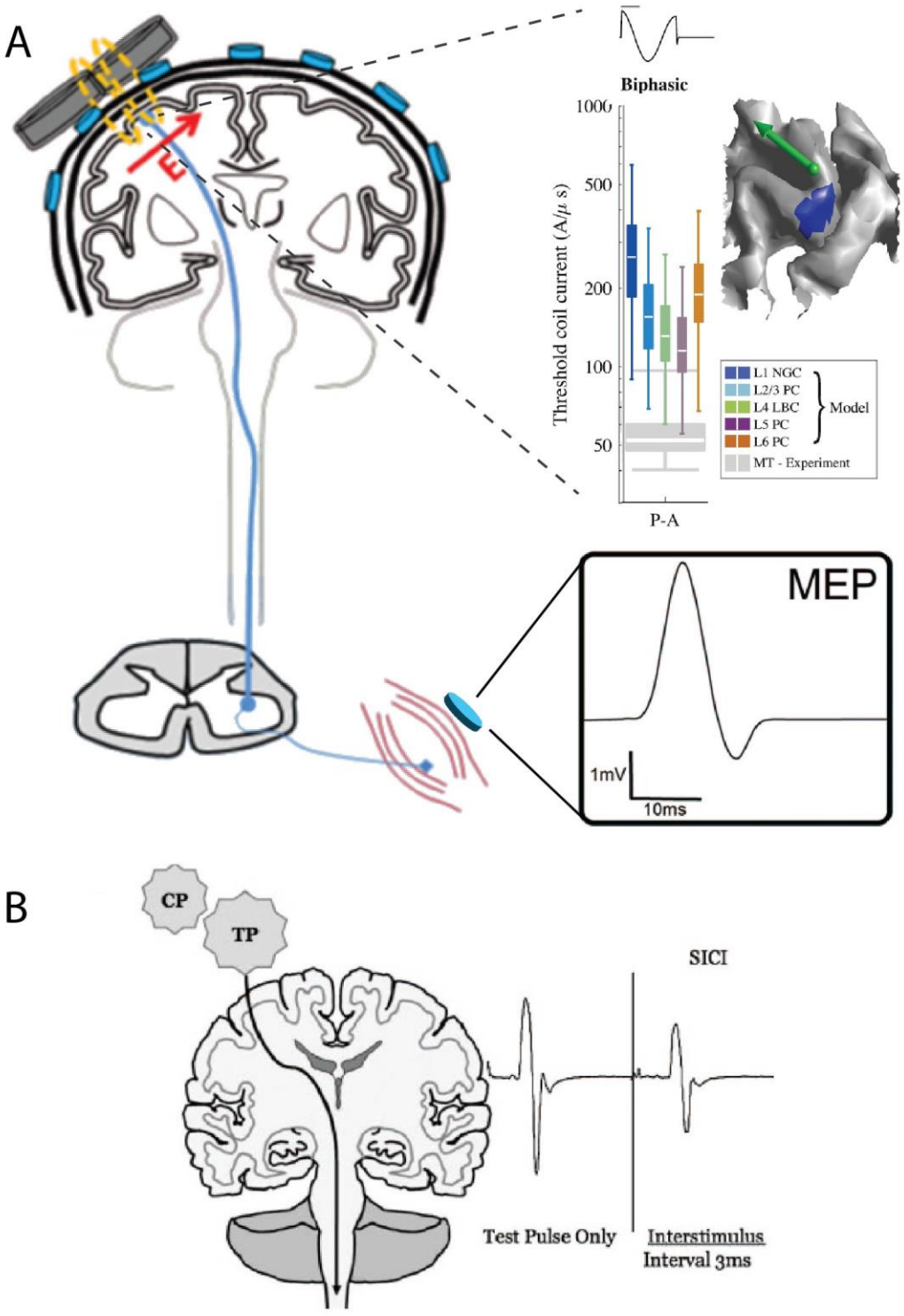


**Figure 1.3 TMS over M1 induces motor evoked potentials (MEPs). A.** The TMS pulse depolarizes excitable neurons in the motor cortex. The most easily excitable cells are the pyramidal neurons from layers 5 (purple) as well as the large basket cells from layer 4 (green). The produced actions potentials will travel along the corticospinal tract until reaching the spinal cord. Motoneurons will then be recruited and will relay the signal to the corresponding muscle. The stereotypical induced electrical activity measured at the muscle

or at the skin surface is called a motor evoked potential (MEP). **B.** Applying a first subthreshold conditioning pulse (CP) can prime the $GABA_A$ receptors, resulting in a MEP of reduced amplitude when tested by a suprathreshold pulse (TP). The interstimulus interval is set to 3ms to study this specific receptor activity (Adapted from Farzan et al. 2016 and Vlachos, Funke, et Ziemann 2017.

The intensity of the delivered stimulation, expressed as the maximal output of the stimulator, greatly influences the volume of excited brain. While increasing the intensity can increase the penetration depth of the induced electric field, deep brain areas cannot be directly stimulated by this technique as the electric field rapidly decays with depth (Gomez–Tames et al. 2020; Deng, Lisanby, et Peterchev 2014).

### Paired-pulses paradigms

Varying the stimulation intensity can also enable the activation of different subpopulations of neurons. Stimulation at an intensity below the motor threshold does not elicit MEPs but can activate cortical interneurons, whose threshold is much lower (Davey et al. 1994; U Ziemann, Rothwell, et Ridding 1996). Lower intensities are also less likely to reach deeper cortical layers and thus stimulate primarily layer 4 interneurons (**Figure 1.3A**). Once activated, the local interneurons will release the neurotransmitter ɣ-aminobutyric acid (GABA) which can suppress the activity of the pyramidal cells. When shortly followed by a suprathreshold pulse, the subthreshold pulse, called conditioning pulse, inhibits the motor output evoked by the suprathreshold test pulse (**Figure 1.3B**). It is thus possible to investigate the status of the local intracortical inhibitory circuits with this paired-pulse protocol called short interval intracortical inhibition (SICI) (Kujirai et al. 1993). More precisely, evidence points towards a specific involvement of the $GABA_A$ receptor activity in the effect seen with the SICI paradigm (U. Ziemann et al. 1996; Ilić et al. 2002). Other paired pulses paradigms exist, such as long-interval intracortical inhibition (LICI), intracortical facilitation (ICF) or interhemispheric inhibition which respectively target the activity of $GABA_B$ receptors (McDonnell, Orekhov, et Ziemann 2006), NMDA receptors (U. Ziemann et al. 1998) and transcallosal fibers (Ferbert et al. 1992). As we have seen that GABA plays a crucial role throughout stroke recovery processes, the SICI paradigm was used in this thesis to investigate one of the receptor subtypes of this neurotransmitter.

### Use of TMS in the study of stroke induced changes

When used to study the structural and functional changes occurring after a stroke, TMS has been found very useful. Indeed, as the presence or absence of MEP inform on the integrity of the CST, a crucial tract for motor function, it can serve as a robust prognosis factor of recovery (Stinear et al. 2012; Byblow et al. 2015; Stinear 2017). According to an algorithm made to predict upper limb recovery, the PREP2, patients without MEPs are likely to achieve only limited recovery at best (Stinear et al. 2017). TMS can also inform on the E/I balance in the hemisphere stimulated. A meta-analysis found that, in both the

acute and chronic stage ,stroke patients have a higher ipsilesional RMT, representing lower excitability, than contralesional RMT or healthy controls (McDonnell et Stinear 2017). Paired-pulse protocols also revealed changes in postsynaptic $GABA_A$, postsynaptic $GABA_B$ and presynaptic $GABA_B$ activity. It was also revealed that ipsilesional postsynaptic $GABA_A$ receptor activity was reduced (less inhibition) early post stroke compared to the unaffected hemisphere and control subjects (McDonnell et Stinear 2017). This effect was however not present in the chronic phase. Inconsistent results were reported regarding postsynaptic $GABA_B$ receptor activity. While it was recently found that this $GABA_B$-mediated inhibition is increased in the ipsilesional hemisphere in the acute and chronic phase compared to controls (Mooney et al. 2019; Cirillo et al. 2020), no difference (Schambra et al. 2015) or even the opposite effect (Swayne et al. 2008) was also reported. However, it is worth noting that results of both recent studies are derived from the same patient cohort (Mooney et al. 2020; Cirillo et al. 2020).

Different GABAergic activities are thus involved with distinct function and time course. Being able to distinguish the activity from different units of the GABAergic system with TMS strengthens its use for the investigation of motor recovery. However, when focusing on single patients, especially for longitudinal investigation, TMS readouts can have limitations. By looking at the reliability of TMS measures, such as RMT and SICI, it was suggested that TMS measures cannot be reliably used to assess individual change (Schambra et al. 2015). Moreover, TMS relies on M1 and cortico-spinal integrity, which both can be severely impacted by a stroke. In patients without functional corticospinal pathways, i.e., without MEP, the use of TMS is limited. This can be of particular importance for the study of stroke patients as it usually prevents the investigation of severely impacted patients and thus the possible discovery of mechanisms specific to these patients. In this way, Cirillo et al. found that in patients without MEP, the MRS unveiled an ipsilesional disinhibition at 6 weeks post stroke which was not present in the group of patients with a functional cortico-spinal pathway (Cirillo et al. 2020). However, MRS could not distinguish between $GABA_A$ and $GABA_B$ activity, which remains to be explored.

Some limitations of the use of TMS-EMG coupling in stroke patients can thus be circumvented when used in combination with other modalities (S. Tremblay et al. 2019; Rafiei et Rahnev 2022), such as electroencephalography.

#### 1.2.2.2 Electroencephalography (EEG)

Developed in humans in 1924 by Hans Berger, electroencephalography (EEG) was one of the first non-invasive brain imaging tools. With magnetoencephalography, EEG is the only non-invasive technique that can record brain activity with a time resolution in the millisecond range (Murakami et Okada 2006; Nunez et Srinivasan 2006).

### Principles of EEG

An EEG system consists of electrodes, amplifiers and a recording device (Bronzino et Peterson 2014). Electrodes are placed in contact of the scalp and can detect the electrochemical activity from the neurons beneath (**Figure 1.4A**). EEG records the electric field potential resulting from the activity of pyramidal neurons organized in parallel columns in the neocortex (Jackson et Bolger 2014). At a single neuron level, its excitation from contacting neurons generates an extracellular voltage near the dendritic trees, called post-synaptic potential. This voltage is more negative than everywhere else in the neuron, creating a region of negative charge (the dendrites) and a region of positive charge (the soma). This leads to what is called, in the physics of electromagnetism, an electric current dipole (**Figure 1.4B**). The surface electrode will capture the sum of the surrounding current dipoles. The magnitude of the potentials observed at the level of the electrodes is thus directly linked to the number, the strength and the orientations of these dipoles (Dugdale 1993; Kandel, Schwartz, et Jessell 2000). In order to be detectable, the neurons need to fire synchronously and to be arranged in a large and highly parallel fashion, forming neuronal columns in the grey matter (Nunez, Nunez, et Srinivasan 2019; Nunez et Srinivasan 2006), otherwise their respective charges could cancel each other out, resulting in a flat signal on the recording. Finally, it has been suggested that pyramidal neurons from layer 5 have the highest contribution to the resulting signal on the surface, due to their stronger current dipole moment compared to the other cells or layers (Murakami et Okada 2006).

The electric field generated by the neurons drops rapidly when travelling through the different tissues (e.g. dura, skull, scalp, hairs) before eventually reaching the electrodes (Hopkins 1999). Surface EEG therefore mostly captures the activity of superficial cortical layers. The activity originating in deeper structures is thus most likely not directly recorded. Moreover, the voltage recorded by a single surface electrode will correspond to the sum of numerous sources in the brain and a single deep source will influence many, if not all, electrodes on the scalp, and not exclusively the one immediately above it. This effect, called spatial smearing, is a consequence of volume conduction and limits conclusions about the localization of neural activity at the electrode level, resulting in poor spatial resolution. However, these structures can greatly influence the firing pattern of the superficial layers by synchronizing their activity. For instance, the dorsal thalamus is considered the main region responsible for cortical neuron oscillations through thalamocortical connectivity (Buzsáki, Anastassiou, et Koch 2012; Olejniczak 2006). From the signal captured by the electrodes, many readouts can the derived, representing just as many windows into the brain’s activity.

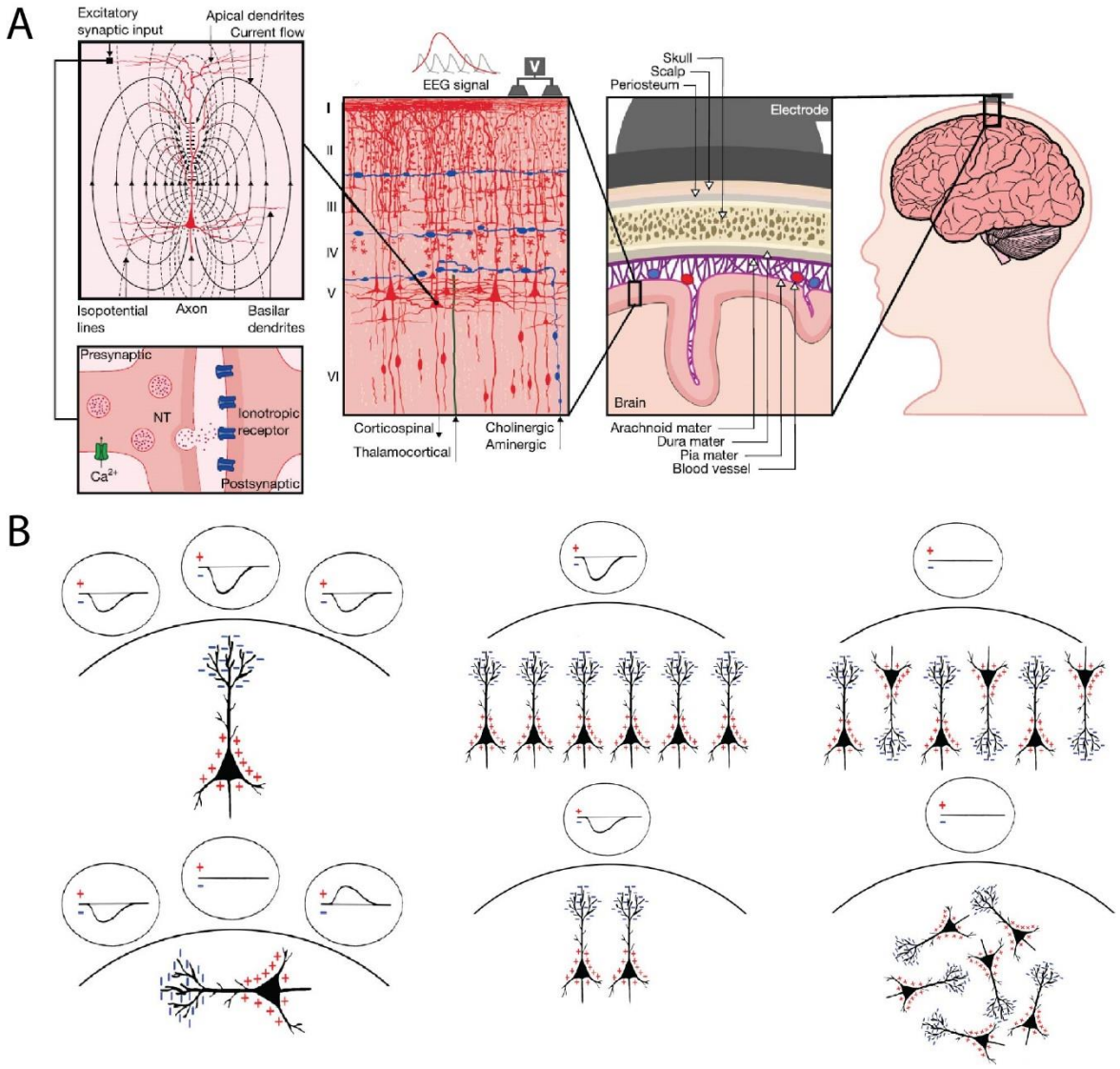


**Figure 1.4 Neurophysiological basis of EEG recordings**. **A**. The cerebral neocortex is organized in six layers (I–VI) with different cytoarchitectural characteristics. The majority of EEG signals are generated by pyramidal neurons located primarily in layers III and V. These neurons are spatially aligned and perpendicular to the cortical surface, which yields a dipole layer orthogonal to the surface of the scalp. Adapted from Portillo-Lara et al. (2021). **B.** Neurons produce dipoles that are measured by the surface electrodes. The deflection seen at the surface will be a factor of the orientation of the dipole, the number of neurons with synchronous activity and the arrangements of dipoles between each other and between their electrical charges. Adapted from Jackson & Bolger (2014).

## Neural oscillations

Local synchronization of neural populations activity and interregional communication can lead to oscillations which constitute one of the most studied features of EEG recordings. The functional relevance of such oscillations has been linked to their frequency. Hence, the frequency domain of EEG data is usually separated in five frequency bands: delta (δ) (0.5-4 Hz), theta (θ) (4-8 Hz), alpha (α) (8-13 Hz), beta (β) (13-30 Hz) and gamma (ɣ) (>30 Hz) (Babiloni et al. 2020). When investigating the sensorimotor cortex, a specific mu (μ) wave, comprising an α- μ (~10Hz) and a β- μ (~20 Hz) can be found. Each of these frequency bands are thought to have distinct functions (Başar et al. 2001) and origin (Olejniczak 2006; da Silva 2009). δ has been shown to be linked with motivation, attention and homeostatic processes (Knyazev 2012; Harmony 2013), and α with functional inhibitory processes (Hummel et al. 2002; Jensen et Mazaheri 2010; Sauseng et al. 2009), supposedly coming from thalamic activity (Hughes et Crunelli 2005; Lörincz, Crunelli, et Hughes 2008; Halgren et al. 2019). Higher frequencies, such as β oscillations, or ɣ when focusing on the motor cortex, have been associated with sensorimotor transmission and communication between sensorimotor areas and other areas (Kilavik et al. 2013), and recently with voluntary movements (Hussain et al. 2022). Its origin lays in the posterior wall of the Rolandic fissure (Tiihonen, Kajola, et Hari 1989; Cole et Voytek 2017). ɣ oscillations are often linked with θ activity through phase-amplitude coupling (Florin et Baillet 2015). Such interaction is thought to support inter-regional communication during cognitive processing (Canolty et al. 2006; Solomon et al. 2017).

## The use of EEG in the study of stroke induced changes

EEG is a low-cost, easy and fast to apply tool. Its application in clinical settings has thus grown rapidly to become one of the most common techniques to record brain activity in patients, especially at the bedside. Following a stroke, the power of these frequency bands is greatly altered. δ power is generally increased in acute stroke patients and associated with worse outcome (Simon P. Finnigan et al. 2004; S.P. Finnigan, Rose, et Chalk 2008; Tecchio et al. 2007). This marker could reflect hyperpolarization and inhibition of cortical neurons, resulting in deafferentation of neural activity (John et Prichep 2006; Fanciullacci et al. 2017). On the contrary, β power is lower in acute stroke patients compared to healthy controls (S. Finnigan, Wong, et Read 2016). Overall, it appears that stroke leads to a general slowing of the cortical rhythms with a lower power of high frequencies and higher power of slow oscillations, possibly resulting from an increase of tonic GABA activity (Lanzone et al. 2022). Overall, EEG resting state can provide insight on the excitation/inhibition activities occurring after a stroke.

However, examining specific cognitive processes or the role of a brain structure in a specific function is limited with resting-state recordings. While it is possible to study them through well-designed tasks (M. Bönstrup et al. 2018; Schulz et al. 2021; Quandt et al.

2019), severe motor and cognitive deficits can be an obstacle for the application of tasks in stroke patients. The selection of patients based on their aptitude to perform a task would in addition limit the type of eligible patients and reduce the generalization of the effects found. Combining EEG recordings with TMS can allow for the stimulation of a target region, without the need of any motor or cognitive task. TMS-EEG coupling could thus be the appropriate tool to explore the activity of the motor cortex after a stroke, its interaction with other cortical regions and how it affects motor recovery.

#### 1.2.2.3 TMS-EEG coupling

Combining TMS with other imaging modalities such as EEG or fMRI (Bergmann et al. 2016a) allows to investigate both the activity in the stimulated region but and the rest of the brain (e.g. the contralateral M1). TMS-EEG can thus be a window into both the local and whole-brain electrophysiological reorganization induced by a stroke.

##### Principle

TMS coupled with EEG has the benefit of inheriting both the excellent temporal resolution of EEG and the good spatial resolution of TMS, with the possibility of differentiating responses from stimulation sites which are 10mm apart (Passera et al. 2022). TMS-EEG coupling has thus been extensively used in the past two decades (Daskalakis et al. 2012), with the first study from Ilmoniemi and colleagues (Ilmoniemi et al. 1997).
Overall, any cortical area can be stimulated by TMS, with EEG providing a direct readout of the activity of the area. The spectrum of possible analyses for TMS-EEG is the same as for EEG alone, with the particularity that the first source of activity is triggered by the TMS (Bortoletto et al. 2015a; Farzan et al. 2016). However, the TMS pulse induces multiple artifacts on the EEG recordings (Rogasch et al. 2017). Despite attempts to develop solutions to suppress or reduce those artifacts (Litvak et al. 2007; Rogasch et al. 2014; ter Braack, de Vos, et van Putten 2015; Tomasevic, Takemi, et Siebner 2017), the extent to which the preprocessed data is still contaminated is under debate (Gordon et al. 2018; Conde et al. 2019; Belardinelli et al. 2019). Nevertheless, TMS-EEG has been applied in clinical studies for a few years and proved to be a valuable method to understand the physiological mechanisms underlying psychiatric and neurological disorders (S. Tremblay et al. 2019).

##### Evoked and induced activity

When a TMS pulse is given while EEG is recorded concurrently, a series of specific waveforms, called TMS-Evoked Potentials (TEP) which are dependent on the cortical region stimulated (Rosanova et al. 2009; Rogasch et al. 2019; Harquel et al. 2016) and coil orientation (Bonato, Miniussi, et Rossini 2006; Pisoni et al. 2018), is generated. When stimulating a certain region, each peak composing these complex TEPs is thought to be

linked to specific physiological mechanisms and to the TMS intensity (Darmani et Ziemann 2019; Raffin et al. 2020) (**Figure 1.5A**). By comparing the amplitude of such peaks between populations or conditions, one can draw conclusions on the neuronal process involved. For instance, the amplitude of the N45 and N100 can inform on the activity of the $GABA_A$ and $GABA_B$ receptors, respectively (Darmani et Ziemann 2019). Similarly, the P70 can also serve as proxy of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors status.

After a single pulse of TMS, the neuronal populations in the motor cortex are synchronized which leads to larger oscillations, especially in α and β frequency bands (Paus, Sipila, et Strafella 2001; Van Der Werf et Paus 2006; Fuggetta, Fiaschi, et Manganotti 2005). Cortical areas differ by their cytoarchitectonic properties, resulting in a specific frequency signature. It is thus believed that TMS provokes a phase resetting of the area's spontaneous oscillations and is, as such, a unique approach to study the generation of oscillatory activity in the human brain (Thut et Miniussi 2009).

Whereas the vast majority of the studies using TMS-EEG have focused on the time-locked, i.e. 'evoked', activity generated by the TMS pulse, the non-phase-locked oscillations have been largely disregarded (Pellicciari, Veniero, et Miniussi 2017). This 'induced' activity corresponds to the non-stationary part of the response to the TMS pulse (**Figure 1.5B**) and might convey information that was hidden when restricting the analysis on the evoked oscillations (Mutanen 2013). In this regard, Premoli et al. found that a single-pulse TMS induced an early synchronization in the α and β bands followed by a late desynchronization in the same frequency bands (Premoli et al. 2017). In a complementary way, recent studies have linked these induced α and β oscillations with GABAergic inhibition and glutamatergic activity, respectively, using pharmacological interventions (Premoli et al. 2017; Tangwiriyasakul et al. 2019; Belardinelli et al. 2021)

Overall, it appears that TMS-EEG is particularly suitable for stroke as the motor cortex can be stimulated without the need of motor output, e.g., in case of a severely damaged cortico-spinal tract. The dependence on motor output could indeed introduce important variability depending on the motor capability of stroke survivors. TMS-EEG therefore allows the recruitment of more heterogeneous and representative patient populations.

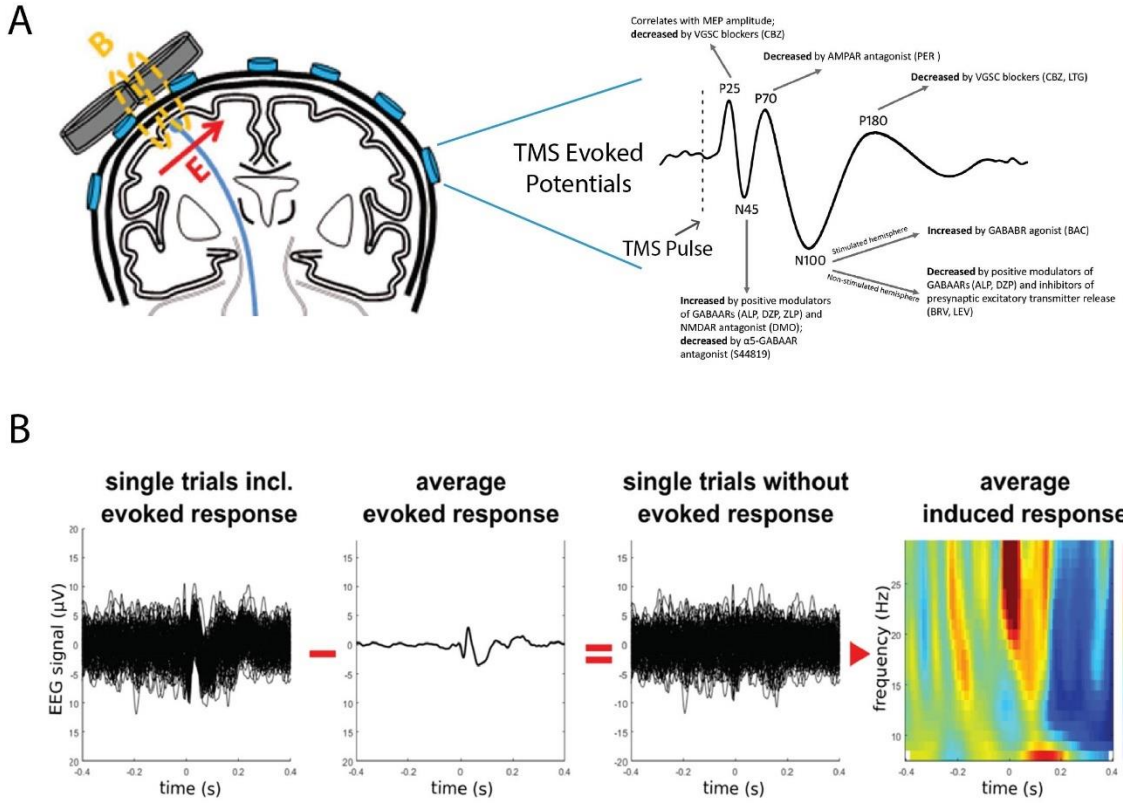


**Figure 1.5 TMS-EEG evoked and induced activity. A.** Typical TEP components and their modulation by pharmacological intervention. Adapted from (Farzan et al. 2016) and (Darmani et Ziemann 2019). **B.** TMS-induced oscillations. The average evoked response is subtracted from each single trial before averaging the trials. The last panel represents the power of each frequency, between -400ms and 400ms post TMS. Adapted from (Premoli et al. 2017).

## The use of TMS-EEG in the study of stroke

Since 2015, several studies have used TMS-EEG coupling to study the impact of a stroke on the neurophysiological activity (Keser et al. 2022).

The presence or absence of a specific TEP peak is on its own already of clinical relevance. Indeed, in the first week post stroke, the presence or absence of TEPs in the ipsilesional hemisphere can serve as a predictor of motor recovery, suggesting that the presence of a TEP can be a marker of neuronal integrity. The presence/absence of TEPs can also disentangle between a lesioned or perilesional area (Gosseries et al. 2015). Binary phenotyping based on TEP can thus be used in complement to MEP-based classification, especially in patients without functional CST.

### Local and global cortical over-excitability after stroke

TMS-EEG can also inform on the cortical excitability of the stimulated region at a given time point and its relationship with recovery. For instance, in the subacute phase (both at 40- and 60-days post stroke), the ipsilesional hemisphere presents higher excitability, reflected by higher global mean field power (GMFP) amplitude between 50 and 100 ms, compared to the contralesional hemisphere (Pellicciari et al. 2018). This increase in TEP amplitude has also been found to be related with anodal tDCS-induced recovery, suggesting a link between this readout of cortical excitability and behavioural outcomes (Cipollari et al. 2015). This was further explored by Tscherpel et al. in a longitudinal study including a large proportion of severely affected patients (Tscherpel et al. 2020). They found that some stroke patients, especially the most severely affected ones, exhibited a large and simple activity in response to the TMS (**Figure 1.6A**). They further unveiled that stroke patients showed larger local mean field potential (LMFP) than healthy subjects in the first hundreds of milliseconds after the TMS pulse. This marker of cortical excitability was also associated with less favourable neurological outcomes. Overall, the observed increase of the amplitude of these early responses to TMS (10-100ms) could reflect a disinhibition of the affected hemisphere in the acute and subacute stages, possibly mediated by a disruption of the tracts between the cortex and the basal ganglia (Tscherpel et al. 2020). While Pellicciari et al. (2018) found that this increased cortical excitability was associated with better functional recovery, Tscherpel et al. (2020) found the inverse relationship. As the timing of the effect differs between both studies, it is possible that an increased excitability in the first week, as seen in Tscherpel et al., could be maladaptive while being supportive in the subacute/early chronic stage. Additional research is however needed to investigate if the cortical responses reported by both studies represent the same physiological processes and to conclude on the role of the ipsilesional disinhibition and its relationship with time post stroke.

### Perturbation of the thalamocortical loops revealed through the alteration of neuronal population's oscillations

When focusing on the TMS-evoked oscillations, both Tscherpel et al. and Pellicciari et al. found slower evoked activity in stroke patients compared to healthy subjects (Tscherpel et al. 2020; Pellicciari et al. 2018) (**Figure 1.6B**). They also revealed a simpler neuronal response to TMS that was interpretated as a perturbation of the thalamocortical loops, which is a major driver of evoked dynamics. Furthermore, Pellicciari et al. (2018) found that stroke patients have a lower α power at 20 days post stroke but that the power increases between 20 and 40 days to reach a similar profile as the healthy subjects after 60 days post stroke. α power is thus interpreted as marker of a spontaneous recovery of the thalamo-cortical network. Indeed, the thalamus is thought to be mainly involved in the

generation of α waves (Sauseng et Klimesch 2008) and fast oscillations (Llinás et al. 2007). The two studies might indicate that the acute disruption of fast oscillations represents an impaired thalamo-cortical loop, while restauration of the tract, indicated by an increase of α oscillations, promote recovery. However, the phenomenon behind this increase in α oscillations and its role for stroke recovery is still unclear. α activity is often associated with cortical inhibition (Hummel et al. 2002; Thut et Miniussi 2009; Sauseng et Klimesch 2008) but was linked here with better performance in the Berg Balance Scale (BBS) at any stage from 20 to 180 days post stroke. Yet, a reduction of inhibition, especially in the acute/subacute stages, has been extensively associated with better recovery (see section 1.1.4). Whether TMS-evoked α oscillations reflect distinct mechanisms in stroke patients compared to healthy controls remains thus to be clarified. Of note, by using TMS-EEG, Pellicciari et al. (2018) were able to stimulate the PPC and to compare its evoked activity to the one derived from the motor cortex, but found no association between the evoked-GMFP or oscillations and functional recovery.

### Evidence for an interhemispheric imbalance

The use of TMS-EEG also helped addressing the possible interhemispheric imbalance resulting from a stroke. Indeed, during the production of voluntary unimanual movements, the fast inhibition of the motor output in the hemisphere contralateral to the moving hand is necessary to suppress mirror movements in the passive hand (Beaulé, Tremblay, et Théoret 2012; Mayston, Harrison, et Stephens 1999). Following a stroke, this model suggests that the lesioned hemisphere exerts a reduced inhibition to the contralesional hemisphere, resulting in a higher inhibition upon the affected motor cortex. This interhemispheric interaction might however have a different influence on recovery based on the extent of the damage to the ipsilesional hemisphere, as suggested by the bimodal-balance recovery model (Di Pino et al. 2014).

Fuelling this theory, interhemispheric β-band imaginary phase coherence was found to be increased in chronic stroke patients compared to healthy controls during voluntary muscle contraction (Borich et al. 2016a). This increased interhemispheric β-band connectivity could reflect altered GABAergic activity (Jensen et al. 2005; Hall et al. 2010) and might be predominant in more impaired patients (Palmer et al. 2019). Interestingly, this effect was found exclusively after ipsilesional stimulation and not in resting-state EEG connectivity analysis. Whether this interhemispheric coupling is specific to movement-related activity is however under debate as this β-band connectivity has also been seen in a recent resting-state study (Hordacre et al. 2020). In addition to this finding, Casula et al. discovered that in severely affected chronic patients who presented no MEPs, stimulation of the ipsilesional motor cortex led to similar TEPs in both hemispheres whereas stimulation of the unaffected M1 resulted in a smaller TEP in the opposite (ipsilesional) hemisphere (Casula et al. 2021). This interhemispheric interaction was more

symmetrical in patients with better upper limb strength. They interpretated their result as a perturbated inhibition from the affected to the unaffected hemisphere and a normal inhibition in the opposite direction, in the most affected patients.

In summary, there is hence one study linking lower inhibition from ipsilesional M1 (iM1) to contralesional M1 (cM1) with greater motor function (Palmer et al. 2019) whereas Casula et al. found less iM1 to cM1 inhibition in more impaired patients (Casula et al. 2021). While previous TMS studies (for a review, see Guggisberg et al. 2019b) tend to favour a link between cM1 to iM1 over-inhibition and poor motor function (Duque et al. 2005; Murase et al. 2004; Joachim Liepert, Hamzei, et Weiller, s. d.; Shimizu et al. 2002), others have suggested otherwise (Dimyan et al. 2014; Mang et al. 2015; Bütefisch et al. 2008; Gerloff et al. 2006; Butefisch 2003). As proposed by the bimodal balance model, the interhemispheric inhibition could be related to the ipsilesional structural reserve. TMS-EEG coupling offers the possibility to test this bimodal balance model by investigating induced interhemispheric inhibition in patients without functional corticospinal pathways, as shown by Casula et al. (2021). Bigger sample sizes are however needed to evaluate this model in a representative patient population.

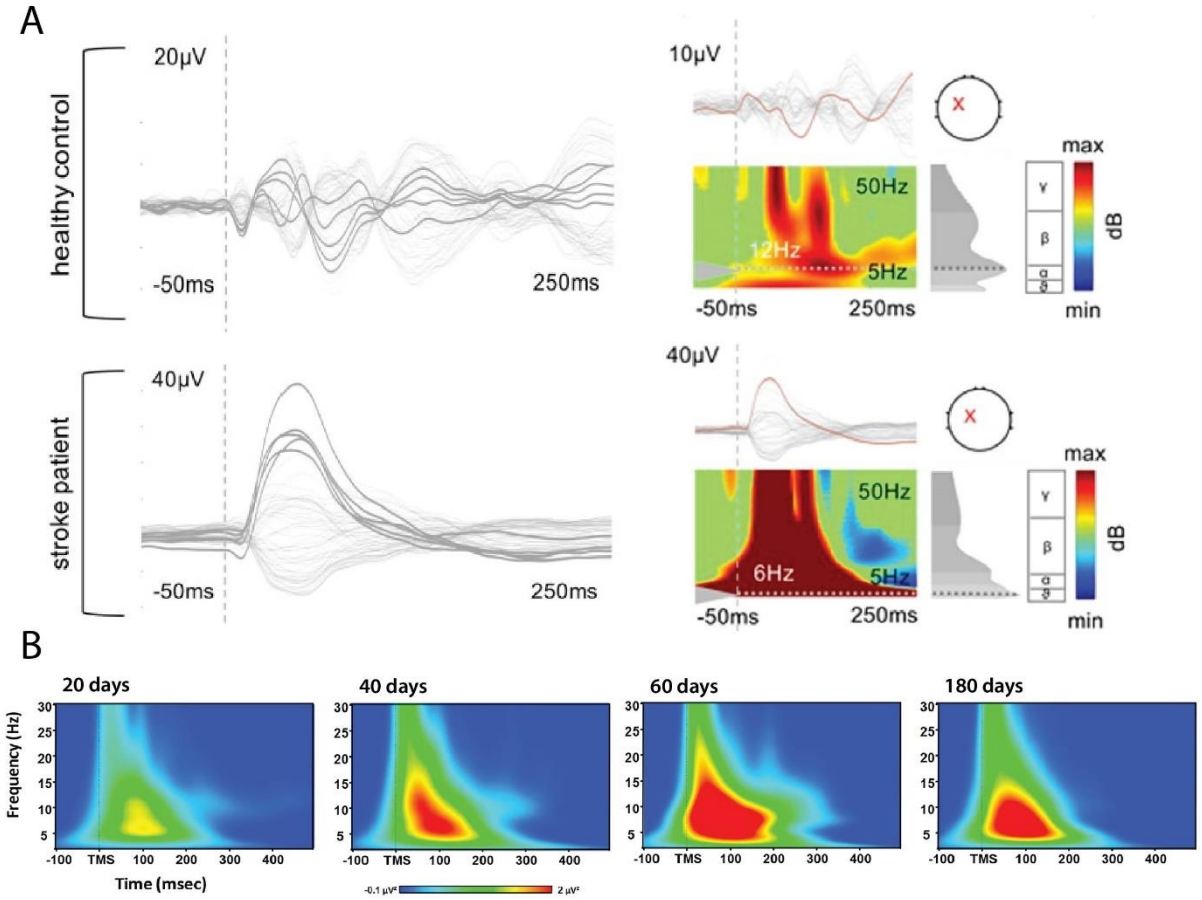


**Figure 1.6 TMS-EEG readouts from stroke patients. A.** Comparison between one acute stroke patient and one healthy control for the TMS-evoked potentials (left) and TMS-evoked oscillations (right). Note that the stroke led to a large and simple TEP and larger power in the lower frequencies in this representative patient. Adapted from (Tscherpel et al. 2020). **B.** Temporal evolution of averaged TMS-evoked oscillation from 13 chronic stroke patients. Note the increase of power in the low frequencies until 60 days post stroke while the power decreased at 180 days. Adapted from (Pellicciari et al. 2018).

Overall, combining both methods allows to gain more information on the physiological mechanisms underlying motor recovery after stroke. However, out of the existing studies using TMS-EEG in stroke, only two were longitudinal (Tscherpel et al. 2020; Pellicciari et al. 2018) and only one had more than 20 patients analysed (Tscherpel et al. 2020). There is thus a critical need for the replication of results. Combining innovative analyses with previously reported analyses would strengthen previous research and extend the current knowledge. Similarly, the use of validated stimulation paradigms such as SICI, allows to draw inferences based on the extensive TMS literature. This is of particular interest as, despite TMS-EEG allowing for the investigation of GABAergic activity in patients without

MEP, no study has yet applied SICI TMS-EEG in stroke patients. Doing so could help better untangle the specific role of $GABA_A$ receptor activity in motor function and post-stroke recovery. Furthermore, TMS-EEG coupling could inform on both the receptor's local and global status by focusing on specific post stimulation time windows as well as on specific cortical regions.

## 1.3 Thesis overview

The main goal of this thesis is to extend the current knowledge on the pathophysiology of stroke. In terms of mechanisms occurring after a stroke, we have described how the E/I balance rapidly changes over time post stroke, with sometimes unclear conclusions on its supportive or deterring function for motor recovery. We thus aspired to better understand the role of the exciting and inhibiting factors depending on the stage of recovery and on the motor recovery in each patient through a large, longitudinal and multidomain study, the TiMeS study.

### 1.3.1 Towards Individualized Medicine in Stroke - The TiMeS study

The aim of the TiMeS study is to address aforementioned challenges and to pave the way for personalized precision medicine through a multimodal approach (Fleury et al. 2022, in appendix). In TiMeS, an extensive multidimensional and longitudinal dataset was collected in a representative cohort of a stroke population in Switzerland, with the aim of identifying new biomarkers for patient stratification. More precisely, through multimodal analyses, we intended to achieve a better understanding of post-stroke recovery and to bring about potential new biomarkers which could eventually lead to a better stratification of patients and the personalization of new therapeutical approaches.
TiMeS targeted patients with upper-limb motor deficits at stroke onset and comprises measurements coming from synergistic state-of-the art systems neuroscience methods, such as structural and functional MRI, combined transcranial magnetic stimulation and electroencephalography (TMS-EEG), and electromyography (EMG). Furthermore, it contains an evaluation of behavioral outcomes such as motor function, but also of all other cognitive domains, in an attempt to have a complete overview of a patients' deficits and recovery. The assessment is longitudinal over the course of recovery, spread over four timepoints: acute (one week post stroke, T1), subacute (3 weeks, T2), early chronic (3 months, T3) and late chronic (1 year, T4). The project was implemented in collaboration with several clinical partners at the Clinique Romande de Réadaptation (CRR) in Sion, Switzerland. Patient recruitment took place at the Cantonal Hospital in Sion (HVS). After inpatient treatment at HVS, patients either went into rehabilitation at the CRR or at the Berner Klinik (BK) in Crans-Montana, or they returned to their homes, depending on their degree of impairment. Behavioral follow-ups took place at either of the rehabilitation

clinics (CRR or BK) for T2 and at the CRR for T3 and T4, whereas MRI and TMS-EEG measurements for all timepoints were conducted at HVS and the CRR, respectively. For an illustration, see **Figure 1.7**.

This thesis focused on the pathophysiological correlates of stroke and their relationship with motor recovery, using the TMS-EEG data of TiMeS. At the time of writing this thesis, 86 patients were included in the study and 221 timepoints were acquired (T1: 69; T2: 59; T3: 49; T4: 44 datasets, see **Figure 1.7**). The electrophysiological part of TiMeS consisted of 8 upper-arm muscles recordings (only at rest and during TMS stimulation), EEG resting states recordings (before and after the TMS-EEG) and TMS-EEG recordings. The TMS-EEG protocol consisted of two conditions: suprathreshold single pulse and SICI (paired pulse) with up to 180 trials per condition. Starting with patient number 66, we also included a third condition, the conditioning subthreshold pulse alone. At this point, the number of

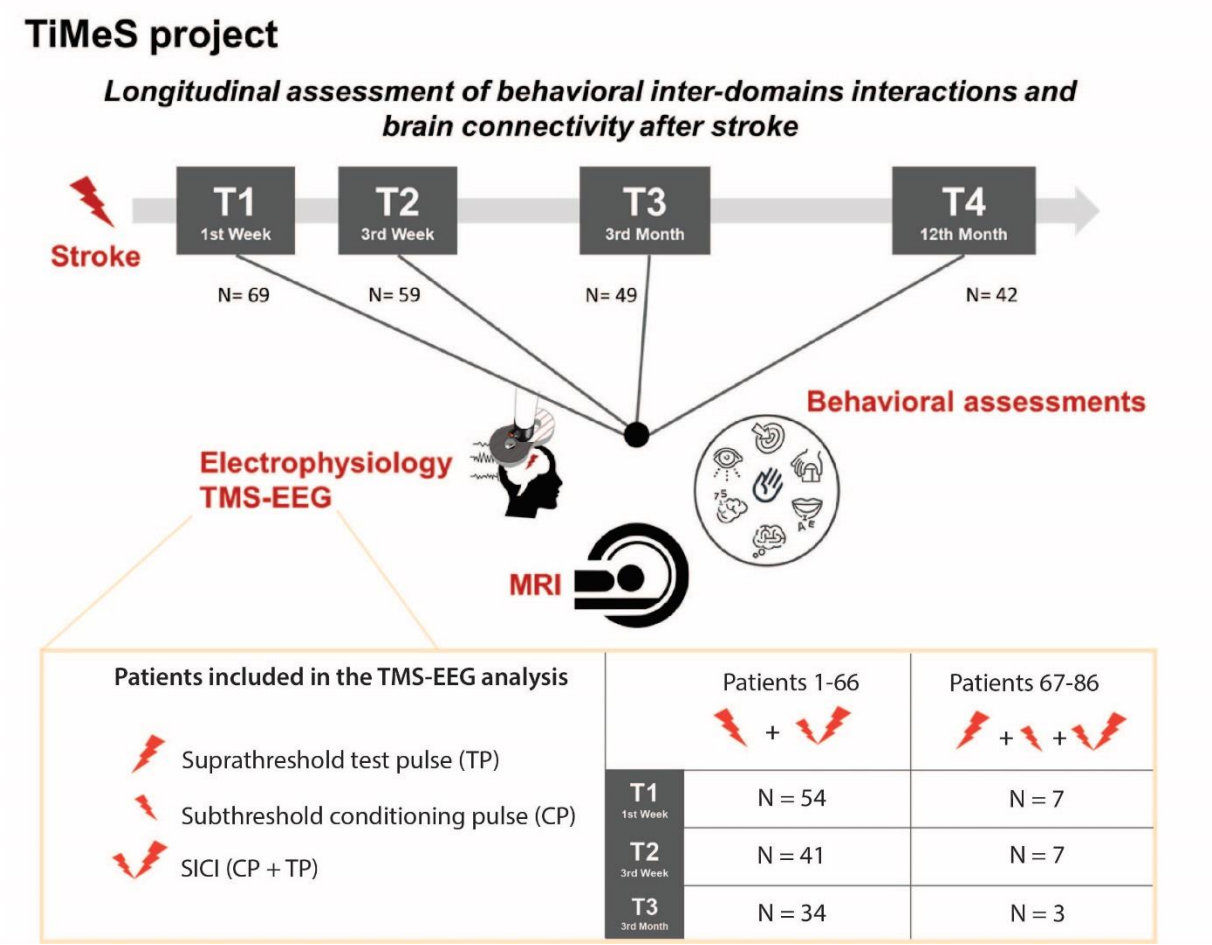


**Figure 1.7 Towards Individualized Medicine in Stroke (TiMeS) project**. N reflects the number of patients who completed the TMS-EEG part of the project at each timepoint **(top)** and the number of patients included in the analysis **(bottom)**. The difference between numbers correspond to the patients assessed after the analysis onset.

trials per condition was lowered to 120 to maintain the same experiment duration.

### 1.3.2 Longitudinal investigation of cortical disinhibition through TMS-EEG coupling

We described earlier how growing evidence point towards different roles of the excitation/inhibition (E/I) balance depending on the severity of stroke-related impairments. TMS-EEG can be a potent tool to examine the status of this E/I balance and the functional integration of the stimulated area with other regions of the network. Furthermore, we have seen that TMS-EEG already revealed important information on the time course of cortical reactivity and its relation with motor function (Cipollari et al. 2015; Pellicciari et al. 2018; Tscherpel et al. 2020; Palmer et al. 2019; Borich et al. 2016a). However, the exact role of the suggested $GABA_A$-mediated disinhibition seen in the acute/subacute stage is still insufficiently known. $GABA_A$-receptor activity might depend on the investigated area (perilesional or distant from the lesion), the time since the stroke and the initial and recovered impairments. In this thesis, we aimed at investigating the longitudinal status of the GABAergic system by coupling the SICI paradigm with EEG. The use of SICI TMS-EEG coupling in longitudinal studies is further justified as, in contrast to the high variability of MEPs, the TEPs are generally highly reproducible for a same subject (Pellicciari et al. 2018).

This thesis will thus present the evidence that we unveiled on the time course of the inhibition mechanisms through two studies. The first study investigated the E/I balance of the ipsilesional hemisphere at each time point by means of the investigation of cortical reactivity to a single pulse. We also examined the relationship between the E/I balance in the acute stage and motor recovery a few months later. In addition, this study investigated the status of the $GABA_A$-receptors activity through the SICI paradigm and its relationship with motor outcome. The second study aimed at unveiling whole-brain post-stroke reorganization through the analysis of induced oscillations, a proxy of high-order processes caused by non-linear interaction between neuronal populations. The latter phenomenon can also distinguish between GABAergic and glutamatergic activity and might thus help to clarify actors sustaining motor recovery.

# 2. STUDY I : Stroke Recovery Related Changes In Brain Reactivity Based On Modulation Of Intracortical Inhibition

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## 2.1 Abstract

The neuronal processes sustaining motor recovery after stroke are still largely unknown. Cortical excitation/inhibition dynamics have been suggested previously as a key mechanism occurring after a stroke. Their supportive or maladaptive role immediately after a stroke and during the process of recovery are still not completely understood; it is hypothesized that similar mechanisms (e.g., disinhibition) might yield differential functional roles depending on the stage after the stroke (e.g., acute vs. subacute vs. chronic) and the degree of deficit. Here, we used TMS-EEG to study brain reactivity, motor cortical excitability as well as intracortical inhibition and their impact on residual motor function and recovery longitudinally in a large cohort of stroke patients.

EEG responses evoked by TMS applied to the ipsilesional motor cortex (iMC) were acquired in 66 stroke patients in the acute (1-week), sub-acute (3-weeks) and chronic stage (3-months). Readouts of ipsilesional cortical reactivity, excitability and intracortical inhibition were drawn from TMS-evoked potentials and derived metrics. Residual function of the upper limb was quantified through a detailed motor evaluation.

A large proportion of patients, especially the most affected ones, exhibited large, simple TMS-evoked neuronal responses. Bayesian correlations revealed a link between higher excitability in iMC in the acute and stronger reduction of impairment determined by the upper extremity Fugl-Meyer (FM-UE) score in the early chronic stage. Furthermore, a decrease of this abnormally large response in the following months was related to better motor recovery. When investigating the underlying mechanisms with a focus on the intracortical GABAergic system, the present results revealed changes in intracortical inhibition in the first week after stroke that were associated with better recovery. Additionally, restoration of intracortical inhibition was present in patients, who recovered the most. Furthermore, the large component observed in a relevant part of the patients masks underlying mechanisms reflecting the importance of changes in intracortical inhibition for successful recovery.

The present results strongly support the view of a beneficial role of cortical disinhibition in the first week after a stroke that promotes neuronal plasticity and recovery. However, to sustain long-term motor recovery, cortical disinhibition needs to be transient with crucial restoration of normal levels of intracortical inhibition. TMS-EEG has the exciting potential to provide proxies to better understand underlying mechanisms of stroke recovery, to determine outcome and to help to tailor interventional treatment strategies to each patient based on the brain reactivity status.

## 2.2 Introduction

Although more knowledge is continuously gained on the neurobiological processes occurring in the first weeks and months after a stroke, the mechanisms sustaining motor improvement are still not fully understood (Stinear et al. 2020). There is substantial evidence that stroke induces functional plasticity partly driven by alterations in neuronal excitability (Carmichael 2012; Murphy et Corbett 2009; Ward 2017). Indeed, in the first phase after a stroke, strong release of glutamate is excitotoxic and contributes to cell death, which is counteracted by the inhibitory neurotransmitter GABA through cell hyperpolarization (Lai, Zhang, et Wang 2014). In mice, this phase in which inhibition in the perilesional area is beneficial lasts approximately 3 days (Clarkson et al. 2010), while its duration in humans remains unknown (Ward 2017). In the longer term, the effects are eventually reversed, so that a shift in the cortical excitatory-inhibitory balance towards excitation becomes beneficial for plasticity (Bavelier et al. 2010; Joy et Carmichael 2021). The resulting increase in excitability has been associated to the induction of structural plasticity, such as axonal sprouting (Carmichael 2003; Lee 2004; Carmichael et al. 2001) and dendritic spine production (Brown et al. 2007; 2009) as well as functional reorganization in motor regions (Bundy et Nudo 2019; Harrison et al. 2013; Cramer et Crafton 2006), which might constitute attempts to compensate for damaged structural and functional circuits (Murphy et Corbett 2009).

Collectively, this evidence suggests that a change in the balance between GABA- and glutamatergic signaling could be one pivotal mechanism at the origin of neural plasticity (Ward 2017; Liuzzi et al. 2014), paving the way toward functional reorganization and recovery after a stroke. Moreover, the phenomena underlying enhanced functional plasticity, which are described above, only occur during a limited amount of time after stroke and different mechanisms might take over in the later stages. Taken together, this points strongly to the need of longitudinal investigations of the time course of these mechanisms to better understand the factors sustaining stroke recovery, to predict the outcome and to unveil potential targets for therapy tailored to the specific phase of the recovery process.

Gathering information on the time course of the excitatory/inhibitory systems in vivo in humans after a stroke is challenging as only few non-invasive methods are currently available to determine these transmitter systems. By using Transcranial Magnetic Stimulation (TMS), one can assess the status of the cortico-spinal and intracortical excitability, and cortico-spinal tract (CST) integrity with the measure of Motor-Evoked Potentials (MEP) generated by stimulation of the primary motor cortex (Siebner et al. 2022). While the use of TMS have helped to investigate crucial mechanisms occurring after a stroke (Hummel et al. 2009; McDonnell et Stinear 2017; Smith et Stinear 2016; Talelli, Greenwood, et Rothwell 2006), a non-negligible subset of stroke patients presents a damaged CST that prevents the formation of MEP (Sato, Bergmann, et Borich 2015)

and thus the use of TMS to extract information on their central and peripheral reactivity. Combining TMS and multichannel- Electro-Encephalography (EEG) overcomes this limitation by offering the possibility to directly assess the neuronal properties of the lesioned motor regions, as well as the propagation of the evoked activity through functionally connected brain areas (Ilmoniemi et al. 1997; Bortoletto et al. 2015a), by studying TMS-Evoked Potentials (TEPs), brain reactivity and derived metrics. Interestingly, growing evidence shows that TEPs are pertinent markers for cortical excitability (Raffin et al. 2020; Rogasch et Fitzgerald 2013), and are modulated by neurotransmitters concentration such as dopamine, glutamate, or GABA (Casula et al. 2017; Casarotto et al. 2019)·(Darmani et Ziemann 2019). Therefore, TMS-EEG coupling is particularly suitable for the study of the central nervous system in stroke patients, also when severely affected (Keser et al. 2022).

TMS-EEG has been successfully applied in stroke. The initial component P30 was reported higher in stroke than in controls (Hordacre et al. 2020) and was related to poorer motor function (Gray et al. 2017). Moreover, a new electrophysiological profile involving large and simple evoked activity in the most affected patients was suggested (Tscherpel et al. 2020; Sarasso et al. 2020). This activity showed a similar profile as responses evoked in sleep and unresponsive wakefulness syndrome patients (Rosanova et al. 2018). GABA receptors are suggested to be the main actors involved in this electrophysiological pattern in sleep and unresponsive patients (Rosanova et al. 2018). However, it is unknown if they are also at the origin of the responses seen in stroke. For that matter, using TMS-EEG offers the benefit of the indirect investigation of inhibitory mechanisms (GABA-ergic) by applying paired-pulse Short-interval Intracortical Inhibition (ppTMS-SICI) TMS paradigm (Liuzzi et al. 2014; Hummel et al. 2009)·(Cash et al. 2017; Ferreri et al. 2011; Paus, Sipila, et Strafella 2001; Ulf Ziemann et al. 2015; Darmani et Ziemann 2019).

Here, we evaluated longitudinally (acute to chronic) a cohort of stroke patients with TMS-EEG. Using complementary TMS-EEG readouts allowed to capture individuals' electrophysiological profiles and their association with motor function at each stage and during the process of motor recovery. Additionally, by using for the first time ppTMS-SICI in TMS-EEG in stroke patients, we investigated the influence of changes of the excitatory/inhibitory balance on the generation of abnormal responses observed in patients and its relationship with residual motor function, impairment and recovery.

## 2.3 Materials and methods

### 2.3.1 Patient population

66 stroke patients (Age: 68.2±13.2yo, 21 females) were enrolled in the study after being admitted at the cantonal hospital in Sion, Switzerland. Patients were recruited during the first week post stroke, inclusion criteria included being older than 18yo, motor deficits of the upper limb and absence of contraindications for magnetic resonance imaging (MRI) or TMS. Patients with first-ever and recurrent strokes were included. With the aim of determining factors specific to recovery, the subset of patients including patients showing motor improvement from the acute stage (TP1) to the following stages was defined as the recovering group (RG, n=40). The study was conducted in accordance with the Declaration of Helsinki and approved by Cantonal Ethics Committee Vaud, Switzerland (2018-01355), written informed consent was obtained.

**Table 2.1 Patients' characteristics.**

| Gender | Handedness | Hemisphere affected | RMT TP1 (% MSO) | FM UL TP1 (/60) | FM UL TP2 (/60) | FM UL TP3 (/60) | Days post stroke TP1 | Days post stroke TP2 | Days post stroke TP3 |
|---|---|---|---|---|---|---|---|---|---|
| 19 F / 47 H | 55 right-handed / 8 ambidextrous | 32 Left / 34 Right | 43 ± 9.8 | 46.8 ± 19 | 50.6 ± 17 | 55.1 ± 12 | 6.6 ± 2.3 | 26.9 ± 4.9 | 98.1 ± 8.6 |

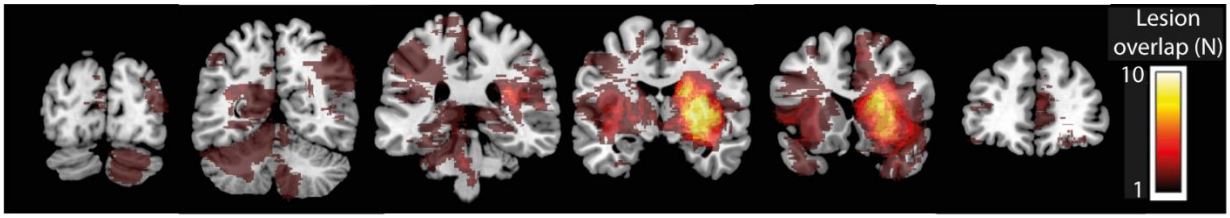


**Figure 2.1 Lesion heat map of the patients in the acute stage (TP1), N = 54.** Please note that few patients of the cohort did not undergo a MRI at the acute stage.

### 2.3.2 Protocol design

Patients were recruited during the first week after the stroke. They underwent three sessions of assessments, at one-week post stroke, three weeks, three months (**Figure 2.2B**). Each session comprised structural and functional MRI, resting state EEG and TMS-EEG, as well as a comprehensive battery of cognitive and motor evaluations. For more details on the protocol and analysis, the reader might refer to Fleury et al. (2022, in appendix).

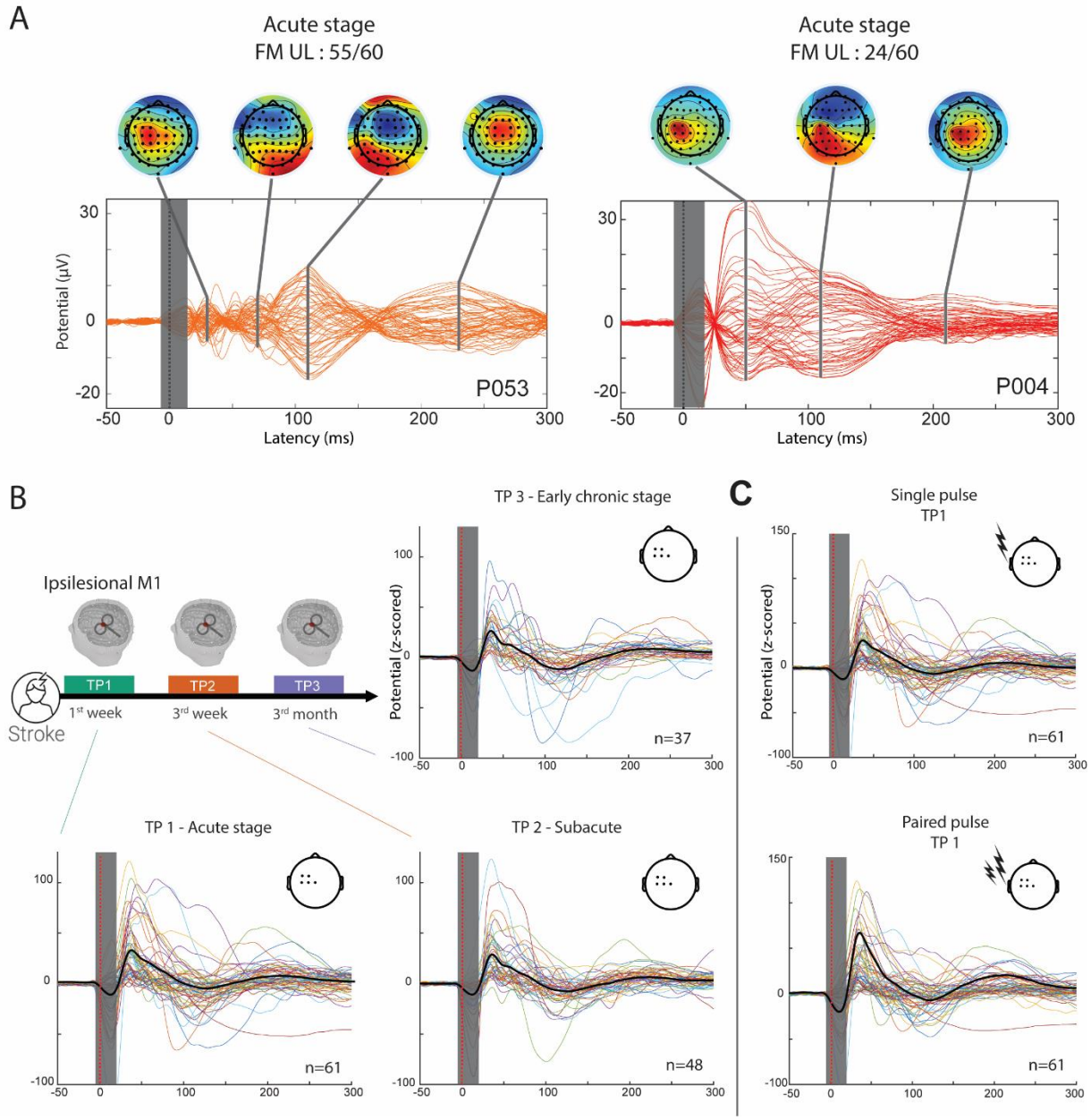


**Figure 2.2 Evoked cortical responses in stroke patients after the stimulation of ipsilesional motor cortex. A.** Examples of TMS-evoked potentials in two representative patients in the acute stage with different initial motor deficit. The signal amplitudes (µV) of the 62 EEG electrodes are overlaid in a butterfly view. Topographies of the evoked activity are plotted at specific latency indicated by black bars. The grey rectangle represents the time window interpolated around the TMS pulse (t = 0ms) not taken in the analysis. Note the difference in both maximum amplitude and spatial distribution of the signals, with the most affected patients exhibiting a simpler, larger and more spatially restricted activity, especially during the first 100ms. **B.** Protocol design and local TMS-evoked potentials from the ipsilesional electrodes close to the stimulation site, across the three timepoints, for each patient (one colored line represents one patient). For representative purpose, the amplitudes were z-scored according to each patient's baseline [-200 to -5ms]. Please note the inter-patients' variability in the evoked response, hampering the use of latency-specific component analysis. **C.** Local TEP

after a single pulse (top) or a paired-pulse (PP, bottom) stimulation, for each patient (one colored line represents one patient). Please note the intra-patients' variability in the evoked pattern depending on the stimulation condition used.

### 2.3.3 Behavioral assessment

The behavioral evaluation battery comprised of the (i) Fugl-Meyer of the upper limb (FM-UL, max 60 points without reflexes) and each of its subscores: the upper extremity (FM-UE, max 32 points), the hand and the wrist (Fugl-Meyer et al. 1975). For each hand, the following was assessed: (ii) the maximum fist, key and pinch force assessed in three trials and performed using a JAMAR® hydraulic hand dynamometer (Mathiowetz et al. 1984); (iii) the Box and Blocks (Mathiowetz, Volland, et al. 1985) (BnB); (iv) the nine-hole peg (Mathiowetz, Weber, et al. 1985) (9HP). For every motor score, with the exception of the Fugl-Meyer, a ratio between the performance of the affected and non-affected hand (affected/unaffected) was used for the analyses.

### 2.3.4 TMS-EEG recordings

Neuronavigation (Localite GmbH, Bonn, Germany) was used to control and record positions of the TMS coil, as well as the EEG electrodes' position with respect to each individual T1-weighted MPRAGE scan.
EEG recordings were acquired using a 64 passive electrodes EEG BrainCap-MR (BrainVision LLC, North Carolina, USA) with the reference electrode at FCz and the ground at AFz. The experiment was performed in a faraday cage (IAC Acoustics, Illinois, USA) to limit interference, such as power line. Electrode impedance was targeted below 5kOhm. Data were recorded with a sampling rate of 5000 Hz, a resolution of 0.5 μV, a high cutoff of 1000 Hz and DC as low cutoff.

### 2.3.5 Experimental procedure

At each TMS-EEG session, biphasic pulses were delivered over the FDI hotspot of the affected arm at an intensity evoking a MEP targeted between 0.5 to 1 mV (S1mV). If no visible MEP (<50μV) was elicited at maximal stimulator output, the intensity was defined from the unaffected hemisphere and the target set anatomically based on neuronavigation.
Two types of stimulation were applied: a single-pulse (SP) at the supra-motor threshold intensity fixed earlier or a paired-pulse (PP) comprised of a conditioning pulse at 80% of the resting Motor Threshold (rMT) followed by an SP set at the S1mV, with an inter-stimulus interval of 3 ms.
For each patient and timepoint, a maximum of 180 SP and 180 PP trials were applied in six separated blocks (mean 169, minimum 80). During each block, the order between

conditions (SP or PP) was pseudo-randomized. Pulses were automatically delivered every 4 seconds with a random 25% jitter.

### 2.3.6 Data analysis

EEG data were analyzed on Matlab (MathWorks, Massachusetts, USA) with EEGLAB (Delorme et Makeig 2004) and following an established pipeline (Rogasch et al. 2017) on the TESA toolbox. Epoch cut at -500 ms and +1000 ms around stimulation were extracted and the data around the TMS pulse [-5,+20 ms] was removed. Two rounds of ICA were performed to remove the remaining TMS artifact and other artifacts, such as eye blinks or large muscle activity (mean number of ICA component removed: 8.5). Band-pass and band-stop filters (1-60Hz, 48-52Hz) and a re-reference to the average channel followed. If one ICA component exhibited a very localized activity of large amplitude, centered around the site of stimulation, and extremely consistent over trials, this component was flagged as “large component” (**Figure 2.3B**). Two datasets were then created, with and without the large component. TMS evoked potentials (TEPs) were computed for each patient and timepoint by averaging the signal across trials and current methods to determine their complex characteristics were applied (Tscherpel et al. 2020; Bridwell et al. 2018; Raffin et al. 2020).
In that view, we computed the local mean field power (LMFP, **Figure 2.3A**) (Casarotto et al. 2013) based on the five electrodes closest to the stimulation target over iMC (FC3-FC1-C3-C1-Cz or FC4-FC2-C4-C2-Cz depending on the lesioned hemisphere). To quantify early activity power, the LMFP was summed in the first 80 ms after the interpolated part.
Regression quality scores (RQSs) were computed using the method presented in (Raffin et al. 2020). In short, the local TEPs xi(t) were derived for each timepoint i, each trial k (from 1 to n trials), and each patient, from +20 to +80 ms, to exclusively encompass the early components of the evoked activity. Then, linear regressions of the local TEPs xi(t) were performed for each timepoint i on single trials sjk(t) extracted from each timepoint j and trial k, so that:

$sjk(t)=\beta ijk*xi(t)+\varepsilon(t)$, $t\in[20, 80]$ms, with $(i, j)\in\{TP1, TP2, TP3\}$.

RQS was finally defined as the t-statistic associated to the local TEP xi factor, averaged across trials for each timepoint and patient.

The term “paired RQS” (pRQS) refers to pairs where i=j, i.e., where the regressed TEP xi and single trials sj are taken from the same timepoint. pRQS allows assessing reactivity level and response stability of a particular site (Raffin et al. 2020). At similar stimulation intensities, the higher the pRQS on M1 at timepoint i, the higher the reactivity and stability of M1 response on timepoint i is. On the other hand, the term “unpaired RQS” (uRQS)

refers to pairs where i≠j, i.e., where the TEP xi computed on timepoint i is regressed on single trials of another timepoint j. uRQS allows assessing the level of similarity between response dynamics of timepoint i and j. The higher the uRQS between timepoints i and j, the higher the similarity in response dynamics between timepoints i and j is.

In order to quantify the complexity of the signal, we measured the number of deflections in the first 200 ms of the local TEP from the electrode C3 or C4 (Tscherpel et al. 2020). For that purpose, an automated detection of significant peaks was used. Using the find_peaks function from the scipy python toolbox, we calculated the average peak-to-peak amplitude from every detected peak in the 200 ms baseline before the TMS pulse. Any peak post-TMS higher than 2 standard deviations from this average was considered as significant.

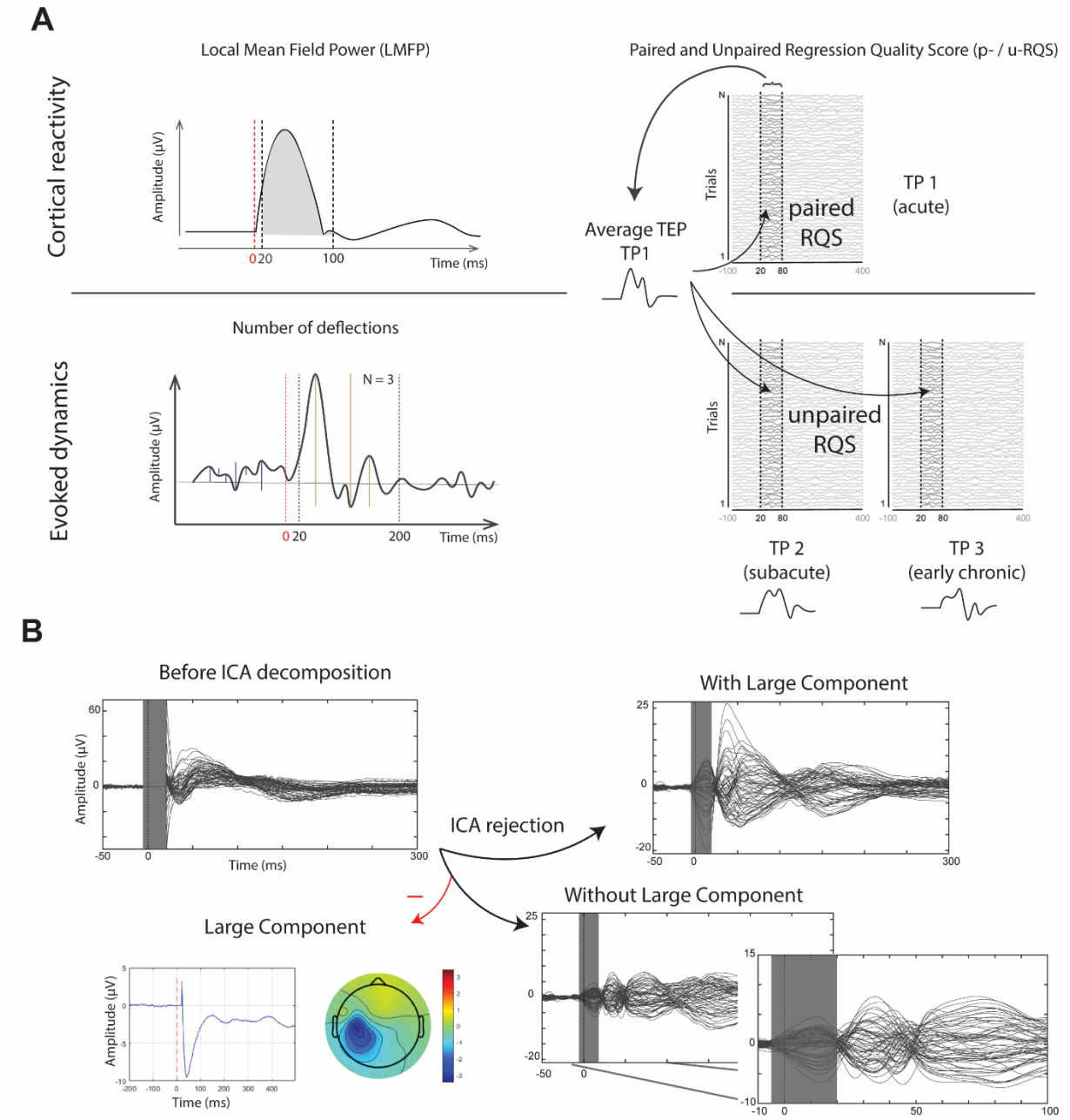


**Figure 2.3 TMS-EEG cortical reactivity and evoked dynamics readouts and removal of the large component**. **A.** Schematic representation of the cortical reactivity (top) and evoked dynamics (bottom) readouts. Cortical reactivity was captured by both the local mean field power (LMFP, top left) and the paired regression quality score (pRQS, top right). The LMFP was calculated by taking the area under the curve of the rectified signals over the local electrodes (see Materials and Methods) during the first 80ms after the interpolated window. The pRQS quantify the cortical reactivity and response stability by calculating the quality of regression of the local TEP into it corresponding trials, in each patient (see (Raffin et al. 2020)). Evoked dynamics were represented by the means of the number of deflections (bottom left) and the unpaired RQS (uRQS, bottom right). The number of deflections in the first 200ms was

computed automatically as the number of peaks higher than two standard deviations from the mean amplitude in the baseline. The uRQS quantifies the similarity in evoked dynamics by computing the average quality of regression of the local TEP of one timepoint into trials of another timepoint. **B.** To investigate if the large component could mask relevant neuronal activity, the component, when visually detected, was removed during the second round of ICA decomposition, which leads to the creation of two datasets, with and without the large component.

### 2.3.7 Statistics

All statistical analyses were performed using the JASP software (JASP Team (2022), Version 0.16.0.0). When referring to the level of evidence toward $H_1$ or $H_0$, we classified the Bayes factor (based on the cut-off values defined by Jeffreys (1998)). In addition, the Bayesian 95% credible interval are reported for each computed parameter. The TMS-EEG readouts across timepoints were evaluated using Bayesian ANCOVAs. Each model comprised of the readout as dependent variable, the timepoints as fixed factors, the patients as random factors and the FM-UL and the supra-threshold TMS intensity as covariates. Additionally, at each timepoint we performed Bayesian correlations between each pair of TMS-EEG readouts and behavioral scores. As the distributions of the motor scores in our patient cohort were not normal, Kendall's nonparametric correlations were performed.

Evolution between timepoints was measured as a percentage of change ([(TPx–TPy)/TPy]*100, with x>y) for each behavioral score and electrophysiological readout. In order to evaluate the influence of the conditioning pulse in the paired-pulse paradigm, we calculated the arithmetic difference between PP and SP. In this way, SP refers to results in the single pulse condition, PP to results in the paired-pulse condition and SICI to results when looking at the subtraction scores.

### 2.3.8 Voxel lesion TEP mapping

Voxel lesion symptom mapping (VLSM) was performed in order to investigate the relationship between the different TMS-EEG readouts and lesion sites. This analysis was conducted using T1 MPRAGE lesion maps with the NiiStat toolbox (https://www.nitrc.org/projects/niistat/). The number of permutations was fixed to 2000. Only voxels presented in at least 10% of the patients were considered. The analysis was restricted to regions of interest from the AAL (Tzourio-Mazoyer et al. 2002) and CAT (Catani et Thiebautdeschotten 2008) atlases.

## 2.4 Results

Overall, TMS-EEG recordings were performed in 60 patients at TP1 (6.7 days post stroke ±2.3), 49 at TP2 (26.9±4.9 days) and 43 at TP3 (98.1±8.6 days). Not all patients completed every session due to time constraints with clinical evaluations, patient unavailability, Covid or the introduction of an exclusion factor, such as benzodiazepine intake. All the patients went through the protocol without reporting any adverse effects.

### 2.4.1 Cortical reactivity of stroke patients

While most of the patients, especially the mildly impaired, exhibited a complex response, some patients showed a larger and simpler reactivity pattern (**Figure 2.2A**). As a means to assess the amplitude and stability of abnormal cortical reactivity, we calculated the LMFP and pRQS of the early response (<100 ms). The dynamical properties of this abnormal cortical reactivity pattern were assessed using both the calculation of the number of evoked deflections and the uRQS.

#### 2.4.1.1 Motor cortical reactivity level, motor impairment and recovery

The Bayesian ANCOVA revealed strong evidence for an effect between the LMFP and the FM-UL ($BF_{10}$ = 21), with larger power being associated with reduced upper limb scores (95% credible interval of the parameter: [-17.6, -1.5]). However, the level of statistical evidence was inconclusive regarding timepoints ($BF_{10}$ = 0.98, **Figure 2.4A**); there was an extreme evidence for an effect of the TMS intensity used ($BF_{10}$ = $1.8.10^4$) with higher LMFP linked with higher intensity used (95% credible interval: [3.4, 21.8]).
Furthermore, for the RG patients, higher LMFP in TP1 was related to a positive change of FM-hand scores between TP1 and TP3 (Kendall's tau ∈ [0.11 0.61], $BF_{10}$=12, see also **Figure 2.4A** (middle)). However, the decrease in power between the two timepoints was associated with a better improvement of FM-UE (Kendall's tau ∈ [-0.69 -0.16, $BF_{10}$=31). Overall, an initial high LMFP associated with a greater decrease over time was seen in patients improving the most. The same relationship was found with only moderate evidence for $H_1$ when pooling all the patients.
As for response stability, pRQS revealed no evidence regarding an effect of timepoints, nor of FM scores ($BF_{10}$ between 0.3 and 3), but extreme evidence of an effect of the TMS intensity ($BF_{10}$>$3.10^4$). Thereby, higher intensities used to stimulate the cortex were linked with greater inter-trials stability.

#### 2.4.1.2 TMS evoked dynamics of the motor cortex and motor impairment and recovery

Regarding the number of deflections in the early part of the evoked response, no effect was found for the factors timepoints, FM score or TMS intensity. Similarly, no evidence of relationships between the number of deflections and any of the motor scores was found. VLSM with the number of deflections in the acute stage revealed an association with the internal capsule, according to the CAT atlas (**Figure 2.4B**). Thus, simpler responses, characterized by fewer deflections, were predominantly related with lesions in the CST.

ANOVA investigating the evoked dynamics in different timepoints, captured by uRQS, revealed extreme evidence for an interaction effect between the factors reference TEP and single trials activity ($BF_{10}>1.10^8$). Post-hoc tests showed strong evidence for a difference between timepoints when using the TEP from TP1 (TP1 vs. TP2, $BF_{10}=44$; TP1vs.TP3, $BF_{10}=23$) and no evidence for a difference or absence of difference between timepoints when using TEP from the other timepoints ($BF_{10} \in [0.24\ 1.3]$) (**Figure 2.4C**). There was no further evidence for presence or absence of any other correlations between TMS-EEG readouts after a single pulse and motor scores.

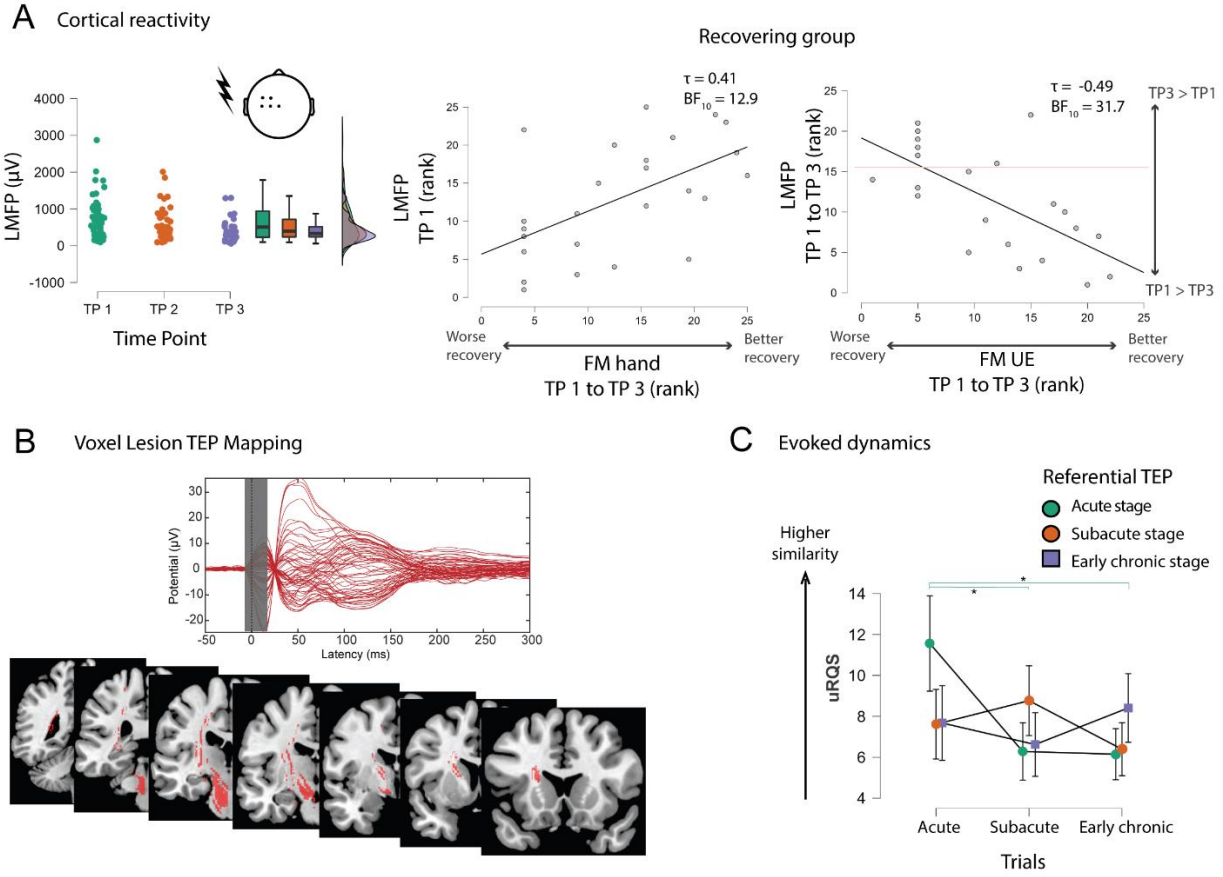


**Figure 2. 4 Longitudinal evolution of cortical reactivity and evoked dynamics and their association with motor improvement**. **A.** The ANCOVA showed a main effect of the Fugl-Meyer (FM) scores, but no effect of time point (left). In the recovering group, LMFP in the acute stage was associated with improvement of the FM hand between the first week (TP1) and the 3rd month (TP3, n = 25, middle) and the reduction of LMFP in TP3 was related with better improvement in FM of the upper extremity (n = 18, right). Kendall's correlations were performed, thus values in the graphs correspond to ranks, some of which may overlap. Motor improvement was calculated as ((TP3 – TP1) / TP1) *100. **B.** Association between TMS-EEG parameters and lesions maps were assessed using a Voxel Lesion Symptoms Mapping. The number of deflections was found negatively correlated with lesions in the ROI of the internal capsule (depicted by red voxels). **C.** Post-hoc tests on uRQS revealed strong evidence for a difference in evoked dynamics between TP1 and both TP2 and TP3 when regressing the average signal of TP1 to trials in each timepoints. There was no evidence for a difference between timepoints when taking as reference the average signal from TP2 and TP3. Stars indicate a $BF_{10} > 10$.

### 2.4.2 Evaluation of motor intracortical inhibitory circuits activity

The paired-pulse paradigm allowed to assess intracortical inhibitory mechanisms ($GABA_A$-ergic). Furthermore, since some patients exhibited an abnormally large activity after TMS that might have hidden weaker neuronal activity, intracortical inhibition was also studied after removing this component.

#### 2.4.2.1 Intracortical inhibitory circuits reactivity of the motor cortex and motor impairment and recovery

When investigating the GABAergic system's status, the relationship between acute cortical reactivity and motor recovery was increased. The Bayesian ANCOVA revealed very strong evidence for an effect of the FM-UL ($BF_{10}$=41) and lower, however still extreme, evidence for an effect of the TMS intensity ($BF_{10}$=1102). The Bayesian correlations also showed strong evidence for a link between acute LMFP in PP and improvement in FM hand and 9HP (tau ∈[0.15 0.55], $BF_{10}$=61; tau ∈ [-0.55 -0.14], $BF_{10}$=41) after 3 months for all patients. When considering only the RG, evidence for $H_1$ became extreme with FM hand (FM hand, tau ∈ [0.21 0.71], $BF_{10}$=148; 9HP, tau ∈ [-0.68 -0.18], $BF_{10}$=64) and extended to the FM wrist (tau ∈ [0.10 0.61], $BF_{10}$=10).
Finally, the analysis of the pRQS of PP condition still revealed no evidence for an effect of timepoints nor of FM scores ($BF_{10}$≈0.5), but extreme evidence – yet much weaker than for SP - for a link with TMS intensity ($BF_{10}$=4372). When analyzing SICI data, the evidence for a link with TMS intensity also dropped to an inconclusive level ($BF_{10}$=0.4). No evidence of relationships between the pRQS and any of the motor scores was found in any of the conditions.

#### 2.4.2.2 TMS evoked dynamics of the inhibitory system in relation to motor impairment and recovery

Patients recovering more exhibited fewer deflections in the acute stage and a greater increase in the complexity of the evoked signal along time post stroke.
First, as opposed to the SP condition where no evidence of a relationship was found between the number of deflections and motor scores, the number of deflections evoked by a PP in the early chronic stage (TP3) was linked with the key force (Kendall's tau ∈ [0.1 0.52], $BF_{10}$=12). More deflections were associated with higher key force ratio between affected and non-affected hands. On top of this relation with motor function at TP3, the number of deflections in the acute stage (TP1) was also associated with motor improvement after 3 months post stroke. Indeed, deflections at TP1 were related with improvement in FM scores of the hand and wrist at T3 (respectively tau ∈ [-0.6 -0.19], $BF_{10}$=231; tau ∈ [-0.51 -0.1], $BF_{10}$=14) (**Figure 2.5A**, left). Interestingly, greater improvement of FM hand was related with increase in the number of deflections between TP1 and TP3 (tau ∈ [0.15 0.60], $BF_{10}$=50) (**Figure 2.5A**, right).
Second, as previously shown in the SP analysis, the uRQS analysis in PP demonstrated an atypical dynamical signature in TP1 compared with the following timepoints (interaction effect: $BF_{10}>6.10^7$; substantial to strong evidence for a difference between TPs only by taking TP1 as a reference TEP, $BF_{10}$ ∈ [ 9 12], $BF_{10}$ ∈ [0.2 0.9] otherwise).

#### 2.4.2.3 Unmasked complementary intracortical inhibition mechanisms

The association between the intracortical inhibition effect on LMFP in the acute stage and motor improvement was only found when removing the large component. This component was detected in 34/60 (57%) datasets at TP1, 27/49 (55%) at TP2 and 17/43 (37%) at TP3. The analysis of SICI revealed interesting results for the whole cohort as well as for the RG, as follows. First, in the RG, moderate evidence was found for an effect between LMFP in PP at TP1 and fist force increase between TP1 and TP2 (tau ∈ [0.08 0.56], $BF_{10}$=8).When investigating the dissimilarity between LMFP in SP and in SICI, removing the Large Component revealed a link between LMFP in SICI at T1 and increase in scores between TP1 and TP2 for the FM-UE and FM hand (tau ∈ [0.09 0.55], $BF_{10}$ =10; tau ∈ [0.13 0.59], $BF_{10}$=24 respectively). Even greater effect was found for the FM hand when considering every patient (tau ∈ [0.13 0.50], $BF_{10}$=46). Strong to extreme evidence with the evolution of FM UL, FM hand and 9HP between TP1 and T3 were also revealed when including the whole population of patients (FM UL, tau ∈ [0.11 0.51], $BF_{10}$=18; FM hand, tau ∈ [0.21 0.62], $BF_{10}$=677; 9HP, tau ∈ [-0.56 -0.15], $BF_{10}$=66, **Figure 2.5B**). In the RG, similar evidence was found with improvement between TP1 and TP3 in pinch and key forces, 9HP as well as in FM hand and wrist (Pinch, tau ∈ [0.09 0.60], $BF_{10}$=8; Key, tau ∈ [0.09 0.60], $BF_{10}$=9; 9HP, tau ∈ [-0.65 -0.15], $BF_{10}$=31; FM hand, tau ∈ [0.13 0.50], $BF_{10}$=76; FM wrist, tau ∈ [0.09 0.60], $BF_{10}$=9, **Figure 2.5C**).

The evaluation of the effect of the SICI paradigm on response stability (pRQS) showed that greater motor improvement was associated with an initial abnormally stable response in PP compared to SP and with a return to a more stable response in SP than in PP in the following timepoints. In details, the ANCOVA revealed no evidence for a link with FM-UL or with TMS intensity through the different timepoints ($BF_{10} \approx 0.2$). However, we found moderate evidence supporting that the short-term (TP2-TP1) changes of the SP-PP difference was linked with better improvement in FM-UE at TP2 and TP3 (tau ∈ [0.07 0.47], $BF_{10}$=7.4; tau ∈ [0.09 0.54], $BF_{10}$=8.7 resp.), in grip force at TP3 (tau ∈ [0.08 0.54], $BF_{10}$=7), and in pinch force at TP3 (tau ∈ [0.08 0.55], $BF_{10}$=7.7), for every patient. The evidence was stronger and concerned a larger number of motor scales when focusing on the recovering group (RG): we found moderate to strong evidence supporting that short-term changes of the SP-PP difference were linked with better improvement in FM-UL at TP3 (tau ∈ [0.1 0.68], $BF_{10}$=8.8), in FM-UE at TP2 and TP3 (tau ∈ [0.1 0.59], $BF_{10}$=9.6; tau ∈ [0.07 0.66], $BF_{10}$=5.7 resp.), in FM wrist at TP3 (tau ∈ [0.06 0.65], $BF_{10}$=4.6), in key force at TP3 (tau ∈ [0.17 0.7], $BF_{10}$=13, **Figure 2.5D** left).

As for the uRQS, when comparing the dynamics at TP1 and TP2 in PP, strong evidence was found with long-term motor improvement at TP3 (FM hand, tau ∈ [-0.66 -0.07], $BF_{10}$=5.8; 9HP, tau ∈ [0.09 0.67], $BF_{10}$=7.3) (**Figure 2.5D** right). Stronger motor

improvements between the acute stage and the following timepoints were linked with greater differences in the pattern of the PP-evoked activity along time.

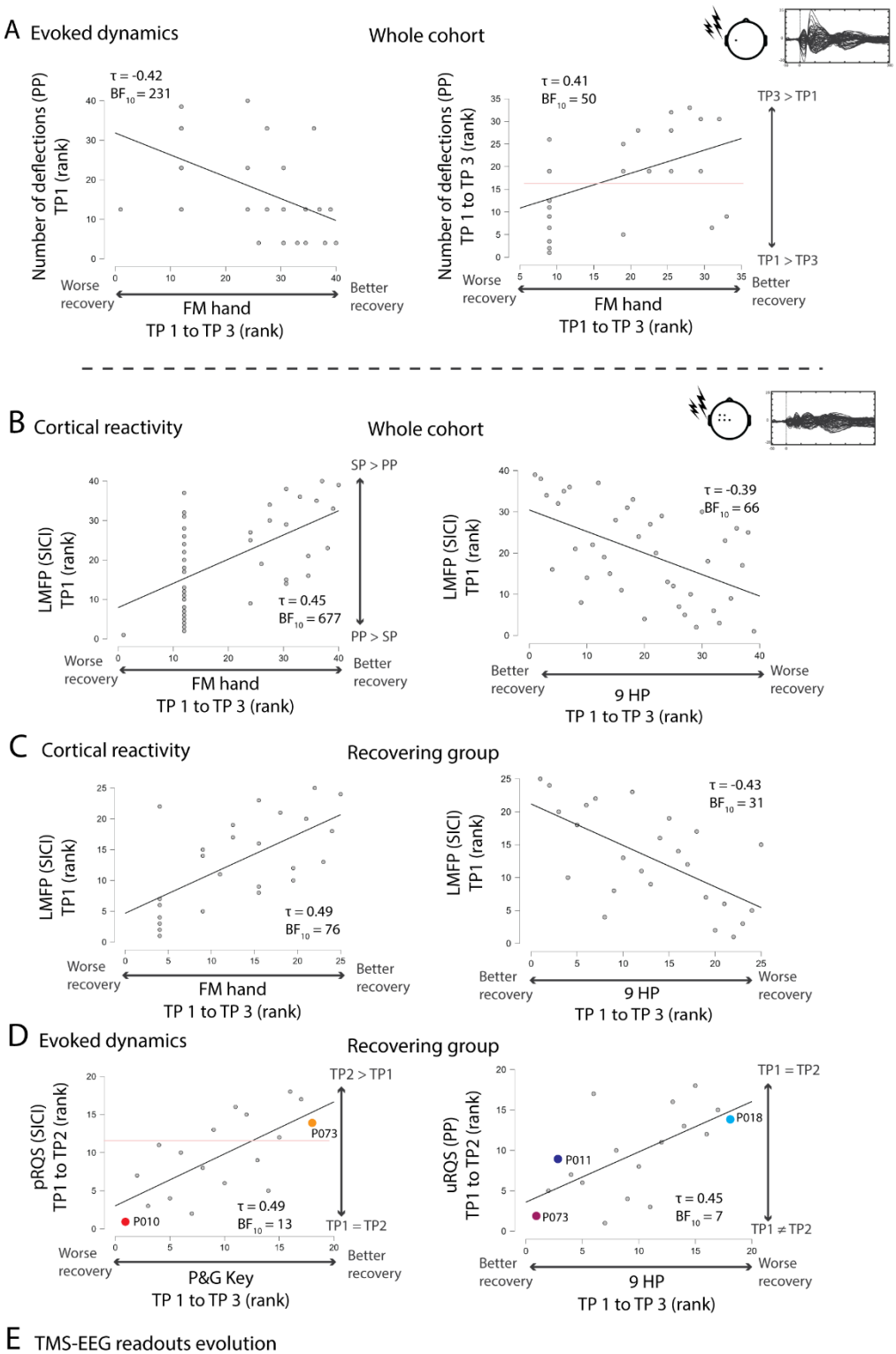
A Evoked dynamics
Whole cohort
τ = -0.42
BF10 = 231
Number of deflections (PP)
TP1 (rank)
Worse recovery
Better recovery
FM hand
TP 1 to TP 3 (rank)
τ = 0.41
BF10 = 50
Number of deflections (PP)
TP 1 to TP 3 (rank)
TP3 > TP1
TP1 > TP3
Worse recovery
Better recovery
FM hand
TP1 to TP 3 (rank)
B Cortical reactivity
Whole cohort
LMFP (SICI)
TP1 (rank)
SP > PP
PP > SP
τ = 0.45
BF10 = 677
Worse recovery
Better recovery
FM hand
TP 1 to TP 3 (rank)
τ = -0.39
BF10 = 66
LMFP (SICI)
TP1 (rank)
Better recovery
Worse recovery
9 HP
TP 1 to TP 3 (rank)
C Cortical reactivity
Recovering group
LMFP (SICI)
TP1 (rank)
τ = 0.49
BF10 = 76
Worse recovery
Better recovery
FM hand
TP 1 to TP 3 (rank)
τ = -0.43
BF10 = 31
LMFP (SICI)
TP1 (rank)
Better recovery
Worse recovery
9 HP
TP 1 to TP 3 (rank)
D Evoked dynamics
Recovering group
pRQS (SICI)
TP1 to TP2 (rank)
TP2 > TP1
TP1 = TP2
P073
P010
τ = 0.49
BF10 = 13
Worse recovery
Better recovery
P&G Key
TP 1 to TP 3 (rank)
uRQS (PP)
TP1 to TP2 (rank)
TP1 = TP2
TP1 ≠ TP2
P018
P011
P073
τ = 0.45
BF10 = 7
Better recovery
Worse recovery
9 HP
TP 1 to TP 3 (rank)
E TMS-EEG readouts evolution
P010
P073
SP
TP 1
PP
TP 2
Trials
Latency (ms)
TP 1
TP 2
TP1 to TP2 :
P073
uRQS: -55%
HP9: -84%
P011
uRQS: -13%
HP9: -83.7%
P018
uRQS: +4.9%
HP9: +18%

**Figure 2.5 Paired-pulse stimulation revealed association between intracortical inhibition activity and motor recovery. A.** The number of deflections evoked in the PP condition in the acute stage was associated with better improvement of the FM hand (n = 40), left panel. Increase in the number of deflections between TP1 and TP3 was found to be related to greater improvement in hand function (n = 33), right panel. **B.** Removing the large component revealed associations with motor recovery. The LMFP difference in the acute stage (TP1) between the single-pulse (SP) and paired-pulse (PP) conditions, called here SICI, was associated with better improvement of FM hand at 3 months post stroke (TP3), in the whole cohort of patients (n = 40), left panel. Similar relationship was found between LMFP in TP1 and improvement of Nine hole-peg (9HP) performance between TP1 and TP3 (n = 39), right panel. **C.** When considering only the subgroup of patients exhibiting a change of performance between time points (n = 25), called the recovering group, the two previous relationships are still present with very strong evidence. **D.** Increase in pRQS in SICI between the first and third weeks was related to increase in key force at 3 months post stroke (n = 18), left panel. Please note that pRQS (SICI) corresponds to pRQS(SP) – pRQS(PP). Pale horizontal lines indicate the direction of the difference between timepoints. Unpaired RQS in PP between TP1 and TP2 showed an association with improvement in 9 Hole peg (9 HP) (n = 18), right panel. The higher the ΔuRQS percentage, the higher the similarity between activities. Kendall's correlations were performed, thus values in the graphs correspond to ranks, some of which may overlap. **E.** Evolution of the TMS-evoked signals in few representative patients. Plots of TEP after a PP in TP1 and TP2, left panel. Respective evolution in uRQS and 9HP are expressed below each signal. Please note that a lower value of uRQS(PP) between timepoints corresponds to a lower similarity of the evoked signals dynamics between timepoints. Amplitude of the evoked signal in each trial, for both conditions, at TP1 and TP2 for two patients, right panel. Note that, whereas patient P018 did not present any longitudinal change in inter-trials stability between SP and PP, patient P073 showed an abnormal high stability in PP compared to SP at TP1, followed by a regularization of this contrast at TP2 (see text).

## 2.5 Discussion

The present results show that moderately to severely affected patients exhibited cortical disinhibition in the acute stage associated to the degree of recovery. Furthermore, motor recovery during the following months is paralleled by the restoration of normal levels of intracortical inhibition. The resulting stroke-related disruption in cortical reactivity was defined in the most affected patients by larger and simpler TMS-evoked potentials, most likely reflecting a hyperexcitability state of the ipsilesional motor cortex. This abnormal reactivity in the acute stage was, at least partly, mediated by the GABAergic system and was specific to the acute stage. The present work provides further insights on the time course of brain reactivity after a stroke, specifically cortical disinhibition and its relationship to motor recovery. The regulation of motor cortical excitability, expressed by the return toward normal intracortical inhibition, was associated with greater motor improvement at three weeks and three months after stroke.

### 2.5.1 Disinhibition of the ipsilesional motor cortex in the acute stage as a key mechanism for successful recovery

Recent animal work suggested that an hyperexcitability state and disinhibition occur between the first week and one-month post stroke and plays an essential role for neuronal plasticity and recovery (Winship et Murphy 2008; Rabiller et al. 2015; Schiene et al. 1996). Indeed, in the acute stage, GABA-mediated ipsilesional intracortical inhibition is reduced compared to the unaffected hemisphere and to healthy controls (McDonnell et Stinear 2017). Animal models (Clarkson et al. 2010; Lake et al. 2015; Caracciolo et al. 2018) and human (Di Pino et al. 2014; Carmichael 2016; Kang, Summers, et Cauraugh 2016) studies suggest that this acute disinhibition is adaptive by enhancing ipsilesional neuronal excitability through reduction of cortical inhibition. This decrease of cortical inhibition is thought to promote plastic changes and reorganization to sustain recovery of the lost functions (Liuzzi et al. 2014; Heise et al. 2014). In humans, this hyperexcitability has been revealed with TMS-EEG especially in the most severely affected stroke patients (Tscherpel et al. 2020), in other cortical injuries (Sarasso et al. 2020), but also in altered brain states (Comolatti et al. 2019). The cortical signature of this hyperexcitability was characterised by an abnormally large and simple response in the electrodes next to the site of stimulation. In the present cohort, EEG-captured cortical activity elicited by TMS exhibited large heterogeneity among stroke patients (**Figure 2.2A**). The most severely affected patients were characterised by previously described large and simple responses, while less impaired patients showed a response pattern closer to what can be observed in healthy individuals (Bonato, Miniussi, et Rossini 2006; Mana Biabani et al. 2019). Although it has been suggested that this large early response could reflect an initial high excitability of the stimulated motor cortical area (S. Tremblay et al. 2019), the adaptive or

maladaptive nature of this process remains largely unknown. In the present study, this increased neuronal excitability in the acute stage was revealed by enhanced LMFPs and was associated with better recovery of the impaired hand function after 3 months, especially in the group of patients showing recovery. Similarly, after removal of the large component, higher pRQS values in the paired-pulse condition compared to the single pulse condition, represent an altered over-stable response state possibly corresponding to ineffective, reduced intracortical inhibition in the affected motor cortex.

Although Tscherpel et al.(2020a) also showed a relation between a large, simple and slow activity in the acute stage and motor recovery, the direction of the effect was opposite to the present results. However, it is worth noting that the two cohorts differed by the proportion of severely affected and of recovering patients. Thus, the link between simple and slow activity and worse improvement reported in the previous study could be explained by a greater proportion of severely affected patients with limited improvement (7 out of 25 remained at 0 in ARAT at 3-months post stroke). While the present cohort contained a higher proportion of mildly to moderately affected patients, with only 2 out of 66 having 0 in ARAT in the early chronic stage, it is possible that the mildly impaired patients exhibited the same physiological response to TMS, but showed more recovery due to their overall less impaired initial status. Moreover, the results in the present study were found exclusively for the subset of patients, who showed an increase in FM scores after the first week (recovering group), supporting the view that the motor status of the patients studied might play a substantial role in the relationship between cortical reactivity and motor recovery.

Furthermore, while the number of deflections of the single-pulse-evoked response was not associated with motor deficits nor recovery, probing of GABA-ergic inhibition (ppTMS-SICI) revealed a link between this readout of response complexity in the acute stage and improvement of motor functions. Moreover, the VLSM revealed that a lower number of evoked deflections in the acute stage was associated with the lesion load in the internal capsule, hosting the main outflow from motor cortical areas containing fibers from the corticospinal, corticorubral and corticopontine tracts (Catani et Thiebautdeschotten 2008) in line with current work (Tscherpel et al. 2020). Such disruption of fibers connecting the cortex to subcortical structures, the brainstem and the spinal cord, prevents propagation and integration of the evoked activity to distant brain areas, leading to simpler responses reflected by fewer deflections. Indeed, similar measures of complexity influenced by the number of deflections were described as driven by the propagation of information to distant areas via thalamo-cortical loops (Casali et al. 2013). In this way, the diminished number of deflections after TMS might reflect the cortico-subcortical disconnection of the affected motor cortex. However, observing a relationship after conditioning the GABAergic system and not only following single pulse stimulation suggests that these findings are not solely driven by corticospinal, but also, maybe mainly, by intracortical mechanisms. Informing on both, local and global processes, the number of deflections

could thus be an indicator of network topology, particularly of segregation. Indeed, Wang et al. (2010) showed that stroke patients exhibited a decrease in network segregation along recovery that follows the same pattern than the increase in number of deflections in the present work. Thus, one could speculate that a more random network, with information flowing to a broader range of areas, could be reflected by an increase in the number of deflections. Whether this reduction in the number of deflections is an adaptive mechanism or a result of more segregated network properties due to the stroke remains to be investigated in upcoming studies.

Overall, our results point toward more cortical disinhibition in the most impaired patients in the acute stage. This disinhibition might be related to a loss of cortico-subcortical connectivity. Both mechanisms could be adaptive or proxies of the recovery as they were correlated with a greater motor improvement in the following weeks and months. Investigating the evolution of these readouts alongside recovery helped untangling their function.

### 2.5.2 Changes of intracortical inhibitory activity within ipsilesional motor cortex and motor recovery

Past work has hypothesized different roles for persistent disinhibition in the chronic stage. While Ding et al. speculated that disinhibition could be detrimental for motor recovery (Ding et al. 2019), other studies showed that a persistent disinhibition in the chronic stage might support recovery through enhanced plasticity in patients with residual deficits (Liuzzi et al. 2014; Hummel et al. 2009; Mooney et al. 2019). The functional role of persistent disinhibition in the chronic stage is thus unclear and the present longitudinal data helped to address this question by investigating the relationship between the evolution of the present TMS-EEG readouts and motor recovery along time.

Several readouts showed an evolution associated with motor recovery and pointed toward a return to normal values, similar to what can be found in healthy subjects. The hyperexcitability represented in the acute stage by the high LMFP was thus the most reduced in the early chronic stage for the patients recovering the most (**Figure 2.4A**). When probing the intracortical inhibition system (ppTMS-SICI), the LMFP was associated with better recovery of especially distal impairment and fine motor skills (**Figure 2.5B**). While this effect was observed in the whole cohort, we were especially interested in the patient group, who showed initially relevant impairment with recovery over time. Also, in this group, we found a strong relationship between the initial level of the LMFP during the SICI protocol and changes of it over time with the degree of recovery of distal, skilled hand functions (**Figure 2.5C**). These findings point strongly to the fact that fine-tuned inhibitory activity is especially critical for more skilled hand functions, e.g., represented by the 9HP test, and the recovery from the impairment of them. Furthermore, both RQS measures indicated that correlates of the intracortical inhibition systems' activity were

increasing in the recovering patients (**Figure 2.4 & 2.5**). Indeed, in the RG only, greater evolution of the two readouts toward healthy values was associated with greater recovery of the distal hand function.
Additionally, both results from the RQS analyses provided information of the time course of this disinhibition to sustain motor recovery. The unpaired RQS analysis, representing the similarity of the evoked responses dynamics across timepoints, showed that the TEPs generated in the acute stage were significantly different from the one observed in the following timepoints (**Figure 2.5D**). Furthermore, changes in the paired RQS between the first timepoint and two weeks later were also associated with recovery. This correlate of the stability across trials was related to the extent of motor recovery up to three months (**Figure 2.5D**). Taken together, these results highlight the strong link between a rapid functional reorganization of the ipsilesional (GABAergic) inhibition and long-term motor recovery. We suggest that the initial disinhibition phase in the acute stage, promoting plasticity, is replaced by a gradual restoration of a more pronounced intracortical inhibition in the following weeks to months in a 'back to normal' fashion. While revival of inhibition might bring back plastic changes to a regular level, it is nevertheless essential for the implementation of highly skilled motor behaviour (Beck et Hallett 2011).
Finally, the number of deflections in the paired pulse condition followed the same return to more complex, normal patterns in the recovering group. It could imply that, in reverse to what we saw in the acute stage, the brain would benefit from better interconnected structures with less segregation in the chronic stage. This would further support the findings from Wang et al. relating motor recovery with an increased inter-hemispheric connectivity and an increased regional centrality of the ipsilesional motor cortex (L. Wang et al. 2010). Therefore, the present findings might point to that both, local and distal reestablishment of inhibiting mechanisms, are necessary for the fine tuning of (recovered) motor functions.
Similarly, removal of the large component seen in a large proportion of the patients unveiled additional and valuable information on the time course of intracortical inhibition, raising the question on the exact physiological nature of this large activity and of the remaining signal.

### 2.5.3 Unmasking complementary intracortical inhibition mechanisms by removing atypical large evoked activity

Hyperexcitability of the lesioned motor system in the most impacted patients induced responses with a large amplitude. We hypothesized that such large responses might mask further underlying effects represented by neuronal activity of smaller amplitude. Indeed, the EEG signal on the electrodes level is a compound recording from spatially and anatomically different neuronal population, which could be masked by a dominant activity from a specific population. Thus, we aimed to determine whether the removal of

these large responses would provide further insights unveiling correlates of important brain activity. By doing so, we captured activity during the second round of ICA and unmasked complementary information on the possible actors responsible for the changes of intracortical inhibition along recovery.

We hypothesized that such large activity might predominantly originate from large layer V (L5) pyramidal cells, since both, the recording and stimulation techniques used, are biased toward this neuronal population (Siebner et al. 2022; Murakami et Okada 2006; Aberra et al. 2020a). On one hand, these cells are known to generate the strongest electrical activity, both at microscale, when measuring the current dipole moment (Murakami et Okada 2006), and at mesoscale, where scalp EEG signal is known to be the integration of the synchronous post-synaptic activity of large populations of such aligned neurons (Portillo-Lara et al. 2021). On the other hand, TMS is known to simultaneously activate different neural populations (pyramidal cells and interneurons) within the stimulated area, with pyramidal V neurons being more prone to be activated. First, their specific shape and spatial orientation within the gyrus makes them more sensitive to the electrical field induced by TMS (Aberra et al. 2020a; Siebner et al. 2022). Second, a recent study by Chameh et al. (2021) using in vitro whole-cell recordings from cortical layer 2 to 5 of the human cortex showed that L5 pyramidal cells were the most excitable neurons. Therefore, TMS-EEG coupling might be oversensitive to L5 pyramidal neurons population and removing this large activity might allow to reveal activity from neurons within superficial layers eliciting weaker electrical potentials, such as inhibitory interneurons (**Figure 2.6**). In fact, when removing this large component, we discovered new relationships between TMS-EEG readouts and motor functions only in the paired-pulse condition, fueling the hypothesis of a GABAergic origin of the effects described. Although the exact actors responsible for this component remains to be precisely investigated, our results provide a first clue on the possible dissociation between distinct neuronal processes with the means of TMS-EEG.

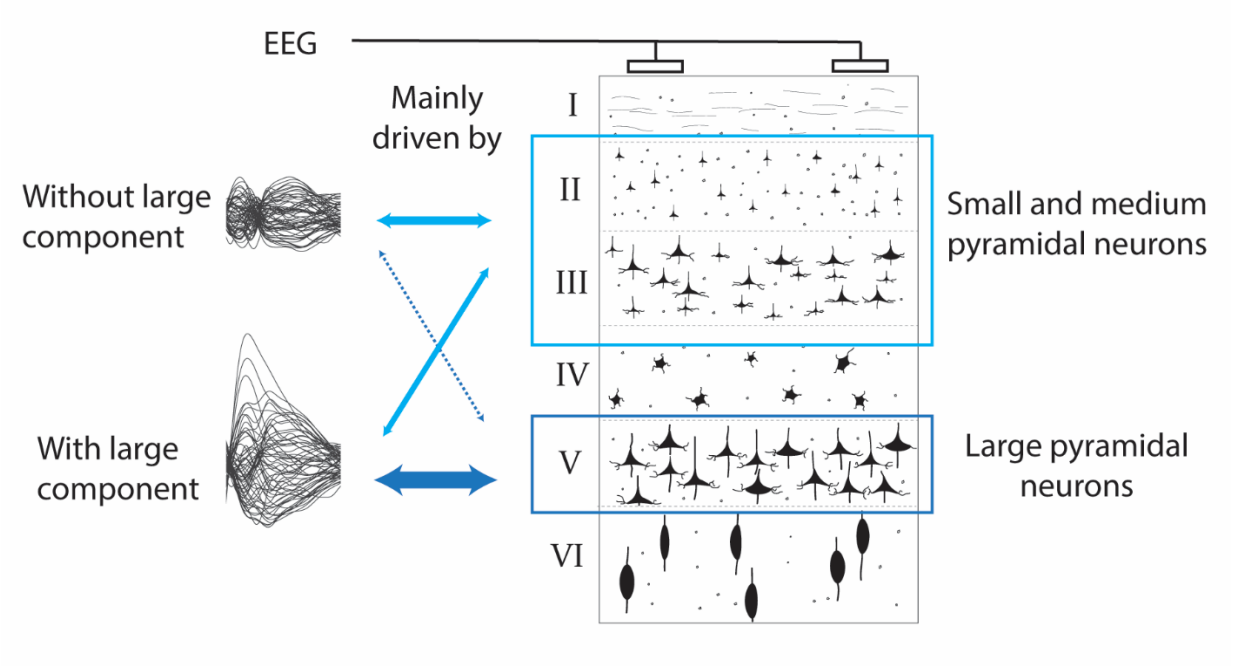


**Figure 2.6 Suggested model for the neural origin of the EEG-captured activity before and after removal of the large component.** The present model suggest that the large component might be mainly driven by the activity generated by large pyramidal cells from layer 5 (Aberra et al. 2020a; Siebner et al. 2022). The remaining signal after removal of the large component would then predominantly be driven by more superficial layers and other neuronal population, such as interneurons.

### 2.5.4 On the use of TMS-EEG in stroke

While evaluating the exact modulation of each neurotransmitters' activity occurring after stroke requires invasive procedures in animal models, it is however possible to investigate the inhibitory system in patients in vivo with the use of methods, such as GABA-edited magnetic resonance spectroscopy (MRS) (Stagg 2014; Blicher et al. 2015) or established paired pulse TMS protocols, e.g., the short-interval intracortical inhibition (SICI) protocol (Hummel et al. 2009; Liuzzi et al. 2014; McDonnell et Stinear 2017). However, spectroscopy focuses solely on extracellular concentration of GABA, has a low temporal resolution and hence cannot determine fast dynamic mechanisms. On the other hand, classical TMS-based SICI evaluation requires a preserved cortico-spinal tract (CST) to evoke measurable MEPs that are the primary read-out. The combination of TMS and EEG by means of neuronavigated TMS-EEG provides the opportunity to determine intracortical GABAergic inhibition in stroke patients with excellent temporal and good spatial resolution (Passera et al. 2022). Furthermore, it allows to evaluate patients with damage to the CST prohibiting the generation of a MEP (S. Tremblay et al. 2019).

### 2.5.5 Limitations

Despite having an extensive number of patients, presenting a wide range of lesion types and motor deficits, the majority of the patients included here are on the rather moderate side of motor impairment.
Secondly, the specific impact of lesion tissue, size and locations on electrical current propagation of TMS-evoked activity is not fully understood. However, the abnormal large activity has been observed here in a substantial proportion of the patients. Thus, it is unlikely that the large component was mostly induced by abnormal current propagation.

## 2.6 Conclusion

In conclusion, this work offers new insights into the longitudinal changes of cortical excitability and local intracortical inhibition in the affected motor cortex after a stroke. The present results strongly support the critical impact of intracortical disinhibition evolving in the acute stage on residual motor function and recovery, especially skilled distal functions, and the importance of the restoration of intracortical inhibition of the lesioned motor cortex to sustain long-term motor recovery. Furthermore, this study demonstrates that TMS-EEG provides an excellent opportunity to determine the reactivity of the brain after a stroke and to reveal cortical mechanisms of recovery from motor deficits even in patients without relevant remaining corticospinal connections due to the lesion. This knowledge provides a strong basis for developing TMS-EEG towards a clinical tool to phenotype patients and to develop biomarkers related to recovery and treatment response.

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## 2.8 Competing interests

The authors report no competing interests.

## 2.9 Data availability

The data related to this article and all the custom scripts and JASP files are available upon reasonable request to the corresponding author.

# 3. STUDY II : Brain Oscillatory Modes As A Proxy Of Stroke Recovery

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## One Sentence Summary

Changes in brain oscillatory modes representing a beneficial phase of cortical disinhibition drive motor recovery after a stroke.

## 3.1 Abstract

Stroke is the leading cause of long-term motor disability, making the search for successful rehabilitation treatment one of the most important public health issues. Providing a better understanding of the neural mechanisms underlying impairment and recovery, and the development of markers that are associated with it, is critically needed to tailor treatments to each individual patient with the ultimate goal to maximize therapeutic outcomes. Here, we used the novel powerful method of combined transcranial magnetic stimulation (TMS) and multi-channel electroencephalography (EEG) and focused on the analyses of brain oscillations induced by TMS in a large cohort of 60 stroke patients longitudinally from the acute to the early chronic phase. A data-driven approach (PARAFAC tensor decomposition) allowed to detect brain oscillatory modes specifically centered on the θ, α and β frequency bands. In the acute stage, patients presented a general slow-down of these oscillatory modes, highlighting the stroke-induced perturbations within thalamocortical processing. Furthermore, low frequency modes evolved across stroke stages, according to the degree of motor recovery, associated with changes in GABA-ergic intracortical inhibition. Overall, the present findings of longitudinal changes provided novel insights in the ongoing functional reorganization of brain networks and its underlying mechanisms after a stroke. Notably, we propose that the observed α mode decrease was supportive of a beneficial disinhibition phase occurring between the subacute and early chronic stage, which fosters structural and functional plasticity for recovery. Monitoring this phenomenon at the individual patient level offers critical information for phenotyping patients, developing electrophysiological biomarkers and programming therapies based on excitatory / inhibitory neuromodulation using non-invasive or invasive brain stimulation techniques.

## 3.2 Introduction

Stroke is the leading cause of motor disability in the adult population. The exact mechanisms underlying motor impairment and supporting recovery are still object of a relentless search (Grefkes et Fink 2020; Guggisberg et al. 2019; Raffin et Hummel 2018; Smajlović 2015). Mechanistic knowledge is critically needed in order to design and optimize future innovative patient-tailored rehabilitation protocols different from current “one-suits-all” strategies with limited treatment success (Coscia et al. 2019; Koch et Hummel 2017; Micera et al. 2020). Neuroimaging tools have been of precious help for that purpose in the past decades (Boyd et al. 2017; Grefkes et Fink 2014; Guggisberg et al. 2019; Koch et Hummel 2017). Among these techniques, electroencephalography (EEG) allows to explore the neural correlates of motor dysfunction with high temporal resolution (Nunez et Srinivasan 2006). Additionally, thanks to its cost and practicality, finding EEG-based biomarkers and predictors of motor impairment and recovery might be of particular interest, since they can quickly and easily be used in daily clinical life even at stroke patient’s bedside. A recent extensive review from Keser et al. (2022) gathered studies exploring the EEG correlates of motor functioning and recovery. Overall, these studies accumulated evidence supporting the fact that stroke is inducing a reduction in high frequency activity (> 8 Hz) and a disruption in interhemispheric activity balance, when probing the brain either at rest or during a motor task. The majority of these findings are based on features computed in the spectral domain, thus highlighting the link between motor impairment and recovery and the alterations of baseline neural oscillations patterns (Keser et al. 2022). Another promising way to directly and causally probe the disruptions of brain oscillatory activity induced by the impaired motor system is to observe its immediate response after a brief and local perturbation through transcranial magnetic stimulation (TMS) (Siebner et al. 2022).

TMS-EEG coupling has recently gained interest in the field of clinical neurosciences (S. Tremblay et al. 2019) for the vast opportunities it offers regarding its applications, such as a diagnostic tool in psychiatry, neurology, and more specifically in stroke (Keser et al. 2022). Considering brain waves as the product of complex interactions between both, local and remote neural oscillators (X.-J. Wang 2010), it is commonly accepted that the TMS pulse mainly acts as a phase reset on them, thus producing stronger oscillations thereafter (Moliadze et al. 2003; Pellicciari, Veniero, et Miniussi 2017). Compared with the resting-state, this subsequent increase in signal-to-noise ratio is of great interest when it comes to characterize the brain dynamics, i.e., the evoked neural oscillatory activity, of an area (Harquel et al. 2016; Rosanova et al. 2009), or the functional connectivity within – and between - brain networks (Bortoletto et al. 2015b; Keser et al. 2022). Therefore, the coupling with TMS allowed for example to unmask maladaptive interhemispheric functional connectivity between the two primary motor (M1) cortices in subacute and

chronic stroke patients (Borich et al. 2016b; Casula et al. 2021; Palmer et al. 2019), which was not noticeable at rest (Keser et al. 2022). It also added to the knowledge of stroke-induced modulation of neural oscillations. The recent cross-sectional work of (Pellicciari et al. 2018; Tscherpel et al. 2020) both pointed towards a reduction of response complexity in stroke, with an increase of low and a decrease of high frequency oscillations respectively. Such neurophysiological readouts might be a marker of functional reorganization processes sustaining motor recovery, especially among thalamocortical networks to which this technique is sensitive (Pellicciari et al. 2018; Rosanova et al. 2009). While all the above-mentioned work relies on the so-called “evoked” activity, i.e., on synchronous neural activity phase-locked to the stimulation, no study has yet been conducted addressing specifically TMS-induced oscillations, i.e., on the non-phase-locked oscillatory activity (Pellicciari, Veniero, et Miniussi 2017). By focusing on the evoked oscillations solely, the non-stationary activity generated by the brain is ruled out and not considered (Mutanen 2013; Pellicciari, Veniero, et Miniussi 2017). This approach eliminates all sources of variability regarding oscillations latency and phase from one stimulation to another (Moliadze et al. 2003; Pellicciari, Veniero, et Miniussi 2017), and therefore misses valuable information, especially in the context of stroke. In a seminal study in healthy subjects, Premoli et al. (2017) explored TMS-induced oscillations over M1 and found specific patterns of oscillations in the α and ß bands. Furthermore, the authors unveiled a link between these patterns and the modulation of the ɣ-aminobutyric acidergic (GABAergic) inhibitory system activity. Modulation of inhibitory processes within the ipsilesional M1 is thought to play an important role along motor recovery, though so far only addressed in animal models or small cohorts of patients (Clarkson et al. 2010; Liuzzi et al. 2014). Thus, this makes the exploration of these oscillations important in the context of stroke, especially when applied to a large cohort longitudinally.

The exploration of TMS-induced oscillations might have major importance in the context of understanding stroke recovery, however its analysis remains challenging. The related datasets are of high dimensionality, to best deal with this complexity they can be represented by multidimensional (3D to 5D) arrays called tensors (Cong et al. 2015). They encompass space (electrodes or reconstructed sources), time, frequency, patients and even experimental sessions as dimensions. Data-driven approaches capable of reducing such complex tensors into a simpler collection of parsimonious and unique components, or modes, have been developed (see e.g., Kolda and Bader, 2009) and tested in the EEG domain (Cong et al. 2015), notably in the detection of epileptic seizure (Aldana et al. 2019; Deburchgraeve et al. 2009). Among them, the PARAFAC (for parallel factor analysis) algorithm (Harshman, 1970) has recently proven its validity in the context of TMS-EEG coupling data (Belardinelli et al. 2021; Tangwiriyasakul et al. 2019). The authors of these two studies were able to extract three to four brain oscillatory modes from the TMS-induced oscillations of M1 that were physiologically meaningful.

Interestingly, these modes did not overlap in frequency, and instead each was primarily driven by one main oscillation pattern in the θ, α or β band. One of the observed modes was mainly driven by the θ band over the stimulated M1 that peaked around 200 ms after the TMS pulse (Belardinelli et al. 2021; Tangwiriyasakul et al. 2019). Such late and local activity might well be the signature of feedback activity from remote areas, engaged after the indirect activation of cortico-cortical and cortico-subcortical networks (Bortoletto et al. 2015b; Siebner et al. 2022). Studying the evolution of this oscillatory mode in the context of stroke might be of importance, since this low-frequency band has been associated with inter-regional communication supporting cognition in humans and animals (Canolty et al. 2006; Solomon et al. 2017; Watrous et al. 2013), which is known to be heavily impacted in brain network diseases (Guggisberg et al. 2019; Keser et al. 2022). Another mode focused on α activity, which was found to be maximal over parieto-occipital (Tangwiriyasakul et al. 2019) and stimulated motor areas (Belardinelli et al. 2021). By choosing a wider time analysis window, Tangwiriyasakul et al. (2019) showed that this late activity was sustained in time up to 850 ms after the stimulation. Given the fact that variations within the α band activity are linked with functional inhibitory processes (Hummel et al. 2002; Jensen et Mazaheri 2010; Klimesch, Sauseng, et Hanslmayr 2007; Pfurtscheller, Stancák, et Neuper 1996; Sauseng et al. 2009; Thut et al. 2006), and that such late TMS-induced α oscillations were found to be mediated by the GABAergic system (Premoli et al. 2017), studying the α mode is of particular interest in monitoring the evolution of inhibitory processes in the time course of post-stroke motor recovery. Finally, one further extracted mode corresponded to the sensorimotor β band activity generated by the stimulated motor cortex, consisting in an early burst (< 50 ms) of activity followed by a rebound 400 ms later (Tangwiriyasakul et al. 2019). This time course is the signature of the local activation of highly excitable layer V pyramidal cells that are connected to the pyramidal tract leading to motor responses (Aberra et al. 2020b), such large cells and the specific cytoarchitectonics of M1 being prone to produce β band activity (Bouyer et al. 1987; Harquel et al. 2016). Interestingly, Belardinelli et al. (2021) linked the β mode with glutamatergic activity, thus bringing an additional interest to its study in stroke, considering the importance of the evolution of excitatory/inhibitory balance in motor recovery (Carmichael 2012).

In the present study, we sought to better understand the underlying mechanisms of motor impairment and recovery after stroke by applying this novel powerful method not yet applied in stroke. We used it to study these brain oscillatory modes unveiled from TMS-induced oscillations and determined their importance for residual motor functions and recovery. To do so, the present analyses are based on the large dataset of the TiMeS protocol (Fleury et al. 2022, in appendix) that consisted of a multimodal, multidomain and longitudinal evaluation of stroke patients, from the acute to the subacute and early chronic stage, constituting the largest longitudinal data set with TMS-EEG. We used the PARAFAC approach in order to extract brain oscillatory modes and to study their

disruption in respect with motor impairment at the acute stage, as well as their modulation through the time course of motor recovery.

## 3.3 Materials and methods

### 3.3.1 Study design

This work is part of the TiMeS project, for which a detailed description can be found in (Fleury et al. 2022, in appendix). We hypothesized that the analysis of TMS-induced oscillations would allow to unveil stroke-induced perturbations in brain rhythmic activity, the strength of which would correlate with motor impairment and recovery. To test this hypothesis, joint collected neuroimaging and behavioral assessments, at three different time points: one-week post stroke (referred here as “acute stage”, A), three weeks (“subacute stage”, SA) and three months (“early chronic stage”, EC) were included in the analyses.

76 stroke patients participated in the study after being admitted at the Regional Hospital of Sion (HVS), Switzerland. Among them, 60 stroke patients (age: 66.9 ± 13.3 years old; 18 females) were included in the analysis of this study, i.e., patients with TMS-EEG recordings at least in the first recording session (acute stage). The reasons for not attending a recording session were multiple and included e.g., weak health status, lack of motivation for participating in follow-up, and COVID-19 global pandemic. Patients were recruited during the first week post stroke. Additionally, 19 healthy young adults (age: 26.9 ± 2.9 years old, 9 females), as well as 15 healthy old adults (aged-matched with patients, age: 67 ± 5 years old, 11 females) were recruited and performed a single TMS-EEG recording session. The inclusion criteria comprised of being older than 18 years of age, having absence of contraindications for MRI or TMS and, for the patient group, having motor deficits of the upper limb and Exclusion criteria included cognitive inability to provide informed consent, history of seizures, pregnancy, severe neuropsychiatric or medical diseases, regular use of narcotic drugs and medication that significantly interact with TMS as well as implanted medical electronic devices or ferromagnetic metal implants which are not compatible with MRI or TMS and the request not to be informed in case of incidental findings. The study was conducted in accordance with the Declaration of Helsinki and was approved by Cantonal Ethics Committee Vaud, Switzerland (project number: 2018-01355), written informed consent was obtained for all participants.

### 3.3.2 Behavioral data

At each time point, bilateral motor capability and impairment of patients were assessed using (i) the Fugl-Meyer (FM) of the upper body (without reflexes), of the upper extremity, of the hand and of the wrist (Fugl-Meyer et al. 1975), (ii) the maximum fist, key and pinch force, (iii) the Box and Blocks, and (iv) the nine-hole peg test (Mathiowetz, Volland, et al. 1985; Mathiowetz, Weber, et al. 1985; Mathiowetz et al. 1984). The maximum grip forces were assessed in three trials using a JAMAR® hydraulic hand dynamometer (Mathiowetz et al. 1984). The ratio between the affected and the non-affected hand was used as the primary outcome for grip forces, box and blocks and nine-hole peg tests. Change ratios between time points were computed for each motor measurement x as follows: $(x_{TP2} - x_{TP1})/x_{TP1}$.
The electrophysiological features were globally inspected over the whole patient cohort, and specifically over the subgroup of recovering patients. Patients were classified as "recovering" whenever a positive change occurred on FM scores of the upper extremity between the acute and subacute stages, or between the early chronic stage and the acute or subacute stages.

### 3.3.3 TMS-EEG acquisition

The details of acquisition parameters can be found in our previously published paper (Cadic-Melchior et al. 2022), which consisted in the analysis of TMS evoked components. In brief, 64 channels TMS-compatible EEG (BrainAmp DC amplifiers, Brain Products GmbH, Germany) was recorded concurrently to the neuronavigated (Localite GmbH, Germany) stimulation of the ipsilesional motor cortex over the first dorsal interosseous (FDI) motor hotspot, using an MC-B70 coil connected to a MagPro X100 stimulator (MagVenture A/S, Denmark). A total of 180 suprathreshold single pulse stimulations were delivered. If no motor activity could have been evoked from the lesional hemisphere, the stimulation parameters were tuned on the contralesional hemisphere. DC and low-pass (1 kHz) filtered EEG was sampled at 5 kHz, and electrode impedance level was kept below 5 kOhms. During the stimulation, the patient was told to remain still, while staring at a fixation cross and listening to white noise through noise-canceling earphones in order to limit eyes movements and the influence of TMS click sound on EEG signal respectively.

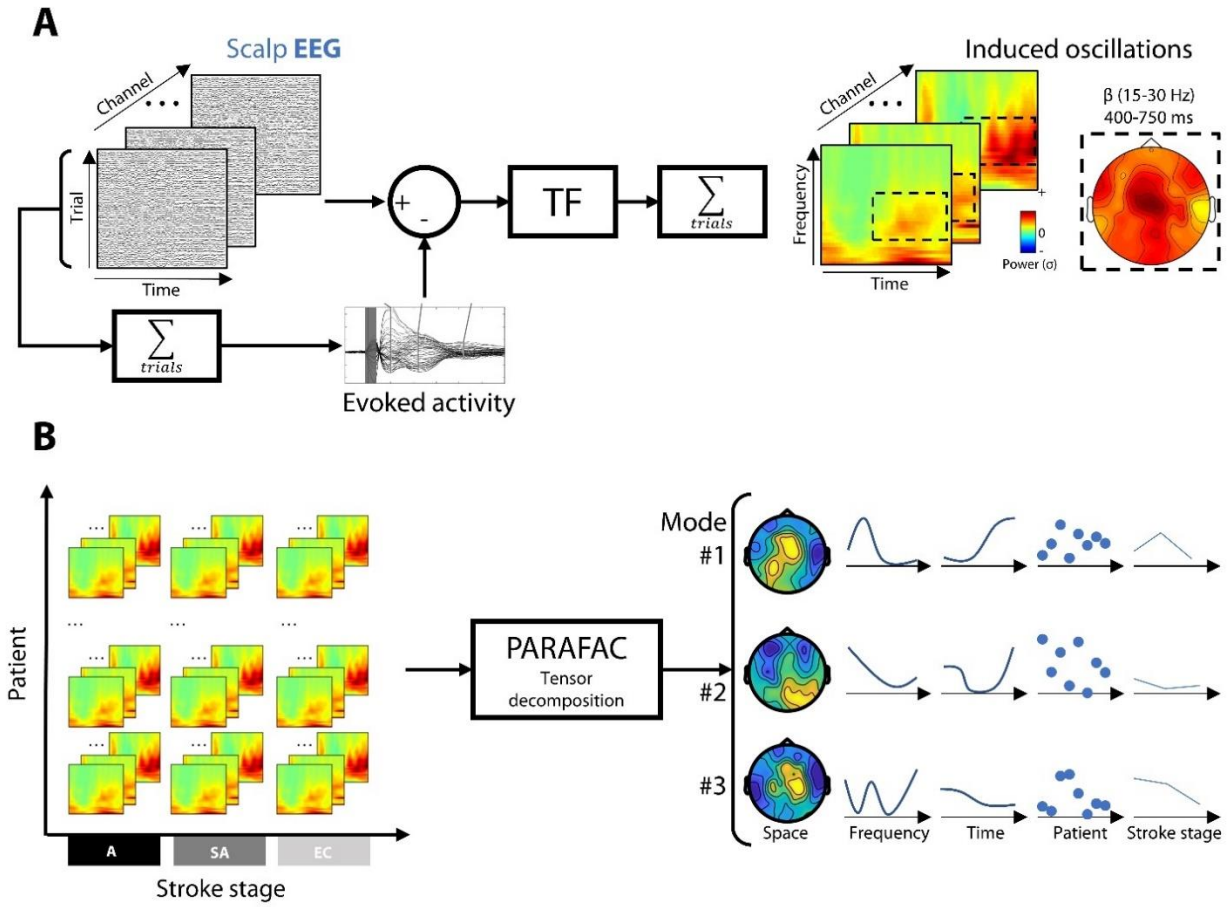


**Figure 3.1. Main data processing pipeline. (A)**. Signal processing pipeline for computing induced oscillations maps. For each patient and channel, the evoked activity (average of the clean signal across trials) is removed from the clean signal prior to the time frequency (TF) transform. Each TF map is z-scored against baseline (-200 to -50 ms prior to TMS pulse) before averaging across trials. Examples of induced oscillations maps (+40 to +750 ms; 7 to 40 Hz), together with a topography of late central β oscillations, are depicted on the right for one representative patient. **(B)**. Tensor decomposition using PARAFAC. Induced oscillation maps are gathered into a tensor, with patient and stroke stage as the 4$^{th}$ and 5$^{th}$ dimension respectively, and decomposed using PARAFAC algorithm. This decomposition leads to several components, or modes, whose weights can be represented in the space (topography), frequency, time, patient and stroke stage dimension, from left to right respectively.

### 3.3.4 TMS-EEG analysis

The analysis methodology used in this study was adapted from the study of Tangwiriyasakul et al. (2019), in which PARAFAC tensor decomposition was for the first time applied on TMS-EEG coupling data.

#### 3.3.4.1 Preprocessing

TMS-EEG data were analyzed on Matlab (The MathWorks, USA), and preprocessed using EEGLAB (Delorme et Makeig 2004) and TESA (Rogasch et al. 2017) toolboxes. Regarding patients, the clean datasets analyzed in this study are identical to the ones of our previously published paper (Cadic-Melchior et al. 2022). In short, raw TMS-EEG data were preprocessed using the double ICA methodology (Rogasch et al. 2014) in order to remove components linked to pulse, muscle, decay and ocular artifacts from the data. The preprocessed dataset resulted in an average of 149 +/- 24 cleaned trials epoched between -500 and +1000 ms around the TMS pulse, and filtered between 1 and 80 Hz.

#### 3.3.4.2 Induced oscillations

Induced oscillations were computed on Matlab using the Fieldtrip toolbox (Oostenveld et al. 2011) (**Figure 3.1A**). First, the TMS evoked potentials (TEPs) were computed by averaging all trials, and were then individually subtracted from the signal each trial in order to filter out as much evoked activity as possible (Cohen et Donner 2013). Then, the time-frequency (TF) map of each corrected trial was computed using a multitapers approach. First, the signal from the -500 to +1000 ms time window (10 ms step) was convoluted with Hanning tapers ranging from 7 to 40 Hz (1 Hz step), with a width of 3.5 cycles per window. For each electrode and trial, the resulting power time series were normalized using z-score against baseline, defined as the -200 to -50 ms period preceding the TMS pulse. Finally, TF maps were obtained for each patient and time point by averaging the normalized maps across trials. Prior to tensor definition, all the TF maps were flipped in RH patients so that the ipsilesional hemisphere was defined as the left for all patients.

#### 3.3.4.3 PARAFAC tensor decomposition

Regarding patient database, four different tensors were built in order to answer the study's main questions: the first one focused on the acute stage (of 4 dimensions: electrode × frequency × time × patient) while the second to the fourth gathered the induced oscillations longitudinally across stroke stages (acute vs. subacute stage, acute vs. early chronic stage, and from acute to early chronic stages, of 5 dimensions: electrode × frequency × time × patient × stroke stage) (**Figure 3.1B**). For each tensor, the TF maps were cropped between +40 and +750 ms in order to avoid missing values from boundaries

effects, resulting in a size of 62 × 34 × 70 for the first three dimensions. 60, 43, 33 and 27 patients were included at the A stage and attended to the A and SA stages, the A and EC stages, and to every stages respectively, so the final size of the four tensors were 62 × 34 × 70 × 60 (8,853,600 datapoints) for the first one (A only), 62 × 34 × 70 × 43 × 2 (12,690,160 datapoints) for the second one (A vs. SA), 62 × 34 × 70 × 33 × 2 (9,738,960 datapoints) for the third one (A vs. EC), and 62 × 34 × 70 × 27 × 3 (11,952,360 datapoints) for the fourth one (A to EC). The link between brain oscillation modes and motor recovery was further inspected by splitting the last 5D tensor in two: the first sub-tensor comprised only of stable patients while the second gathered recovering patients. Regarding healthy adults, the final tensor was of size 62 × 34 × 70 × 19 (2,803,640 datapoints) for the young group, and of size 62 × 34 × 70 × 15 (2,213,400 datapoints) for the aged-match group.

### 3.3.5 Statistical analysis

The longitudinal difference between stroke stages when decomposing the 5D tensors were assessed using the same permutation-based approach proposed in Tangwiriyasakul et al. (2019). In short, 1,000 surrogate tensors were obtained by permuting data on the $4^{th}$ and $5^{th}$ dimensions (patients and stroke stages), while keeping the data structure unchanged over the 3 first dimensions. A PARAFAC decomposition was then performed on each surrogate tensor while using the old loadings of the original data decomposition in the first three dimensions, i.e., forcing the extracted modes to be identical to the original data in the space, frequency and time dimensions. The corresponding mean differences between stroke stages (differences between data in the $5^{th}$ dimension) were gathered across all decompositions to form the surrogate data distributions. Differences between time points in the original tensors were considered as significant if greater or lower than 2.5% of these surrogate distributions ($p < 0.05$, two-sided).

The link between patients' weights (data in the $4^{th}$ dimension) within the extracted modes and motor scores were explored using the Bayesian equivalent of nonparametric Kendall correlation testing using JASP software (JASP Team - 2022). Weights of each extracted mode were compared with the initial motor scores in the acute stage, and to the change ratio between stroke stages (see Behavioral data). The default values proposed within JASP framework were used in order to keep priors on effect sizes relatively large. Correlation values were reported using the 95% confidence interval of Kendall's τ, while the statistical evidence of the tests was reported using Bayes factors ($BF_{10}$) and the cut-off values defined by Jeffreys (1998) for interpretation.

## 3.4 Results

All 60 patients, whose characteristics are detailed in Table 1, went through the longitudinal TMS-EEG evaluations without any adverse events. The lesion heat map of the patient cohort at inclusion is depicted in **Figure 3.2**. Overall, patients recovered from their stroke-induced motor impairment from the acute (one week after stroke) to the early chronic (three months after stroke) stages, reducing the impairment in average of 7.7 points on the Fugl-Meyer scale of the upper limb (FM UL), improving in motor functions such as in the box and block and nine-hole peg test, in spasticity with an average decrease of 1.7 points on the Modified Ashworth Scale (MAS), and in autonomy with an average increase of 10.8 points on the Barthel scale (Table 1). These motor improvements were also accompanied by cognitive improvements, with an average increase of 3.2 points on the MOCA scale.

## Table 3. 1 Patients' characteristics.

| Gender | Age (y.o.) | Handedness | Hemisphere affected | RMT | Days post stroke | | | FM UL (/60) | | | NIHSS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Acute | Acute | Subacute | Early chronic | Acute | Subacute | Early chronic | Acute | Subacute | Early chronic |
| 18 F / 42 M | 66.9 ± 13.3 | 54 right-handed | 30 Left / 30 Right | 43 ± 10 | 6.6 ± 2.3 | 27 ± 5 | 98.6 ± 8.8 | 47.3 ± 18.5 | 50.9 ± 16.5 | 55 ± 12.1 | 5.7 ± 5.4 | 2.0 ± 3.0 | 0.6 ± 1.3 |

| MAS (/48) | | | MOCA (/30) | | | Barthel (/100) | | | Box and Block (aff./non-aff.) | | | Nine-hole peg (aff./non-aff.) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acute | Subacute | Early chronic | Acute | Subacute | Early chronic | Acute | Subacute | Early chronic | Acute | Subacute | Early chronic | Acute | Subacute | Early chronic |
| 3 ± 5.6 | 2.5 ± 4.9 | 1.3 ± 2.4 | 22.7 ± 4.9 | 24.1 ± 4.9 | 25.9 ± 3.5 | 88.2 ± 19.5 | 93.8 ± 13 | 99 ± 3.1 | 0.74 ± 0.34 | 0.79 ± 0.31 | 0.89 ± 0.23 | 2.6 ± 2.4 | 2.1 ± 2.2 | 1.6 ± 1.6 |

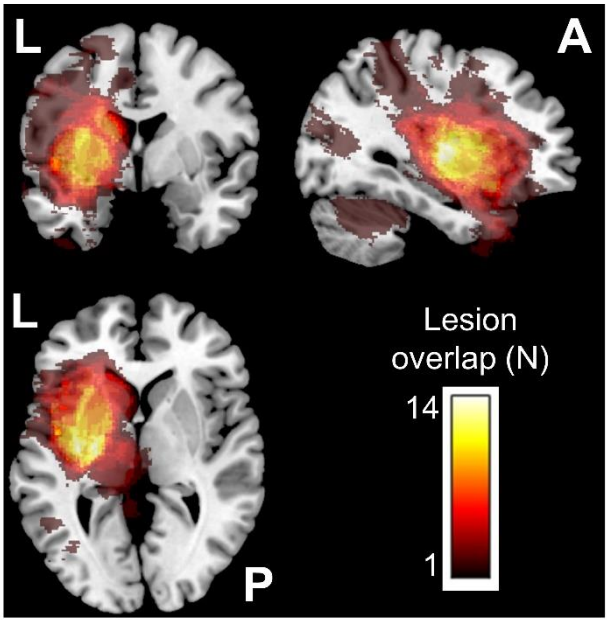


**Figure 3.2 Lesion heat map of the patient cohort at the acute (or subacute, if inexistent) stage**, N = 54. Right-hemispheric lesions are flipped to the left side. Note that 6 patients out of 60 did not perform MRI at the acute or subacute stage.

The TMS-induced oscillations were recorded longitudinally in the patient cohort at three different stages (**Figure 3.3A**) referred here as the acute (A), subacute (SA) and early chronic (EC) stage (one week, one month and three months after stroke onset respectively). The preprocessed EEG signal was concatenated in 4D and 5D tensors with space (scalp topography), time (post-TMS), frequency (brain oscillations), patients (inter-individual variability) and stroke stages (longitudinal changes) as dimensions. If needed, data were flipped so that the ipsilesional hemisphere was defined as the left for all patients. These tensors were finally decomposed in components, or "brain oscillatory modes" as they refer to TMS-induced oscillations, using a PARAFAC tensor decomposition approach (**Figure 3.3B**). Each mode was characterized with unique sets of weights in each of the tensors' dimension.

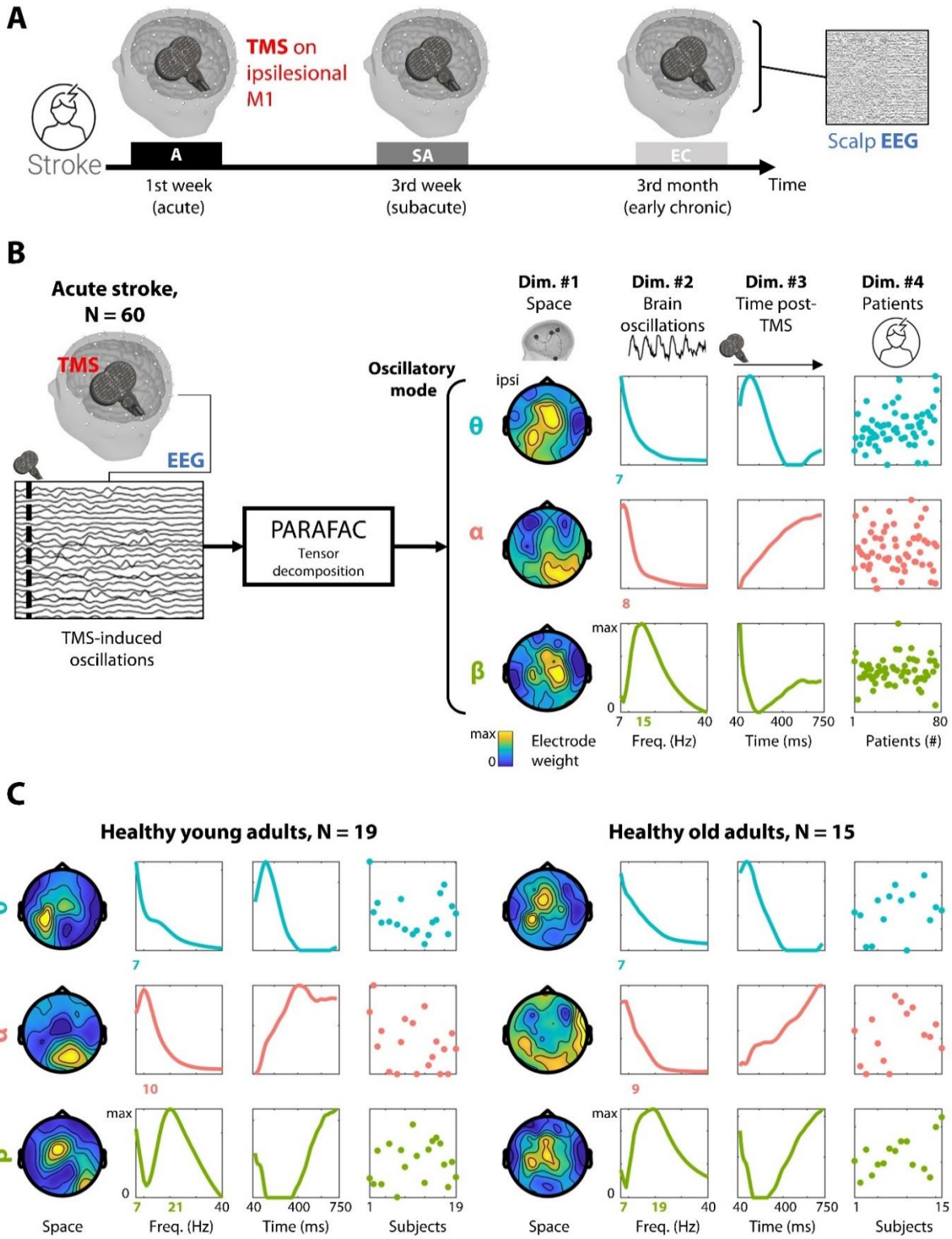


**Figure 3.3 Brain oscillatory modes extracted from stroke patients and healthy adults. (A)**. Protocol design including 3 TMS-EEG coupling session during the 1st, 3rd week and 3rd month after stroke (referred as acute, subacute and early chronic stages respectively). **(B)** PARAFAC decomposition of the 4D tensor of the TMS-induced oscillations in acute stroke patients. Modes are sorted by row according to their main frequency peak, from θ (7 Hz, blue), α (8 and 10 Hz, red) to high β (15 and 21 Hz, green) frequency bands (top to bottom). Each column depicts the relative weights (from 0 to max) of each mode in the space, frequency, time and patient dimensions (from left to right). The mode frequency peak is highlighted in color on the y-axis. Data were flipped for patients whose lesion was located on the right

hemisphere, so that the ipsilesional side is on the left. **(C)** Results of the same tensor decomposition in healthy young (left) and old (right) adults, modes being similarly sorted.

### 3.4.1 Perturbation of brain oscillatory modes in acute stroke patients

**Figure 3.2B** shows the induced oscillation modes obtained after the 4D tensor decomposition in stroke patients in the acute phase (N = 60) and in healthy young (N = 19) and old adults (N = 15). If the three identified modes were of same nature between the three groups, acute stroke patients presented overall a slowdown of brain oscillatory activity, unveiled by a decrease of the peak frequency of the different modes. The first mode was centered around θ oscillations (7 Hz peak) that were distributed over the stimulation site, i.e., the ipsilesional hemisphere, which corresponds to central and central left electrodes (right-lesioned data were flipped for analysis purpose). The time course of the mode shows a peak around 80 ms, followed by a decrease until 400 ms. The second mode converged on the parieto-occipital α waves that emerged with time from 150-200 ms after stimulation, healthy young adults presenting a steeper increase than older and patients. The main frequency for this mode was lower in stroke patients (8 Hz) than in healthy young (10 Hz) and older adults (9 Hz). Lastly, the third mode mainly focused on sensorimotor β and μ waves. These oscillation patterns emerged from central electrodes, over the stimulation site. The peak frequency differed between the three groups, stroke patients presenting one peak at 15 Hz, while healthy young adults showing two peaks in 7 and 21 Hz, and older adults one peak at 19 Hz. In addition, the lateralization of this activity on the left stimulated hemisphere was more pronounced in healthy adults, whereas the activity was shifted to the right contralesional hemisphere in stroke patients. Finally, the overall time course of these β oscillations were the same, with one early peak activity at 40 ms followed by a decrease and a rebound after 400 ms, the exact ratio between early and late activity differed between the groups. The early peak activity was more pronounced in stroke patients, whereas the rebound was stronger in both healthy adult groups.

### 3.4.2 Evolution of brain oscillatory modes within the time course of recovery

The results of the decomposition of the 5D tensors gathering all stroke stages, including the acute (A), subacute (SA) and early chronic (EC) stage, are presented in **Figure 3.4**. The 5D tensors gather all the patients that have been systematically recorded at each required stage (27 patients for all stroke stages comparison, 43 for A vs. SA, and 33 for A vs. EC). The longitudinal differences between stroke stages were assessed using the permutation-based approach proposed in (Tangwiriyasakul et al. 2019), in which the observed difference is compared with those obtained using 1,000 permuted surrogate tensors on the $4^{th}$ and $5^{th}$ dimensions (patients and stroke

stages, see Statistical analysis). Overall, the three first modes extracted by PARAFAC were of the same nature as the ones obtained using the 4D tensor at the acute stage (**Figure 3.4A**, N = 27). However, both the spectra and time courses were less specific after the addition of the most remote session (EC, three months after stroke onset) within the 5$^{th}$ dimension, and started to overlap between modes within these dimensions. In particular, the β and α spectra were less specific, with flatter spectral peaks covering wider frequency bands. The time course of the β oscillation was less contrasted between peak and trough activity periods, while α and θ bands overlapped and followed the same pattern as the one previously described for the α mode (**Figure 3.3**).

Interestingly, the mode weights were significantly modulated across stroke stages (permutation tests, $p < 0.05$, N = 27). This change was specific to α and θ band modes that significantly differed from the acute stage to the subacute and the early chronic stage with opposite directions and different strength across stages. While the relative weight of the α band mode increased at the subacute stage before decreasing at the early chronic stage, the θ band mode modulated in the opposite direction with a decrease at the subacute stage followed by an increase at the early chronic stage. Overall, the changes were much stronger at the early chronic stage, which was confirmed on larger groups of patients by the pairwise comparisons between acute and the two later stroke stages. No change was found for any of the modes when comparing the acute to the subacute stage (N = 43, **Figure 3.4B(a)**), whereas a strong increase and decrease of the θ and α mode respectively was found towards the early chronic stage (permutation tests, $p < 0.05$, N = 33, **Figure 3.4B(b)**). Finally, no significant modulation through stroke stages was found for the β band mode, in any of the tensor decompositions.

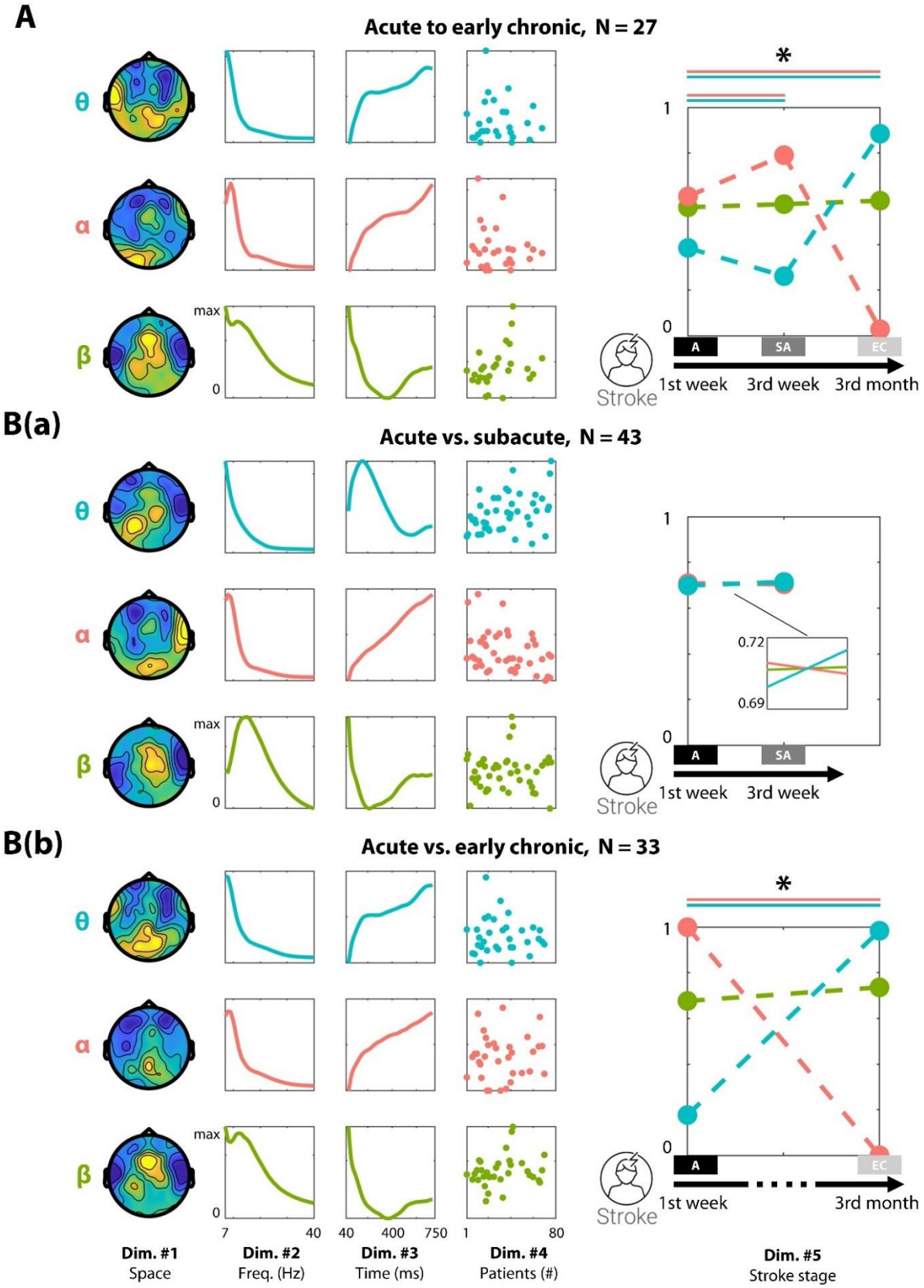


**Figure 3.4 Evolution of brain oscillatory modes from acute to early chronic stages.** **(A)** PARAFAC decomposition of the 5D tensor in all patients leading to 3 main modes. The modes are sorted by peak frequency, from θ (blue) and α (red) to β (green) bands. Each column depicts the relative weights (from 0 to max) of each mode in the space, frequency, time, patient and stroke stage dimensions (from left to right). Star and colored lines indicate

significant effects of the pairwise comparisons of the stroke stages within the θ (blue lines) and α (red lines) modes, for the acute (A) vs. the subacute (SA) stage, and the acute (A) vs. the early chronic (EC) stage (permutation test, $p < 0.05$, see Statistical analysis). **(B)**. Results of the same decomposition ran separately on the A and SA stage **(a)**, and on A and EC stage **(b)**. Note that mode weights are overlapping in the 0-1 y-axis scale for A vs. SA **(B(a))**. Taken together, the results indicate that there were relevant changes in the θ and α modes over time, especially large changes from A to EC for the θ and α modes, but no relevant changes between A and SA, and in generally for the β mode.

### 3.4.3 Modulation of brain oscillatory modes as a proxy of motor recovery

We further explored the modulation across stroke stages by distinguishing patients that actually recovered along the evaluated stroke stages (recovering group) from patients that presented stable motor functions since their inclusion in the acute stage (stable group, for definitions of groups please see Materials and Methods). The decomposition of the two corresponding 5D sub-tensors led to the brain modes depicted in **Figure 3.5A**. Overall the three modes were of same nature in the 3 first dimensions, the two groups drastically diverged regarding the modulation across stroke stages ($5^{th}$ dimension). These data indicate that the previously observed modulations were mainly driven by the recovering group, in which the same significant effects were observed across stroke stages (permutation tests, $N = 17$, $p < 0.05$; see **Figure 3.5A**, right, to be compared with **Figure 3.4**), while only a mild increase of the α band mode was significant within the stable group between the A and EC stages (permutation test, $N = 10$, $p < 0.05$; **Figure 3.5A**, left).

All tensor decompositions showed variability in the weights of the modes between patients, i.e., within the $4^{th}$ dimension. We then aimed to explain the variability in the patients in impairment, function and recovery, e.g., upper limb motor function, gross and fine dexterity, impairment and changes over the recovery process, by linking it with the different modes and their changes (**Figure 3.5B**). No statistical evidence was found neither for a link nor an absence of links between θ and β oscillations modes on motor scores or their modulation through stroke stages (Bayesian Kendall correlation, $N = 17$, all $1/3 < BF_{10} < 3$) in any of the tested patient cohorts (full, or only stable or only recovering group patients). However, substantial to strong statistical evidence was found for a link between the α mode and motor scores at the A stage, and its evolution across the SA and EC stages in the recovering group (**Figure 3.5B**). First, patients exhibiting a stronger weight associated to this mode were more impaired in the acute stage (**Figure 3.5B(a)**), with lower FM hand score at the A stage ($N = 17$, $\tau = [-0.09\ -0.7]$, $BF_{10} = 7.3$). A stronger association with the α mode was also found in better recovering patients between the A and SA stage (**Figure 3.5B(b)**), as revealed by stronger change ratio between the A and SA stages in FM hand ($\tau = [0.22\ 0.8]$, $BF_{10} = 91$), FM wrist ($\tau = [0.05\ 0.65]$, $BF_{10} = 3.9$), FM total ($\tau = [0.07\ 0.67]$, $BF_{10} = 5.8$) and maximum fist force ($\tau = [0.07\ 0.67]$, $BF_{10} = 5.9$). The stronger the patients were associated to this α mode, the better they improved at the SA stage. Finally, a similar

association was found in the longer term, with stronger change ratios between the A and EC stages in FM hand ($\tau$ = [0.2 0.8], $BF_{10}$ = 56), BnB ($\tau$ = [0.08 0.7], $BF_{10}$ = 6.0) and nine-hole peg tests ($\tau$ = [-0.08 -0.7], $BF_{10}$ = 6.0) tests (**Figure 3.5B(c)**), indicating that the more change in the α mode was associated with the larger improvement in motor functions, respectively the larger the reduction in impairment.

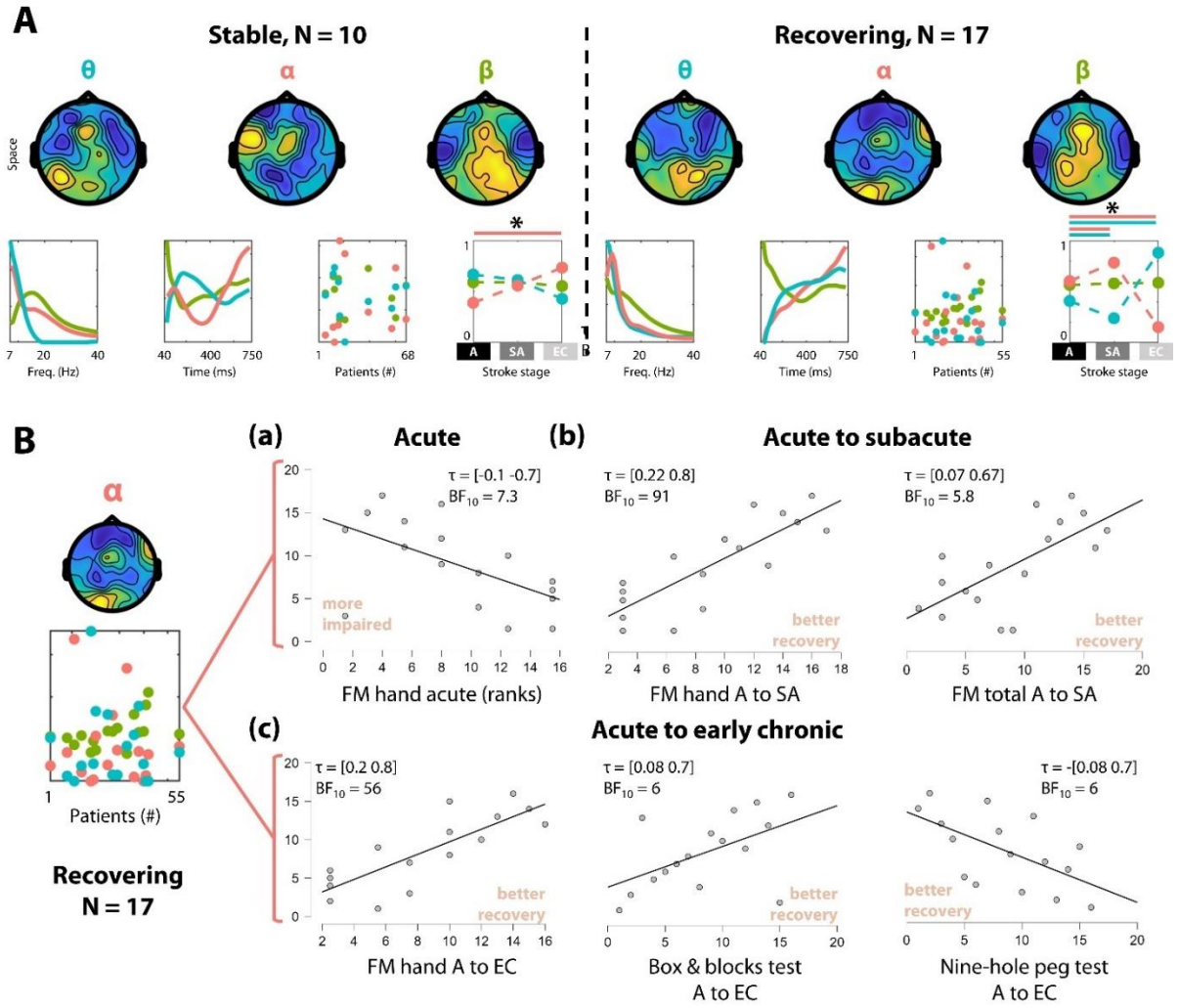


**Figure 3.5 Link between brain oscillatory modes, motor impairment and motor recovery. (A)**. PARAFAC decomposition of the 5D tensor in stable (left) and recovering (right) patients. The mode relative weights in space dimension are depicted on the first row using topographies. The mode relative weights in frequency, time, patient and stroke stage dimension are plotted in the second row. Star and colored lines indicate significant effects of the pairwise comparisons of the stroke stages within the θ (blue lines) and α (red lines) modes (permutation test, $p < 0.05$, see Statistical analysis), indicating a significant change in the α mode in the stable group (left) and significant large changes of the θ and α modes in the recovering group (right). **(B)** Association between the α mode and motor scores (FM, box & block, nine-hole peg tests) in the recovering group. For each comparison, Kendall rank correlation coefficient ($\tau$) and Bayesian factors ($BF_{10}$) are indicated for each comparison, and all data are plotted according to their rank (see Statistical analysis). **(a)**. Moderate evidence for an anticorrelation between weights associated with α mode and motor impairment in the acute stage indicating a more positive α mode in the acute stage led to more relevant impairment. **(b)**. Moderate to strong evidence for a correlation between weights associated

with the α mode and changes in motor impairment to the subacute stage (change ratio between A and SA) indicating the more change in the α mode the larger the reduction in impairment. **(c)**. Moderate to strong evidence for a correlation between weights associated with the α mode and changes in motor functions and impairment to the early chronic stage (change ratio between A and EC) indicating the more change in the α mode the better the improvement in motor functions, respectively the larger the reduction in impairment.

## 3.5 Discussion

Here, we report changes in induced oscillatory activity modes determined longitudinally (acute to chronic) in a large cohort of stroke patients by means of TMS-EEG coupling and their association to functional motor recovery. The results point to dynamic changes of correlates of inhibitory activity from enhanced inhibitory activity in the acute stage to recovery supporting disinhibition from the subacute toward

s the chronic stage (**Figure 3.6**).

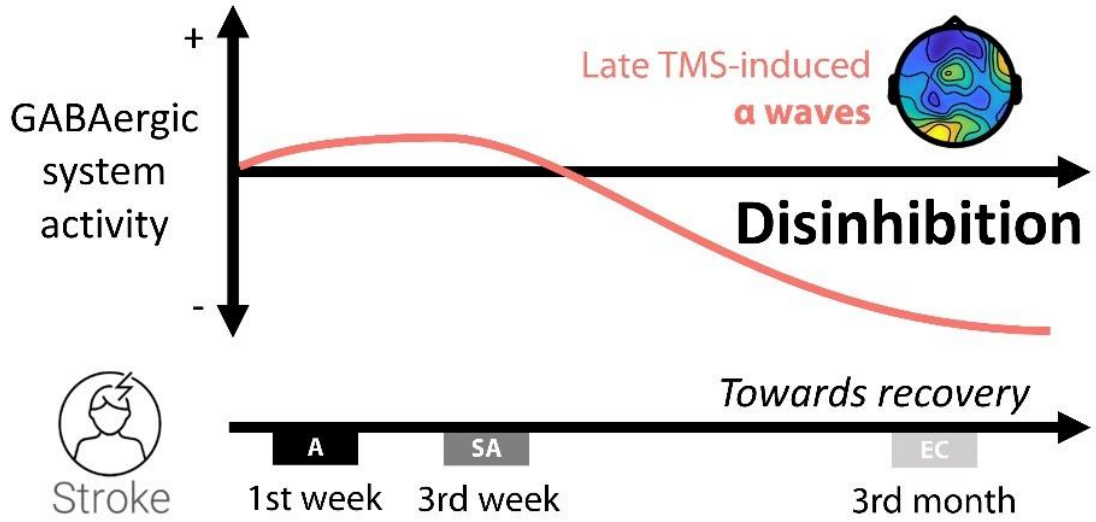


**Figure 3.6 Course of GABA-ergic inhibition and its relation to recovery.** The decrease of the late TMS-induced α waves (correlate of activity of the GABAergic system) from an initially high level represents a global and recovery beneficial functional disinhibition phenomenon occurring after a rather detrimental hyper-inhibition period in the acute stage. This disinhibition fosters structural and functional plasticity supporting motor recovery towards the early chronic stage.

### 3.5.1 Perturbation of brain oscillatory modes in the acute phase after a stroke

The decomposition of TMS-induced oscillations in stroke patients revealed several discrepancies in brain dynamics occurring in the acute stage. The most noticeable might be the global slowdown of the oscillatory patterns drawn from the decomposition, compared with healthy adults (**Figure 3.3**). Most of the knowledge

about the disruption of the neural oscillatory activity induced by ischemic strokes mainly comes from resting-state EEG studies (Keser et al. 2022) that accumulated evidence pointing to an increase in low (δ, θ) and a decrease in higher (α, β) frequency bands' power (S. Finnigan et van Putten 2013; Jordan 2004). Notably, such slow EEG abnormality was found to be an accurate index for discriminating between acute stroke patients and age-matched controls (S. Finnigan, Wong, et Read 2016). We extended these results by showing that, more than pure variations of spectral power within one frequency band or the ratio between several bands, the structural damage caused by stroke may have also changed the resonance frequency of brain oscillators, which could not be solely explained by normal ageing (**Figure 3.3C**). By taking advantage of the higher spatial resolution of MEG, Tecchio and colleagues (2005) found a similar slowdown within higher frequency bands between the unaffected and the affected hemisphere. The exact origin of induced oscillations remains in debate, but it has been shown that TMS was particularly prone to generate and amplify thalamocortical loop oscillations (Pellicciari, Veniero, et Miniussi 2017; Rosanova et al. 2009). Such slowdown of high frequency oscillations has also been observed using TMS-EEG coupling in several psychiatric pathologies, and has been linked with the disruption of thalamocortical circuits (Canali et al. 2015; Ferrarelli et al. 2012; 2008). That this cortical-subcortical functional connectivity was severely impaired in our cohort of patients, is supported given the fact that lesions were largely present in subcortical areas (**Figure 3.2**).

The β mode showed the largest change in acute stroke patients, compared with healthy adults. First, instead of being centered over the stimulated ipsilesional motor cortex as in healthy adults, its topography extended to a broader central area that peaked over the contralesional motor cortex. The over-activation of the contralesional motor cortex, as a compensatory mechanism for the breakdown of cortical activity within the damaged hemisphere, is a phenomenon that is well described – yet the functional meaning still debated during the course of recovery (Guggisberg et al. 2019; Hummel et al. 2008). Second, in addition to a decrease of the high frequency peak of nearly 30 %, the frequency pattern turned unimodal with the absence of a low frequency peak. This might correspond to the disturbance of the waveform shape of the sensorimotor μ oscillation, going from its stereotyped arch-shaped (Kuhlman 1978) to uncommon sinusoidal waveforms. The waveform shape has been proposed to carry valuable neurophysiological information, from microscale mechanisms, such as the exact pace of depolarization and hyperpolarization of layer V neurons or the stimulated population firing rate, to mesoscale parameters, such as the exact spatial position of the current source within the gyral anatomy (see (Cole et Voytek 2017) for a review). Regarding this last point, the μ rhythm is supposed to be mainly generated by the primary somato-sensory area S1, on the posterior wall of Rolandic fissure (Cole et Voytek 2017; Tiihonen, Kajola, et Hari 1989). Such micro to mesoscale properties might be strongly affected after a stroke, due to the cellular damage caused by the lesion and edema leading to spatial shifts of current sources (G et al. 2015).

### 3.5.2 Evolution of TMS-induced oscillations as a proxy of functional reorganization and its underlying mechanisms

In order to assess the evolution of the observed induced oscillation patterns through the different stages of recovery, we added a fifth dimension encompassing the longitudinal aspect of the present data in the tensors. Their decomposition allowed to observe interesting functional reorganization phenomena occurring between the acute and early chronic stages that were beneficial to motor recovery. The θ and α band modes were associated with significant changes through time, with final weights at early chronic stage being respectively larger for the θ and smaller for the α mode than the initial ones linked to the acute phase, that the decomposition was performed on the three stages (**Figure 3.4A**), or on only two of the three over larger groups of patients (**Figure 3.4B**). Of importance, the changes among stroke stages observed in the θ and α were mainly driven by the recovering patients' group (**Figure 3.5A**), in which the strength of the link was positively correlated with global and task-related motor recovery scores at the subacute and early chronic stage (**Figure 3.5B**).

Considering the presence of θ oscillations as an important basis for inter-regional communication, its positive modulation along recovery might be the signature of the re-establishment of large-scale functional connectivity within the motor network to foster functional recovery. There is growing evidence suggesting that stroke, more than inducing dysfunction that remains localized to the lesioned area, has a direct impact on functional connectivity (Guggisberg et al. 2019), i.e., neural communication within connected brain areas. The level of disturbance on functional connectivity has been associated with proportional neurological deficits in stroke patients (see, e.g., Urbin et al., 2014; Allegra et al., 2021; Carter et al., 2010), its normalization with time being furthermore linked with recovery (see, e.g., Golestani et al., 2013; Wu et al., 2015). Even though the increase observed toward the early chronic stage within the θ oscillatory mode was not directly linked with motor scores, it was observable when recovering patients were included in the data tensor, pointing towards a normalization of interregional interactions. On the other hand, the longitudinal decrease observed in the α mode, together with the absence of any significant change within the β band mode, may underline the importance of the evolution of the GABAergic over the glutamatergic system activity and the respective excitation/inhibition balance throughout the stroke stages. This points to the existence of a beneficial disinhibition phase, especially in the recovering patients' group, which will be discussed in the next section.

Former studies have shown the importance of the presence of low frequency oscillations, such as δ and θ bands, in the lesioned hemisphere that were linked with better motor recovery (for review see Keser et al. (2022)). Interestingly, this phenomenon was unveiled by studying brain oscillations either at rest (Marlene Bönstrup et al. 2019) or during an active state when patients were performing a visuomotor task (Cassidy et al. 2020). However, findings at rest have the caveat that they might not be functionally relevant and the findings during tasks have always the

confounder of the individual level of task performance/impairment and the respective effort needed that both impact significantly on oscillatory activity. In contrast, TMS-EEG allows to address both shortcomings by (a) a controlled input to the motor system that (b) is functionally meaningful. The use of TMS thus allows to directly observe controlled brain oscillations, that can be analyzed and classified either as evoked or induced by the stimulation, depending on whether one wishes to observe the result of coherent firing (evoked) or nonlinear interactions (induced) of neurons following the stimulus (Mutanen 2013; Pellicciari, Veniero, et Miniussi 2017). By fully taking into consideration the variability regarding phase and latency of the generated neural oscillations (Moliadze et al. 2003), focusing on TMS-induced oscillations allows to become even more sensitive to stroke-related changes in brain dynamics. Lastly, induced oscillations are known to rather reflect higher-order processing (Henao et al. 2020; Tallon-Baudry et al. 1996), which is of particular importance when studying post-stroke recovery. In this vain, the analysis of TMS-induced oscillations explained the observed variability in motor recovery of fine motor tasks, such as the nine-hole peg and box and blocks tests, tests relying on higher-order motor processes, such as grasping and manipulation, which engage complex motor networks distributed among motor, premotor and parietal cortices among other (Errante et al. 2021).

### 3.5.3 Disinhibition to support motor recovery

α band modulations found here can be considered as a proxy of the dynamical evolution of the intra-cortical inhibitory system that has been suggested to sustain motor recovery (Liuzzi et al. 2014; Mooney et al. 2019) (**Figure 3.6**). As stated above, previous evidence suggested that late TMS-induced oscillations occurring in the α band are linked with GABAergic mediated inhibition (Premoli et al. 2017). Immediately after stroke, during the so called hyper-acute phase, it has been shown that an over-inhibition of the perilesional cortical areas prevents additional tissue damage from the excitotoxicity induced by the ischemia (Clarkson et al. 2010; Michalettos et Ruscher 2022; Rabiller et al. 2015). However, the persistence of such over-inhibition state in time was correlated with poorer motor outcomes (Clarkson et al. 2010; Liuzzi et al. 2014) and pharmacological reduction of GABAergic inhibition led to better recovery in animal models (Clarkson et al. 2010; Lamtahri et al. 2021; Lebrun et al. 2022). Further evidence has confirmed this last point, by linking better motor recovery with the presence of a period of a plastic state driven by molecular changes, such as cellular excitability (Joy et Carmichael 2021), or by a sustained disinhibition phase during the first weeks post stroke. It has been suggested that this disinhibition phase promotes functional reorganization within the lesioned hemisphere (Clarkson et al. 2010; Liuzzi et al. 2014; Mooney et al. 2019). Following this reasoning, the initially high level of the α mode weights in the acute to subacute stages may be the signature of the enduring and detrimental nature of a GABA-mediated hyper inhibition state, as revealed by its association with acute residual motor functions. Furthermore, the decrease of the α mode found in the recovering patients' group will most likely be a correlate of the

disinhibition that occurred between the subacute and early chronic stage (three weeks to three months post stroke) that is supportive of the recovery process.
The time frame of this phenomena is somehow coherent with the previous findings of Liuzzi et al. (2014), who found disinhibition to occur from the first days up to three weeks after stroke onset. Despite the fact that in this previous work a very small and homogenous mildly impaired patient group was studied, the slight differences in the precise timing of this effect might in fact also come from the brain areas represented by the specific measures. While the short-interval intracortical inhibition protocol used by (Liuzzi et al. 2014) allows to measure the intracortical GABAergic system activity locally within the motor cortex, the late induced α oscillations found in the present work are linked with the inhibitory system activity at a rather more global scale, i.e., engaged in higher-order processes within larger-scale brain networks (see above). The disinhibition phenomena might first occur locally within the lesioned motor cortex in the subacute stage before spreading to larger areas in order to promote functional plasticity more broadly to support more complex motor (and cognitive) functions in later stages. Since patients presenting these particular changes of inhibitory activity over time were linked with better motor improvement (**Figure 3.5B**), our results support the idea that the exact timing of the evolution of the inhibitory system after stroke is of importance for the degree of motor recovery (Liuzzi et al. 2014). Finally, the presence of a slow increase of α activity in stable patients (**Figure 3.5A**) might be the signature of the normalization of the inhibitory system activity. A beneficial disinhibition phase might have already occurred during the early acute stage in this patient group, which was outside the scope of this study, explaining their stable and high motor function at their inclusion in the protocol. Overall, these results are supportive of the continuous evolution of a precarious balance between excitatory and inhibitory systems, which disequilibria in either direction may be beneficial or deleterious, depending on when they occur after stroke (Carmichael 2012).

### 3.5.4 Limitations

Despite the exciting opportunities that the present analytical method provides, there are a few points worth to consider to mention. One point to be aware of is the arbitrary choice of the number of modes to be extracted. Fixing this number to 3 appeared to be the best choice for several reasons. First, it is a good trade-off between achieving a plateau of at least 50 % of explained variance while preventing worse diagnosis regarding the proportion of variation that can effectively be explained by multidimension linear phenomenon, as the corcondia value (Bro et Kiers 2003) was already weak (15 %) or null (see SOM and Table S1). Second, the 3 computed components are physiologically meaningful in all five analyses, extra components being only the repetition or overlap of these three first components, as also found earlier by (Tangwiriyasakul et al. 2019). A limitation comes from the distribution of our patient cohort with respect to the severity of motor impairment in the acute stage and the degree of recovery. Most of the patients were rather mildly impaired. Additional

analyses on more heterogenous groups will help in future to refine the present conclusions of the link between changes of brain oscillatory modes and motor recovery.

## 3.6 Conclusion

In summary, the present study with a large stroke patient cohort recorded longitudinally using TMS-EEG allowed to better understand the neural mechanisms linked to motor recovery. The present results are supportive of the existence of a disinhibition phase occurring between the subacute and early chronic stage that is beneficial for motor recovery. The acquired knowledge might pave the way to develop novel biomarkers for determining and predict stroke recovery and to personalize innovative therapies based on modulation of brain oscillatory activity by e.g., non-invasive or invasive brain stimulation.

## 3.7 List of Supplementary Materials

Supplementary Table S1 shows the percentage of explained variance and the core consistency diagnosis (corcondia, (Bro et Kiers 2003)) obtained by decomposing the tensor using from 1 to 8 components. The corcondia is a feature specially designed for such decomposition methods, that allows to check if the data can be fully multilinearly modeled (in %, 100 % meaning perfect multilinear data). For all the tested models, the explained variance increased non-linearly together with the number of computed components, while the corcondia dropped from 100 % to 0 % in parallel.

**Table S3.1 Explained variance and core consistency diagnosis (corcondia – cor.) of each of the PARAFAC decomposition, using from 1 to 8 components (N)**

| N | Stroke A stage | | Healthy young adults | | Healthy old adults | | Stroke A to EC stage | | Recovering patients | | Stable patients | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | % Var | Cor. | % Var | Cor. | % Var | Cor. | % Var | Cor. | % Var | Cor. | % Var | Cor. |
| 1 | 49.9 | 100 | 45.4 | 100 | 41.1 | 100 | 47.5 | 100 | 48.1 | 100 | 47.2 | 100 |
| 2 | 53.9 | 59.9 | 53.5 | 69 | 46.7 | 32.1 | 49.6 | 1.3 | 51.8 | 37 | 50.2 | 76.5 |
| 3 | 56.8 | 15.1 | 60.3 | 15.5 | 50.4 | 4.9 | 53.5 | 0 | 55.8 | 0 | 53.7 | -1 |
| 4 | 58.7 | 0.2 | 63.7 | 0.8 | 52.5 | 0.5 | 56.2 | 0 | 58.7 | 0 | 55.0 | 0.4 |
| 5 | 60.4 | 0 | 66.4 | 0.3 | 54.2 | 0.1 | 57.7 | 0 | 60.6 | 0.1 | 58.0 | 0.1 |
| 6 | 61.7 | 0 | 69.4 | 0 | 55.7 | 0.1 | 59.2 | 0 | 62.2 | 0 | 59.4 | 0 |
| 7 | 63 | 0 | 70.8 | 0 | 57.8 | 0 | 60.6 | 0 | 63.5 | 0 | 60.7 | 0 |
| 8 | 64 | 0 | 72 | 0 | 59 | 0 | 61.4 | 0 | 64.4 | 0 | 61.7 | 0 |

# 4. GENERAL DISCUSSION

The main objective of this thesis was to extend the current knowledge on the mechanisms underlying motor recovery after a stroke. In a healthy brain, the balance between excitation and inhibition is dynamic and depends on the function studied. For instance, one can observe a release of inhibition before a movement (Reynolds et Ashby 1999). It is known that this balance is mostly mediated by glutamate- and GABA-ergic processes (Carmichael 2012; Joy et Carmichael 2021). A stroke perturbates this equilibrium through a cascade of cellular and molecular events. The resulting changes vary among patients and can be either adaptive or maladaptive, i.e. can promote or hinder post-stroke recovery. Uncovering the underlying mechanisms for these divergent outcomes would be a game changer for the development of future innovative therapies, as it would pave the way towards a modulation of these mechanisms in a personalized manner. In this thesis, we approached this challenge with a large, longitudinal and multimodal project on stroke patients with the goal to investigate the neurophysiological correlates of motor recovery in each patient. In Study I, we used TMS-evoked activity to investigate local cortical excitability, while in Study II, TMS-induced activity informed us about whole-brain reorganization, with a focus on the GABAergic status in both studies. This offered us a complementary and novel view on neural activity, by examining both local and global markers of the excitation/inhibition (E/I) balance in a cohort of patients with heterogenous impairment levels.

In this last chapter, the different findings resulting from both studies will be summarized and related with each other. We will discuss how the higher cortical reactivity of the ipsilesional hemisphere in the acute stage and the large-scale disinhibition in the subacute stage contribute to post-stroke motor recovery. We will put our findings in context with what has been found in other modalities or in animal studies. Next, challenges and limitations of the presented studies will be considered. Finally, an overview of possible next steps will be presented.

## 4.1 Local increase of excitability in the acute stage is linked with better recovery

We know from previous research that the electrical activity captured by the EEG electrodes next to the site of TMS is mostly due to the activity of the excited neuronal columns located beneath them (Jackson et Bolger 2014). Time-locking this activity to the TMS pulse and averaging the trials centered around it, will remove the neurophysiological background activity. The time-locked evoked activity will lead to a noticeable signal on the EEG, whose amplitude on the neighboring electrodes will be representative of the number of cells recruited. Thus, the magnitude of the early activity generated during the first tens of milliseconds informs on the cortical excitability

of the area stimulated. By focusing the analysis on the electrodes close to the motor cortex, the recorded signal is influenced predominantly by the local activity. It is however essential to bear in mind that this signal, to a lesser extent, also includes neural activity from the rest of the brain.

To characterize the cortical excitability, we calculated in Study I the local mean field potential (LMFP). Indeed, the neuronal activity produced by a single stimulation is mainly driven by glutamatergic pyramidal neurons (Jackson et Bolger 2014; Nunez, Nunez, et Srinivasan 2019; Murakami et Okada 2006; Aberra et al. 2020a; Siebner et al. 2022). Hence, the higher the excitability, the larger the recruitment of neurons and thus the larger the LMFP (Casarotto et al. 2013; Romero Lauro et al. 2014) of the motor cortex. The LMFP is therefore a common readout for the local excitability of the stimulated area and has been previously applied to stroke (Tscherpel et al. 2020). In Study I, we found that a higher LMFP in the first week post stroke was associated with a better improvement in distal motor function, indicating that a higher excitability of the motor cortex in the acute stage is highly beneficial for motor recovery.

Furthermore, we established a link between the activity of the inhibitory system and motor recovery. In Study I, we used a paired pulses TMS paradigm, meaning that we primed the GABAergic interneurons with a conditioning pulse, before evoking a signal with a test pulse. Following a paired-pulse, a greater LMFP will thus represent a greater disinhibition of the layer V pyramidal cells. In Study I, we linked a greater LMFP (i.e., a greater disinhibition) in the acute stage to better motor improvement three months post stroke (**Figure 2. *4***), indicating a beneficial role of cortical disinhibition for stroke recovery.

Overall, a supportive role of an increase of excitability in the acute stage, mediated by GABAergic disinhibition, is in line with previous studies in rodents (Clarkson et al. 2010; Lake et al. 2015; Alia et al. 2017; Lamtahri et al. 2021; Lebrun et al. 2022) and humans (Liuzzi et al. 2014; Takechi et al. 2014; Ferreiro de Andrade et Conforto 2018; Cirillo et al. 2020). Similarly, increasing the excitability of ipsilesional motor cortex in the acute stage by non-invasive brain stimulation (NIBS) improved motor function through LTP-like plasticity (Khedr et al. 2005; Di Lazzaro et al. 2010). Finally, a link between greater acute ipsilesional disinhibition and better motor recovery has been reported before (Liuzzi et al. 2014; Di Lazzaro et al. 2012).

This mechanism would be responsible for the instauration of a plastic phase during which neuronal reorganization is facilitated. Enhancing the excitability of the lesioned motor cortex in the acute stage could thus be required for motor learning. This would be in line with previous studies in healthy participants which showed that an increase in excitability enhanced motor learning (Pascual-Leone et al. 1998; Muellbacher et al. 2002; Reis et al. 2009; Censor, Dimyan, et Cohen 2010; Schambra et al. 2011; Buch et al. 2017). However, while we focused so far on the activity predominantly emerging from the region around the site of stimulation, i.e. the motor cortex, stroke is a network disease that provokes large-scale reorganization, which we will discuss in the next section.

## 4.2 Large-scale modulation of functional integration promotes recovery

To further investigate the disinhibition time course and its relationship with recovery, we looked in Study II at whole brain activity through the oscillations induced from a single pulse. Indeed, the activity generated by a single stimulation will propagate to distant connected areas (Casali et al. 2010; Bortoletto et al. 2015a) and generated synchronized activity (Rosanova et al. 2009; Thut et Miniussi 2009; Pellicciari et al. 2018). Depending on their spatial, temporal and frequency profile, oscillations can reflect GABAergic and glutamatergic signaling. Indeed, recent pharmacological studies have linked reduced α oscillations to $GABA_A$ receptors inhibition (Premoli et al. 2017; Tangwiriyasakul et al. 2019) and, similarly, β oscillation and AMPA-R activity (Belardinelli et al. 2021). Θ band oscillations can inform as well on thalamo-cortical and cortico-cortical interactions (Canolty et al. 2006; Solomon et al. 2017) (see section 1.2.2.2). In addition, it has been suggested that synchronous network oscillations may be important for axon myelination and reflect the creation of new synaptic connections (Carmichael et Chesselet 2002; Nunez, Srinivasan, et Fields 2015; Fields 2015).

Using a new and innovative data-driven analysis method (PARAFAC) in Study II, we decomposed the TMS induced-oscillations of the stroke patients, as well as of the two healthy cohorts (young and elder adults), into components - or “brain oscillatory modes” - that were mainly driven by θ, α and β oscillations. Interestingly, the α mode of stroke patients had spatial and frequency profiles similar to those found in healthy adults from our cohort and previous studies on TMS-generated oscillations (Premoli et al. 2017; Tangwiriyasakul et al. 2019), even if some disruptions were found in the acute stage. We therefore used the extracted brain oscillatory α mode as a proxy of the GABAergic activity.

The longitudinal analysis on the patient cohort in Study II showed that the α mode was significantly reduced between the subacute and early chronic stages, especially for patients showing an improvement of upper limb function. More precisely, we found that this mode was linked to poorer motor function in the acute stage but also related to better improvement of distal function in the following stages (subacute and early chronic). Altogether it appears that a reduction of α mode over time is associated with a better recovery, revealing a global disinhibition phase, especially between the subacute and early chronic stages. This reduced inhibition was correlated with a better recovery of motor function, similar to the local increase of excitability described in the previous section. However, this global disinhibition arrived later than the local phenomenon, which we will further discuss in section 4.4.

Concerning the timing of this disinhibition, our results are in line with animal works showing a reduction in GABAergic markers i.e., perineuronal nets and parvalbumin interneurons, after 30 days post lesion but not after 7 days (Alia et al. 2016b). It would correspond to the suggested peak of circuit plasticity in humans, thought to occur between the first and third months (Zeiler et Krakauer 2013; Krakauer et al. 2012). Yet, these results mainly concerned the perilesional tissue, whereas our results

suggest a more global phenomenon. However, fMRI studies have reported inter-hemispheric changes of excitability and functional connectivity in a similar timeframe as ours. Indeed, according to these studies, the reorganization of the motor network occurs predominantly between two weeks and 6 months (for review, see Rehme et Grefkes 2013).
Overall, the α mode described in our work could reflect a global change of inhibition over the first weeks to months after stroke. This phenomenon is most likely to be mediated by $GABA_A$ signalling rather than glutamate as we found significant changes of the α mode, but not on the β mode, the latter one being a proxy of AMPA-receptor activity (Belardinelli et al. 2021). This disinhibition between the subacute and early chronic stage could thus support functional reorganization within the network affected by the stroke. Additional results from our work indeed support the notion of restoration of thalamo-cortical and cortico-cortical connectivity.

## 4.3 Restoration of thalamocortical pathways and inter-regional connections

Aside from local and global changes in the E/I balance, Study I and II both revealed an evolution of markers of inter-regional communications. As the number of deflections is likely resulting from thalamo-cortical loops (Casali et al. 2013), the low number of deflections seen in the more affected patients in Study I are thought to be the result of perturbated cortico-subcortical. This was further confirmed by our voxel lesion TEP mapping linking fewer deflections to lesions in the internal capsule. Similarly, Tscherpel et al. (2020) found a relationship between the number of deflections and lesions in the subcortical white matter of the corona radiata. Furthermore, our results from the paired-pulse protocol (Study I), which reflect intracortical inhibition, suggested that the deflections inform on both cortico-subcortical and local inter-layers interactions. In that sense, the increase of deflections between the acute and early chronic stage and its association with better motor recovery could suggest the need of greater functional connectivity to promote recovery. Similarly, this hypothesis is supported by the increase of the θ mode between the 3$^{rd}$ week and the 3$^{rd}$ months post stroke seen in Study II. This oscillation is thought to arise through feedback activity from remote areas (Siebner et al. 2022) and is associated with inter-regional communication during cognitive processes (Canolty et al. 2006; Solomon et al. 2017). Although this mode was not directly associated with improvement of motor function, its increase between the subacute and early chronic stage was predominantly found in the subgroup of recovering patients (see **Figure 3.4**).
The increase of inter-regional connectivity along with recovery revealed in this thesis is in line with previous works about the effect of stroke on network properties. In term of graph-theory metrics, stroke is known to reduce node degree, i.e. the number of functional connections between one node and the others (Philips, Daly, et Príncipe 2017; Zhang et al. 2017) and integration capacity (De Vico Fallani et al. 2013; E. S.

Duncan et Small 2016; Adhikari et al. 2017; Caliandro et al. 2017). This results in a more segregated network with less communication between functional modules (Páscoa dos Santos et Verschure 2022; Guggisberg et al. 2019). However, an increase of interaction between ipsilesional M1 and other cortical regions is associated with better motor recovery (L. Wang et al. 2010). This link between node degree and recovery has been reported for motor, language and spatial attention functions using resting-state recordings (Dubovik et al. 2012; Westlake et al. 2012; Guggisberg et al. 2015; E. S. Duncan et Small 2016). The evidence gained from our work reinforces the link between the restoration of inter-regional communication and better motor recovery.

Overall, we have described the importance of both local and global functional reorganization in motor recovery after stroke. However, the temporality of these mechanisms appears to differ depending on the location of the process. The next chapter will provide a model of the time course of local and global disinhibition based on the results from this thesis.

## 4.4 Time course of the E/I balance

Putting together the findings from this thesis, it appears that we revealed a link between local and global disinhibition (likely mediated by $GABA_A$-receptor activity) and motor recovery. In addition, our data revealed that a decrease of this disinhibition in the early chronic stage is associated with better recovery. Indeed, LMFP analysis revealed a decrease of the cortical excitability between the acute and the early chronic stage, whereas paired-regression quality score revealed a return of SICI activity closer to values seen in the healthy population (Raffin et al. 2020). Although LMFP has been previously linked with motor function in the acute stage (Tscherpel et al. 2020), it is the first time that the time course of this proxy of cortical reactivity is associated with recovery.

Concerning the local E/I balance around the ipsilesional motor cortex, our data indicate a local disinhibition mediated by $GABA_A$-receptors in the first week post stroke, followed by a progressive return to a more balanced E/I equilibrium. It has been shown before that relief of inhibition in the acute stage, at rest in rodents (Clarkson et al. 2010; Lake et al. 2015; Alia et al. 2016b; Lebrun et al. 2022; Lamtahri et al. 2021) and during movement in humans (Liuzzi et al. 2014), is positively related with motor recovery. The acute disinhibition is known to counter the initial over-inhibition protecting the perilesional area from the toxic excessive post-stroke glutamate release (Clarkson et al. 2010; Lai, Zhang, et Wang 2014; Rabiller et al. 2015). This disinhibition is thought to allow plastic changes and the reorganization necessary for the recovery of the lost function (Moskowitz, Lo, et Iadecola 2010; Carmichael 2012; Krakauer et al. 2012). Moreover, our data showed a return to a balanced E/I ratio in the subgroups of patients recovering. This phenomenon could thus appear once patients recover their motor

functions, i.e. when the pro-plastic physiological environment is not necessary anymore.

There are similar reports of ipsilesional overactivity returning to physiological levels after 6-12 months in well recovered patients (Calautti et al. 2001; Loubinoux 2003; Ward 2003; Rehme et Grefkes 2013) whereas persistent ipsilesional fMRI over-activity is found in chronic patients with greater motor deficits (Ward et al. 2004; Loubinoux et al. 2007; Marshall et al. 2009). Returning to a normal amount of E/I balance after recovery could support the consolidation of the new functional circuitry and prevent further remodelling, as seen in the developing visual system (for reviews see (Zeiler et Krakauer 2013) and (Joy et Carmichael 2021)). Indeed, following the period of visual cortical development, characterised by intermediate level of inhibition that provides the optimal balance between sensitivity and specificity, increasing amounts of inhibition maintain these adult circuits and shut down the robust plasticity seen only during the critical period (Hensch 2003).

On whole-brain level however, we saw a different time course of inhibition, as reflected by the evolution of the α mode. A slight overinhibition in the acute stage was followed by a strong reduction of inhibition between the subacute and early chronic stage. This late time window could correspond to the reorganization of regions previously connected to the lesioned area. Indeed, after a stroke, the remote areas previously connected to the lost region are also progressively affected. This phenomenon is called diaschisis and corresponds to the loss of excitation from long-range cortico-cortical excitatory connections (Páscoa dos Santos et Verschure 2022; Stepanyants et al. 2009; Aronoff et al. 2010; R. Tremblay, Lee, et Rudy 2016). The α mode showed in Study II could thus reflect global reorganization, with an initial loss of excitability in the first week, corresponding to diaschisis, followed by reorganization of remote areas up to 3 months post stroke. This timing is coherent with report of remote plasticity until the early chronic stage in both rodents (van Meer et al. 2012)and humans (Joy et Carmichael 2021; Bernhardt et al. 2017; Corbett et al. 2017; Obando et al. 2022). Another possible origin of this large-scale disinhibition could come from the regulation of the interhemispheric balance with the relief of over-inhibition from the contralesional M1 (cM1) to the ipsilesional M1 (cM1) (Murase et al. 2004; Duque et al. 2005; Hummel et Cohen 2005; Grefkes et al. 2008). However, more specific analysis, such as M1-M1 functional connectivity, would be necessary to address this question.

Taken together, we suggest a temporal profile of the inhibition levels across space and time that encompasses the local and global processes revealed by this thesis (see **Figure 4.1**).

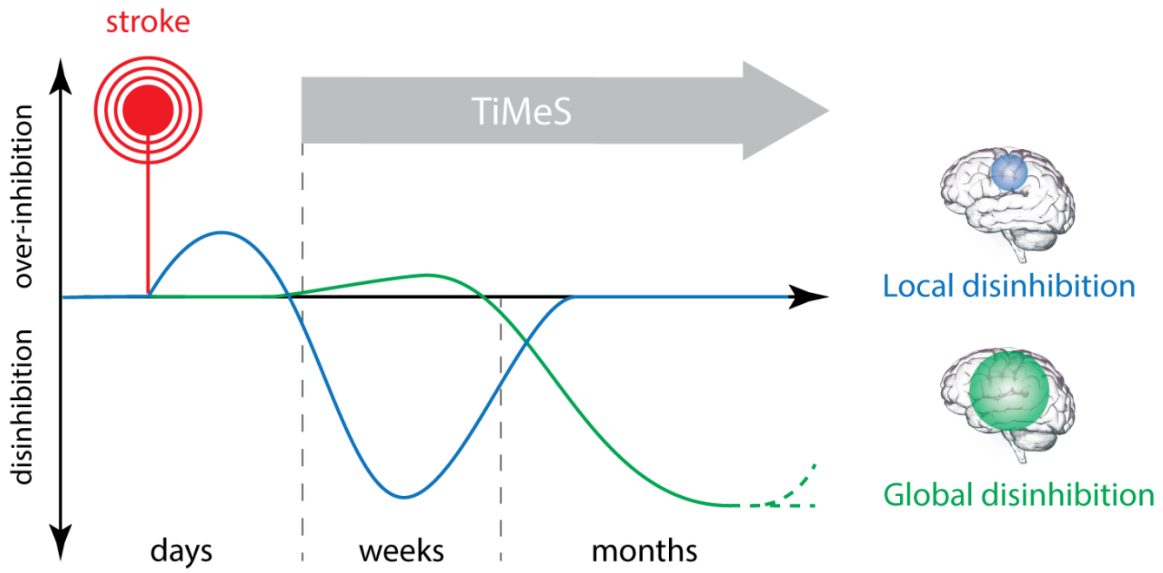


**Figure 4.1. Model of the modulation of inhibition as a function of time post stroke, for well recovering patients.** In the first days following a stroke there is a local over-inhibition (blue line) around the lesion to counteract the excitotoxicity from the excessive release of glutamate. Subsequently, our current results from the TiMeS project show that there is a local disinhibition phenomenon in the acute to subacute phase, followed by a return to normal level for the patients who are recovering. Later on, we see a global disinhibition (green line) from the subacute to early chronic phase, associated with better motor recovery. The time course of the global phenomenon after the first three months post stroke is yet to be elucidated.

## 4.5 Methodological considerations

Despite being a potent tool for the investigation of local cortical activity and long-range communication, TMS-EEG present certain limitations resulting from the coupling between both electrophysiological technics and its only recent use in clinical settings. The next sections will discuss the technical challenges behind TMS-EEG coupling and the question of choosing the right analytical methods depending on the population studied.

### 4.5.1 Challenges of TMS-EEG

Prior to establishing hypotheses regarding the physiological mechanisms underlying the E/I balance and its relationship with motor recovery, it was important to ensure that the signals we recorded corresponded to physiologically meaningful activity. Combining TMS and EEG is not straightforward as the magnetic field generated by the TMS directly interacts with the EEG electrodes, creating multiple artifacts which are challenging to remove (Ilmoniemi et Kičić 2010; Rogasch et al. 2013; 2014; Van Doren, Langguth, et Schecklmann 2015; Freedberg et al. 2020). The complexity of these artifacts lies in the diversity of their origin, ranging from technical artifacts such

as amplifier saturation and build-up of electrical charge in the electrodes, to cofounded physiological responses in the form of somatosensory and auditory responses. To tackle these issues, several pre-processing pipelines and experimental guidelines have been applied to the analyses performed in the context of this thesis (e.g., TMSEEG (Atluri et al. 2016) or TESA, (Rogasch et al. 2017)). However, the field is still lacking a standardized procedure to remove artifacts, resulting in large inconsistencies between studies (Belardinelli et al. 2019; M. Biabani et al. 2019; Conde et al. 2019; Siebner et al. 2019). In particular, differences in pre-processing pipelines can have a major impact on the final results (Bertazzoli et al. 2021), and lead, for instance, to significant differences in topographies and amplitude for the same dataset, especially in the first 100ms. As the analyses performed in the first study were focused on this early period, we made sure to follow the state-of-the-art procedure and pipelines suggested by Rogasch et al. (2017). Moreover, as it is a longitudinal study, the exact same methods were used for each patient, as recommended by Bertazzoli et al. (2021) in order to limit the influence of the pre-processing steps. In an attempt to find a common solution to this problem, several groups are currently addressing this issue through joint projects to address the reliability, validity and the biomarkers development of specific TMS-EEG indexes, such as the TEPs (e.g., the Team for TMS-EEG (T4TE) initiative).

Another alternative to TMS-evoked signals consists of looking at induced activity. This is done by subtracting the average TMS time-locked signal from every trial in order to unveil the non-linear activity induced by the stimulation (Premoli et al. 2017; Tangwiriyasakul et al. 2019). As all possible artifacts stemming from the TMS are consistent and time-locked to the stimulation, removing the time-locked signal will also remove any potential TMS-related artifact. The PARAFAC analysis used in this thesis is one possible way investigate induced activity (Tangwiriyasakul et al. 2019). In our case, it also offered the advantage of circumventing the issue of masked activity related to the large and simple cortical signal captured in some patients. Indeed, we saw in the first study that such signals have a considerable impact on the recorded cortical activity, masking other relevant activity. However, despite being confident that this large signal also contains important information on the cortical excitability because of its correlation with motor recovery, we cannot completely rule out that some part of the signal variance of this atypical component might be unrelated to the stroke and coming from, for instance, muscle activation or electrical charges accumulated at the electrode level (Rogasch et al. 2013). By removing any evoked activity – and therefore also the large and simple cortical signal - with the PARAFAC analysis, we solved this issue.

### 4.5.2 Finding the appropriate analysis to capture stroke-specific activity

As expressed earlier, the inter-subject reliability of TEPs is still a source of debate in the TMS-EEG community even in healthy subjects (ter Braack, de Goede, et van Putten 2019; Kerwin et al. 2018). The heterogeneity of TEPs in stroke patients is even greater than in the general population, because a stroke has a large impact on the neuronal physiology and on the resulting EEG signal. Additionally, this impact can be highly variable across patients. In our cohort, but also in previous studies (Tscherpel et al. 2020), the dissimilarities were such that they made classical analyses of TEPs impossible, such as those focused on specific components (e.g. P30 or N45, for review see Darmani et Ziemann (2019)). It led the teams working on TMS-EEG with stroke patients to come up with new metrics, tailored to the atypical signal observed in patients (Casula et al. 2021; Hussain et al. 2020; Hussain et Quentin 2022). Nevertheless, the use of such novel approaches could further complexify the task of bringing together results from different teams, if radically different analyses were performed. Here, we used classical methods, such as LMFP, as well as more complex types of analyses, such as the paired and unpaired regression quality scores to address both reproducibility and expansion of knowledge. Moreover, we also opted for a data-driven technique that keeps the high dimensionality of the EEG data and thus preserves most of the information about the neuronal activity induced by the TMS. PARAFAC does not rely on many assumptions and can thus be applied in a multitude of situations. However, as the three modes extracted from our data only explained 50 to 60% of the signal variance, important information could have been lost in the factorisation. Furthermore, a data-driven analysis will automatically capture signal having the most influence in the data, with limited selection from the experimenter. This could prevent the investigation of specific mechanisms such as specific frequency bands or regional activity. We thus believe that combining data-driven analyses with more traditional ones can ease drawing the link between evidence reported in different studies and further extend the knowledge gathered on the mechanisms sustaining recovery.

## 4.6 Limitations and Perspectives

The findings included in this thesis shed additional light into the role and time course of disinhibition in motor recovery after stroke. While revealing the decisive role of the GABAergic signalling, numerous other factors also are responsible for post-stroke plastic changes (Guggisberg et al. 2019; Alia et al. 2017; Joy et Carmichael 2021). More research is needed to define and understand the exact perilesional and remote mechanisms which sustain motor recovery in each patient. For instance, while this work unveiled both local and global processes, ranging from the 1$^{st}$ week to the 3$^{rd}$ month post stroke, our current analysis cannot answer questions about the processes involved in the chronic stage. Moreover, as a single structure can be connected to

several other brain regions, a stroke can lead to a multitude of deficits in domains other than motor (Evangelista et al., s. d.; Joshua Sarfaty Siegel et al. 2016; Joshua S. Siegel et al. 2018; Corbetta et al. 2015; Griffis et al. 2019). However, how these structural and functional networks evolve along time post stroke and their relationship with recovery of motor and cognitive functions is still only partially understood. Investigating both local and global networks in a longitudinal fashion and putting their properties in relation with deficits in different domains will further help to comprehend the full picture of the mechanisms underlying post-stroke recovery. TMS-EEG can provide great advantages in the study of functional networks (Bortoletto et al. 2015a), but every modality has its own limitations. Bringing together the different modalities performed in TiMeS (e.g., TMS-EEG, diffusion-weighted imaging, functional MRI) can unlock new windows on the post-stroke neurophysiological mechanisms and circumvent the limitations of each modality. The longitudinal data which the TiMeS project offers is unique in its size and combination of modalities and many further questions can be addressed with such a rich dataset.

### 4.6.1 Expanding time

We have seen before that the global disinhibition does not return to normal values in our current dataset (Study II). It remains an open question whether this neuroplastic state corresponds to a new equilibrium or if it will return to normal levels once full recovery is achieved. Furthermore, as therapies in the chronic stage still achieve only limited results (Stinear et al. 2020), investigating the status of this global disinhibition in the last time point of our project (i.e. one year post stroke) and whether its time course is only dependent on time post stroke or evolves depending on recovery, could reveal new potential targets for future therapies (e.g. by pharmacological intervention or neuromodulation protocols).

### 4.6.2 Expanding domains

While this thesis focused exclusively on the motor cortex, stroke frequently induces deficits in a large variety of cognitive domains (Massa et al. 2015; Delavaran et al. 2017) which can also be major hindrances in returning to a normal daily life. Our cohort presents indeed a large diversity of cognitive impairment despite being recruited based on their upper limb motor deficits (see **Figure 4.2**). Indeed, 80% of them also showed a cognitive deficit in the acute stage, as assessed by a general screening tool (MoCA). In addition, 75% of patients presented a deficit in at least 2 other cognitive domains in addition to their upper limb motor deficit. Investigating whether the markers extracted in this work, and especially whole brain analysis - such as PARAFAC - extend to other domains could bring valuable information. We have seen that modes extracted from this analysis likely reflect large-scale activity, which could also be involved in high order cognitive processes. Namely, it could inform us about the specificity of the markers to one domain and indicate to what extent they could serve as either precise or multifaceted targets for intervention. Complementary, interactions between the

motor cortex and regions involved in high order cognitive processes, such as the frontal lobe, could be explored using effective functional connectivity analysis (Bortoletto et al. 2015a). Indeed, deficits in cognitive functions can be incapacitant per se, but might also slowdown the course of motor recovery (Mullick, Subramanian, et Levin 2015; Ramsey et al. 2017; Lingo VanGilder et al. 2020; Verstraeten et al. 2020). More specifically, previous literature reported some possible associations between executive and motor deficits both in older adults and stroke patients (Einstad et al. 2021; Elliott 2003). Furthermore, attentional functions are intrinsically involved in motor outcomes (Barker-Collo et al. 2010) and clustered with motor deficits (Corbetta et al. 2015). Therefore, it remains to be investigated how deficits in executive and/or attentional functions are related to worse motor recovery. Examining specific networks dynamics with functional connectivity analysis could help the phenotyping of patients and unveil new factors responsible for their heterogenous recovery.

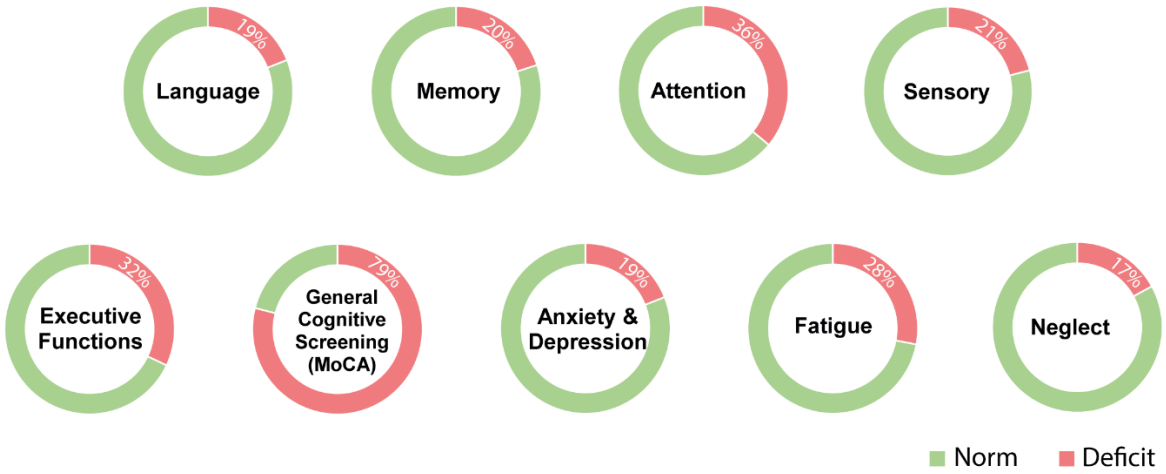


**Figure 4.2. Proportion of patients from the TiMeS cohort with deficits in specific domains**. N = 69. The percentage of patients with deficits is calculated for each assessment. The percentage in each domain correspond to the mean percentage of patients with deficits in the tests included in that domain. The cut-offs for norm and deficit are drawn from the literature. For more information on the behavioral tests, see (Fleury et al. 2022, in appendix)

### 4.6.3 Expanding modalities

Despite being a great tool for the evaluation of cortical physiology after stroke, TMS-EEG also has its limitations (see section 4.5). The main limitation being its poor spatial resolution. Combining other modalities, such as MRI, could provide complementary information on the structural correlates of the neurophysiological activity in the millimetre range. Feeding structural connectivity measures from diffusion MRI (dMRI) to TMS-EEG can reveal how structure-function (de)coupling is influenced by a stroke (Rossini et al. 2019; Bergmann et al. 2016b). Investigating interhemispheric balance through the proportion of activity generated in the ipsi- compared to the contralateral hemisphere (Casula et al. 2020) and examining whether it is linked with corpus

callosum integrity obtained through dMRI (J. L. Chen et Schlaug 2013), could inform on the factors responsible for different roles of the contralesional M1 after stroke (Murase et al. 2004; Duque et al. 2005; Hummel et Cohen 2005; Grefkes et al. 2008). Such analyses combining functional and structural information with TMS-EEG and dMRI have already been developed (Amico et al. 2017), but its application to stroke patients is limited (Brügger 2022).

Although TMS-EEG coupling allows the non-invasive stimulation and recording of any cortical region, it also limits the analysis to processes linked with the stimulated area. Resting-state EEG could then complement the gathered information, especially for the study of large-scale resting-state activity. Indeed, global scale resting-state functional connectivity could be of particular interest to investigate the relationship between cognitive and motor function throughout time after stroke. Although resting-state EEG connectivity studies have already been performed on stroke patients (Romeo et al. 2021; Dubovik et al. 2012; Cassidy, Mark, et Cramer 2022), longitudinal studies studying specific cognitive functions are still missing (Keser et al. 2022).

Finally, combining analyses with MRI data could add a supplementary dimension of complexity to help phenotyping patients. By combining the time resolution of TMS-EEG, the spatial resolution and information on deep structures from the structural and functional MRI along with the high dimensionality of the behavioural assessments, one could have the elements necessary to draw a nearly complete profile of each patient. Building such profiles would be a step forward in the direction of a better understanding of the physiological mechanisms underlying cognitive and motor deficits, as well as their restorative processes. This would open the door for better recovery predictions and better personalization of interventions. However, every layer of complexity comes with additional challenges. Finding the appropriate analysis to combine all these modalities will involve extensive work before being able to extract the full potential of multimodal datasets. The rapid expansion of machine learning algorithms, such as multivariate regression, support vector machine or clustering analysis offers exciting possibilities and has the potential to close the gap between our the present days and the age of personalized medicine (Bonkhoff et Grefkes 2022).

## 4.7 Conclusions

In summary, the present thesis aimed at uncovering the pathophysiological mechanisms provoked by a stroke, how they are linked with upper limb motor deficits, and what the mechanisms sustaining the restoration of functions are. We focused on the excitation/inhibition balance as it is thought to play a major role in stroke recovery (Páscoa dos Santos et Verschure 2022; Joy et Carmichael 2021; Guggisberg et al. 2019; Zeiler et Krakauer 2013; Carmichael 2012). By using TMS-EEG, we were able to investigate longitudinally the status of the GABAergic system in a large patient cohort. This work has shown that there is both a local and global disinhibition in the first weeks to months post stroke, with distinct dynamics for the two processes. Their

association with behavioural recovery reinforces the theory of a supportive role of a disinhibition. In this thesis, we used established as well as innovative TMS-EEG analyses to extend the knowledge of the role of inhibition in stroke recovery. The combination of two modalities took advantage of their respective strength, while reducing their limitations. These results advocate for the integration of complementary modalities and their use with extensive behavioural assessments to fully depict each patient's profile. We believe that achieving a detailed phenotype for a single patient is the key towards better individualized therapies and optimal recovery.

# 5. Appendix

## **T**owards **i**ndividualized **M**edicin**e** in **S**troke – the TiMeS project: protocol of longitudinal, multi-modal, multi-domain study in stroke

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## Abstract

Despite recent improvements, complete motor recovery occurs in less than 15% of stroke patients. To improve the therapeutic outcomes, there is a strong need to tailor treatments to each individual patient. However, there is a lack of knowledge concerning the precise neuronal mechanisms underlying the degree and course of motor recovery and its individual differences, especially in the view of network properties despite the fact that it became more and more clear that stroke is a network disorder. The TiMeS project is a longitudinal exploratory study aiming at characterizing stroke phenotypes of a large, representative stroke cohort through an extensive, multi-modal and multi-domain evaluation. The ultimate goal of the study is to identify prognostic biomarkers allowing to predict the individual degree and course of motor recovery and its underlying neuronal mechanisms paving the way for novel interventions and treatment stratification for the individual patients. A total of up to 100 patients will be assessed at 4 timepoints over the first year after the stroke: during the first (T1) and third (T2) week, then three (T3) and twelve (T4) months after stroke onset. To assess underlying mechanisms of recovery with a focus on network analyses and brain connectivity, we will apply synergistic state-of-the-art systems neuroscience methods including functional, diffusion, and structural magnetic resonance imaging (MRI), and electrophysiological evaluation based on transcranial magnetic stimulation (TMS) coupled with electroencephalography (EEG) and electromyography (EMG). In addition, an extensive, multi-domain neuropsychological evaluation will be performed at each timepoint, covering all sensorimotor and cognitive domains. This project will significantly add to the understanding of underlying mechanisms of motor recovery with a strong focus on the interactions between the motor and other cognitive domains and multimodal network analyses. The population-based, multi-dimensional dataset will serve as a basis to develop biomarkers to predict outcome and promote personalized stratification towards individually tailored treatment concepts using neuro-technologies, thus paving the way towards personalized precision medicine approaches in stroke rehabilitation.

Keywords: stroke, precision medicine, transcranial magnetic stimulation, electroencephalography, neuroimaging, biomarkers, recovery, neuropsychology

## Introduction and rationale

With 80 million survivors in 2016, stroke is the second most common cause of acquired disabilities in the world (1,2). This number is still increasing due to the population growth and ageing (3). Better acute stroke management results in an improved stroke survival, but implies a higher prevalence of chronic stroke (2). Yet, complete motor recovery still occurs in less than 15% of patients (4). Moreover, although motor deficits are the most debilitating and investigated (5–7), patients also show consistent long-lasting cognitive deficits (8,9), with a relevant proportion of patients having multiple domains affected. These long-term impairing behavioral deficits have a strong impact on patients' reintegration, on patients and their relatives' daily life, but also on socioeconomics and health care systems (10,11). Therefore, the call for effective strategies of neurorehabilitation in order to maximize the rate of recovery is recognized as a priority to substantially reduce the burden of stroke survivors (2,12). However, the heterogeneity in stroke outcome and in individual recovery potential is an important challenge to address, in order to provide optimal rehabilitative therapies. A crucial aspect to take up this challenge is to deepen our understanding of individual courses of recovery and the underlying neuronal mechanisms through the identification of associated biomarkers (13).

On the behavioral level, stroke is known to yield multiple deficits. The most reported and debilitating ones are the motor impairments, present in 50% to 80% of stroke survivors (7). In particular, damages to the upper extremity function are common and significantly impact the patients' capacity to retrieve independence, as well as to reintegrate to professional life (14,15). Besides motor deficits, cognitive impairment is common in stroke survivors although initially less obvious: half of stroke survivors report difficulties in at least one cognitive domain, but this area is much less studied than the motor domain (8,16). Cognitive impairment could be found in multiple domains most frequently in, e.g., executive functions, attentional functions or memory. Such deficits are significantly persistent after one to several years after the stroke (8,17). Cognitive deficits also represent an obstacle for patients to go back into a normal daily life (10,18,19). Furthermore, these dysfunctions might strongly impact, slow or even prevent proper motor recovery and response to treatment (20). For example, it is known that executive functions, such as information processing and motor planning are essential in the processes of motor (re)learning (21), which is crucial in motor rehabilitation following stroke. However, despite few investigations of the relationships between these domains (e.g. 17,22), research mainly focused so far on deficits in only one domain, e.g. motor (23), language (24) or attention (25) and neglected largely the interaction between them. Thus, there is a strong lack of knowledge about how deficits in different domains depend on and influence each other in regard of impairment, residual functions and the process of regaining lost functions after a stroke.

Recovery is often incomplete among stroke survivors, and the potential of restoring lost functions is crucially highly heterogeneous between patients (26,27). For example,

spontaneous natural recovery in motor domain occurs in roughly 2/3 of patients (13) who recover about ~70% in average of their maximum recovery potential given their initial impairment (28). In contrast, roughly 1/3 of patients presents altered or insufficient intrinsic plasticity after stroke leading to a poor natural recovery (13). Such heterogeneity has also been reported in other cognitive deficits e.g., neglect and aphasia (29). In addition, stroke survivors act highly heterogeneous in the view of the response towards specific treatment strategies, resulting in the distinction between responders and non-responders (30–32). For instance, patients with cortical lesions specifically demonstrated low responsiveness to repetitive Transcranial Magnetic Stimulation (rTMS) protocols (33). Therefore, a key challenging aspect for enhancing neuro-rehabilitation efficacy might be to shed light on the heterogeneity of stroke patients and leverage this information to determine and predict the degree of impairment and potential for individual functional recovery (34,35). This heterogeneity in stroke ranges from brain reorganization to behavioral outcomes and needs to be accounted for when planning rehabilitation strategies (32,34).

The identification of specific individual patterns of recovery through a multi-domain perspective during the first weeks/months post-stroke, and crucially the uncovering of the underlying brain reorganization mechanisms would be a massive step towards the optimization of treatment strategies for each patient. However, there is a lack of understanding concerning the detailed neuronal mechanisms following a stroke lesion and during the course of recovery. Accumulating evidence suggests that stroke is not a focal disorder, but a network disorder (36,37). In addition to local brain tissue damage, stroke also impacts the functioning of connected areas (close or remote from the lesion) as a result of alterations in brain networks (38). In addition, functional reorganization associated with recovery is also not restricted to a focal area. For instance, cortical plasticity associated with motor recovery is not restricted to the primary motor cortex (M1), but rather embraces the complete motor network, including primary and secondary motor cortical areas in both hemispheres, subcortical areas like the basal ganglia and the cerebellum (35, 39, 40). Factors such as lesion size and location (e.g., 41,42), as well as structural and functional prerequisites and dynamics (43) might relevantly influence recovery-associated plasticity processes in the brain leading to heterogeneous, widespread and time-dependent changes of brain reorganization and connectivity between patients. To improve rehabilitative strategies, it is therefore crucial to take this heterogeneity into account and understand how it relates to the pattern of network reorganization and the range of behavioral outcomes following a stroke.

On the basis of this reasoning, there is a strong need for an exact phenotyping of patients that would consider stroke heterogeneity in order to predict outcome and course of recovery and to further improve stroke recovery and treatment outcomes. Such challenge requires to gain a detailed and fundamental knowledge about the precise neuronal mechanisms associated with behavioral recovery, with a particular emphasis on brain networks changes. In addition, is essential to investigate the different domains impacted by the stroke instead of focusing on one behavioral

outcome. As network and behavioral alterations following stroke are dynamic and not linear, a longitudinal investigation is of great importance. Such phenotyping will allow to distinguish distinct profiles of patients with associated dynamics of brain reorganization over the course of recovery. Enhancing the fundamental knowledge of stroke diversity through a multimodal and multidomain approach would serve as a basis to pave the way for personalized precision medicine in the field of stroke recovery to achieve maximal treatment effects.

To take up this challenge, the TiMeS project aims at characterizing in details phenotypes of stroke patients allowing to determine the individual course and degree of recovery following stroke and to identify relevant biomarkers associated with recovery. To that purpose, the goal is to collect a large multidimensional dataset that would be representative for the stroke population. Measurements will come from synergistic state-of-the-art systems neuroscience methods including magnetic resonance imaging (MRI), transcranial magnetic stimulation (TMS) coupled with electroencephalography (EEG), in a longitudinal assessment from acute to chronic stage during the first year after the stroke. As stroke is not a focal disorder, subsequent analyses will focus on networks properties within the whole brain and their changes over time, in combination with stroke behavioral outcomes with a focus on motor domain and further investigations of other neurocognitive domains. To provide detailed knowledge about the behavioral patterns and relationships between domains, the procedure will contain an extensive evaluation of behavioral outcomes in multiple domains, including a multi-cognitive assessment. The multidimensional dataset acquired through this research will enable to assess for the first time the complex interactions of structural and functional brain connectivity parameters within certain domain-specific networks as well as within the whole brain, and to associate them with stroke behavioral outcomes and functional recovery.

## Methods

### Study design

The present project is an on-going longitudinal observational study. We follow-up a total of up to 100 stroke patients at four timepoints over one year after the ictal event (T1: 1$^{st}$ week, T2: three weeks, T3: three months, T4: twelve months) from the acute to the chronic phase of recovery. At each timepoint, we investigate the neural correlates of recovery and the underlying plasticity through a multi-modal and multi-domain set of evaluations including structural, diffusion, and functional neuroimaging (MRI), electrophysiology (resting-state EEG, and TMS coupled with EEG) and an extensive battery of tests assessing the multi-domain functional and behavioral outcomes of the patients.

### Objectives

The main goal of the study is to assess the inter-individual variance and different phenotypes of patients after a stroke (ischemic or hemorrhagic). The main goal is divided into two related objectives: 1) to evaluate the dynamics of neuro-imaging and

neurophysiological factors associated with post-stroke course and degree of recovery with a focus on motor domain and structural and functional connectomics, 2) to determine the interactions between multiple cognitive, visual, sensory, and motor functions, how they influence each other following a stroke, and their impact on impairment, residual functions and recovery.

To complete these objectives, we apply a multimodal assessment of neuro-imaging and neurophysiological parameters to leverage the advantages of each method and account for their specific limitations to achieve a very detailed picture, especially in the view of the importance of network analyses. In addition, we use an extensive battery of behavioral tests to acquire detailed information concerning the patients' motor and cognitive profiles as well as their dynamics. The overall goal of this research will be to integrate and combine the multimodal data (i.e. neuroimaging, electrophysiology, and behavioral) together to obtain detailed and complete phenotypes of stroke patients. A list of all the measurements is provided in Table 1.

**Primary outcome**

As upper extremity function and impairment are the main reason for long-term disability and predictors of reintegration in normal life and functional independence after stroke, longitudinal recovery of the upper limb function and its underlying mechanisms are the primary interest of this study. Upper limb motor function includes multiple aspects, fine and gross dexterity, gross motor function, strength, spasticity, etc (44). These aspects are assessed longitudinally using the same set of reliable and validated clinical tests at each timepoint (see Appendix n°1 for details). We are especially interested in how other cognitive domains and their alterations after a stroke impact on motor recovery.

**Secondary outcomes**

Secondary outcomes are specific readouts based on the multi-domain cognitive evaluation and the multi-modal data from system neurosciences techniques, i.e. neuro-imaging and electrophysiological methods.

Magnetic Resonance Imaging (MRI)

Structural, diffusion-weighted and resting-state functional MRI are used to obtain individual structural and functional network properties to evaluate lesion-related neuronal alterations as well as their dynamics throughout the recovery phase, i.e. neuronal plasticity, reorganization and degeneration. Analyses will mainly focus on brain network alterations and changes over time through disconnectomics (45) and by applying computational approaches such as graph theory methods (46), e.g the Rich-Club approach (47). In addition, integrated analyses of brain structure and function will be emphasized, e.g. by using the Structural Decoupling Index (SDI), a metric that allows to quantify the coupling strength between structure and function (48). MRI methods and sequences are detailed in Appendix n°2.

Electrophysiological recordings

Functional measurements of the cortical excitability are provided by means of Transcranial Magnetic Stimulation (TMS). We use single pulses delivered to the primary motor cortex (M1) to generate motor evoked potential (MEPs) and to screen

for cortico-spinal tract integrity. We also apply paired-pulses to assess the short-interval intracortical inhibition (SICI; 49). This is thought to reflect $GABA_A$-mediated inhibition in the motor cortex (50). Electroencephalography (EEG) allows to assess the resting state brain connectivity (51). More importantly, in combination with TMS, EEG is used to assess interregional connectivity in the brain and to characterize the TMS-evoked potential and its evolution during the course of recovery. Therefore, TMS-EEG represents a unique method to study brain dynamics and their changes over time as it allows to record directly and non-invasively various neurophysiological processes across motor and non-motor areas e.g. cortical responsiveness, cortico-cortical interactions, local excitation and inhibition, oscillatory activity etc (see Tremblay et al., 2019 for a recent review). Electrophysiological methods are detailed in Appendix n°3.

Behavioral outcomes

To assess precisely the motor and cognitive profiles of the patients, an extensive battery of 40 tests is performed at each timepoint by a trained neuropsychologist. The battery covers sensory-motor domains as well as each neuro-cognitive domain as defined in the DSM-V, i.e. executive functions, language, complex attention, learning and memory, social cognition, perceptual-motor domains (53). Multiple questionnaires complete this battery to evaluate additional aspects such as fatigue, mood, functional independence and recovery. See Appendix n°1 for details.

# LIST OF MEASURMENTS

## NEUROIMAGING

Diffusion-weighted imaging (DWI)
T1-weighted image
Multi-echo GRASE
BOLD functional MRI – Resting-state
GRE field mapping
Mp2rage
Susceptibility-weighted imaging

## ELECTROPHYSIOLOGY

Resting-state EEG
TMS-EEG coupling
- Single pulse
- Double pulse (SICI)

## BEHAVIOR

### *Clinical evaluation*
NIHSS

### *Motor functions*
Fugl-Meyer
Pinch&Grip
Medical Research Council muscle strength testing
Nine-Hole Peg Test
Box and Blocks test
Purdue Pegboard Test
Action Research Arm Test*
Modified Ashworth Scale
2 minutes walk test*
10 meters walk test*
Time Up and Go test*
Berg Balance Scale

### *Sensory functions*
Rivermead Assessment of Sensory performance

### *General cognitive screening*
Montreal Cognitive Assessment

### *Attentional functions*
TAP – Phasic alert test
TAP – Divided attention test
D2-R

## BEHAVIOR *(continuation)*

### *Social cognition*
Geneva Emotions Recognition Test – Short*

### *Executive functions*
Frontal Assessment Battery
Stroop Victoria
Bimanual coordination
Apraxia Screen of Test for Upper-Limb Apraxia
CERAD Constructional Praxis
Color Trail Test
Bisiach anosognosia scale
Somatoparaphrenia test
5-points tests*

### *Learning and Memory*
Hopkins Verbal Learning Test revised* Doors test*
Digit span
Corsi-Kessels

### *Perceptual function*
Overlapping figures test
Bisection line test
Bells cancellation test

### *Questionnaires*
Stroke Impact Scale (SIS)
Hospital Anxiety and Depression Scale (HADS)
State/Trait Anxiety Inventory for adults (STAI)
Fear and stress scale
Medical Outcome Study Short Form 12
Modified Reintegration to Normal Living Index
Social Comparison Scale
Generalized Self Efficacy Scale
Pittsburgh Sleep Quality Index
Multidimensional Fatigue Inventory
Feeling of foreigness questionnaire
Neurobehavioral questionnaire
Barthel index
mRS modified Rankin Scale
FAC functional ambulation category
FIM functional independence
Edinburgh handedness inventory

1

**Study organization**

Ethical considerations

The study was designed and is conducted according to the guidelines of the Declaration of Helsinki. All the procedures were approved by the cantonal ethics committee (Project ID 2018-01355).

Eligibility

We look for stroke patients presenting some upper limb motor impairment in the acute stage. In order to get a heterogeneous cohort, we screen patients with first-ever as well as recurrent stroke, either ischemic or hemorrhagic. Detailed inclusion and exclusion criteria are following:

- Inclusion criteria
    - Age > 18 years old
    - First-ever or recurrent stroke
    - Ischemic or hemorrhagic stroke
    - Stroke incident < 7 days at consent
    - Motor impairment in the acute stage, objectified by a clinical assessment
    - Absence of contraindication for NIBS and MRI

- Exclusion criteria
    - Severe neuropsychiatric (e.g. major depression, severe dementia) or medical disease
    - Not able to consent
    - Severe sensory or cognitive impairment or musculoskeletal dysfuntions prohibiting to understand instructions or the perform the experimental tasks
    - Implanted medical electronic devices or ferromagnetic metal implants, which are not MRI and TMS compatible
    - History of seizures
    - Medication that significantly interacts with NIBS being benzodiazepines, tricyclic antidepressant and antipsychotics
    - Pregnancy
    - Regular use of narcotic drugs
    - Request of not being informed in case of incidental findings

Recruitment and screening

Stroke patients are recruited at the stroke unit of the Hôpital du Valais (HVS). The member of staff in charge of the recruitment daily checks the list of new entries at the hospital. When a patient is eligible (see Inclusion and Exclusion criteria), the medical staff is consulted, and a first screening visit is organized with the patient. The study is presented in details to the patient, and eligibility is further evaluated. Patients are provided with 24-hours for reflection in regard of participation before signing the consent to participate. If the patient consents, the first visit (T1) is organized during the

first week after the stroke, while the patient is most of the time still hospitalized. The procedures are performed in accordance with the ethical approval.

Data acquisition and follow-up

The 1st behavioral evaluation and the MRI acquisition are performed at the HVS. The electrophysiological measurements are performed in the laboratory, located in the Clinique Romande de Réadaptation (CRR) physically connected to the HVS. The total measurement time is of around 10 hours, distributed in several sessions.

The patients enrolled in the study are then transferred for rehabilitation from the HVS to one of the two rehabilitation clinics collaborating within the present study, that is the CRR and the Berner Klinik (BK; Crans-Montana) or to home. The 3 weeks (T2) behavioral evaluation is performed during the in-patient stay, or in the laboratory if the patient was sent back home after the acute phase. For the 3 months (T3) and 12 months follow-ups (T4), patients are are invited to our laboratory on the HVS/CRR campus for behavioral, MRI and electrophysiological recordings. We will analyze the different behavioral domains individually but we also aim to integrate the multimodal data together in statistical models and computational approaches, in order to determine interactions between the different parameters.

**Data management, planned analyses and statistical considerations**

Based on previous comparable project (e.g. 41; N=132 patients) and given the estimated feasibility of our extensive multi-modal and multi-domain evaluations, we aimed to recruit up to 100 patients, with a recruitment rate of up to 40 patients a year. The minimal number of patients to be recruited is **XX**. So far, we recruited **XX** patients in the acute phase. As the study is mainly explorative in its nature, we do not use a classical power calculation. The multi-modal aspect of the project includes a very large number of behavioral outcomes as well as numerous neuroimaging and electrophysiological variables. Because of this, the high risk of Type 1 error due to the use of a large number of statistical tests might be carefully considered through appropriate corrections (e.g. XXX) and the reduction of data dimensionality. We report here the strategies planned to analyses the multi-dimensional data obtained

Behavioral planned analyses

The purpose of using an in-detailed set of behavioral assessments is to get a complete picture of behavioral functions after stroke and their dynamics in all domains, while avoiding the unique use of component scores to describe behavior. However, our extensive assessment battery entails a very large number of variables, which could lead to some redundancy between tests. Therefore, the first planned analyses regarding the behavioral dataset will be mainly descriptive to better understand the dispersion of performances and inter-individual variability for each test within each behavioral domain. Demographic and clinical information (i.e. sex, age, level of education, side and type of lesion, etc) will be systematically added in analyses as covariates. A second step will be to do a first investigation of relationships between variables using correlation matrices both within and between domains. These steps will enable a qualitative selection of variables to restrain the number of informative features for further analyses.

Clustering (e.g. k-means) analyses will then be used to investigate the emergence of different behavioral profiles within the cohort based on specific subset of variables, as well as their dynamics across time. These variables of interest will be selected based on previous exploratory analyses and/or on specific hypotheses from the previous literature (e.g. the existence of a strong relationship between motor impairment and attention; 70).

Further analyses using mixed models and multivariate linear regressions will enable to investigate early behavioral cognitive predictors of the post-stroke motor recovery, i.e. whether specific cognitive performances in the acute phase predict the course of motor recovery.

Finally, dimensionality-reduction methods such as principal component analysis and nonnegative matrix factorization (54) will be used to transform the large number of variables into smaller number of component scores specific to each behavioral domain. Therefore, the investigations of relationships between behavioral outcomes and neuro-imaging / electrophysiological features will be conducted using qualitatively selected variables from the battery and/or using component scores.

Neuroimaging planned analyses

Voxel lesion symptom mapping will be used to investigate the relationships between behavioral outcomes and lesion sites. Neuroimaging analyses will then focus on brain connectivity features through structural connectomics, which rely on models of white matter tractography computed from diffusion-weighted imaging. For each patient, we will compute a total connectome and an unaffected connectome, in order to incorporate the paths that have been disrupted by the lesion, together with their respective global efficiency, a metric reflecting the functional integration within networks (55,56). These features will be then related to post-stroke impairments, with a first focus on the sensorimotor and attentional domains as the networks underlying those functions are known to be respectively heavily localized versus more global (57).

Besides, integrated analyses of brain structure and functions will be performed using the Structural Decoupling Index (SDI; 48) to quantify the coupling strength between structure and function and how this could be impacted by stroke within the different brain networks. Using individual and functional structural connectome, SDI will be computed for each patient, each timepoint and within each Yeo brain network (58). Partial Least Square Correlations PLSC;(PLSC; 59) will be then used to identify multivariate correlation patterns between patient-specific nodal SDI measures and behavioral component scores for each domain (60).

Electrophysiological planned analyses

We expect a large heterogeneity of TMS evoked activity patterns within the brain among stroke patients and between single-pulse and double-pulse paradigms. In addition, the purpose is to compute TMS-EEG readouts that can be individualized in order to phenotype patients. Therefore, we plan to employ complex analytic measures beyond the classical use of grand average event-related potential (61–63).

We will compute the local mean field power (LMFP) which reflects the cortical reactivity (64) and the number of deflections of the local TMS evoked potential, which reflects

the complexity of the signal (62). Besides, Regression Quality Scores (RQS) will be used to assess the cortical response stability within one given timepoint (paired RQS) and level of similarity of cortical responses dynamics between two given timepoints (63). Those specific readouts will be then correlated with specific motor scores as well as their evolutions across the different timepoints.

Therefore, we will use a broad spectrum of statistical tools designed for high-dimensional datasets, like mixed-effects models but also Bayesian statistics including Bayes Factor and Bayesian ANCOVAs. All the statistics will be performed using either R software (2017, R Core Team, Vienna, https://www.Rproject.org), the SPSS software (2017, IBM SPSS Statistics for Windows, IBM Corp, Armonk, New York), the JASP software, Matlab (v2020b, Mathworks, The MathWorks, Massachusetts, http://www.mathworks.ch) and/or Python (2009, CreateSpace, Scotts Valley, California).

Implementing strategies to reduce the dimensionality of the data while keeping the richness of the planned multi-modal together with the planification of a priori specific analyses to conduct enable to anticipate issues related to multiple comparisons. Nevertheless, it is important to mention that due to the exploratory nature of the project, the initially planned specific analyses will certainly drive further complementary analysis based on specific hypotheses arising from the first insights. Overall, the ultimate objective will be to apply machine learning tools as classifiers, supervised, unsupervised and deep learning algorithms as they provide the opportunity to derive insights from imaging and electrophysiological data coupled with behavior to produce predictive models and to discovering phenotypes of patients (65,66).

## Discussion

As depicted in the introduction, stroke results in multi-domain behavioral deficits in survivors. Although motor deficits (in particular in the upper extremity) are the most impairing, the prevalence of cognitive deficits is also highly important and concerns multiple domains. In addition, they were demonstrated to likely impact the functional recovery and the reintegration in life following stroke, as well as the outcomes of motor rehabilitation (20). Yet, little attention has been paid so far to how cognitive and motor domains are related and influence each other following stroke. Consequently, there is a lack of detailed phenotyping of behavioral outcomes and their evolution though it would be of high interest to improve rehabilitation tailoring (41,67)

Some studies have investigated the relationships between cognitive and motor outcomes (17,22,41,68–70) and showed that cognitive impairments were common even in patients with mild strokes, and that relationships exist between motor and cognitive domains. This highlights the relevance of such multi-domain approaches, emphasizing that motricity and cognition should not be investigated separately. For instance, Einstad and colleagues (2021) have recently demonstrated that poor motor performances are associated with impaired global cognition scores and executive dysfunctions. However, such studies made use of a limited battery of tests and/or focused on one particular timeframe during stroke recovery without any longitudinal assessment (i.e. acute, sub-acute, chronic). Ramsey and colleagues (2017) employed a battery of motor and cognitive tests to evaluate the patients over the course of recovery during the first year; at 1-2 weeks, three months and one year after the stroke. They reported that across multiple domains, sub-acute scores were strong predictors of the performance in the chronic stage and that the magnitude and time course of recovery were comparable between cognitive and motor domains. Specific behavioral clusters were identified (e.g., a strong relationship between motor impairment and attention) and shown as being stable over the three timepoints. In addition, the authors described relationships of interest between domains over the course of recovery (e.g. language deficits influenced the recovery of verbal memory). Interestingly, the authors studied how lesion topography could explain behavior, as it was done in another study from the same group (41) and pointed out that white matter damage could be a key feature in explaining behavioral recovery. Other studies from the same cohort independently investigated the relationships between resting-state fMRI data and behavior by showing that altered functional connectivity correlated with behavioral deficits in the motor and attention domains (71) and in hemi-spatial neglect (72). In addition, the authors demonstrated that memory deficits are better predicted by functional connectivity than by lesion topography while the motor and visual deficits might be better predicted by lesion location than functional connectivity (42). Altogether, these studies emphasized the importance of multi-domain behavioral assessments and the interest of investigating brain-behavior relationships both through structural and functional measures as they provide complementary insights. However, patients enrolled in this cohort were substantially younger than the natural population of stroke survivors (average age 54 ± 11 years old, range 19-83, benchmark 69.2 years

in 2005 Greater Cincinnati/Northern Kentucky cohort; 62) and executive functions were not assessed in the battery. Plus, the authors focused on one modality (MRI) to assess brain features which provides rich but limited insights about the neuronal mechanisms underlying post-stroke recovery. To date, no study provided any extensive behavioral evaluation (with an approach centered on the individuals rather than the whole cohort) and during the course of recovery following stroke while combining data with multimodal assessments of brain network plasticity.

A common factor in many of these studies is the interplay between structural and functional connectivity. Structure influences function in the obvious way, while function influences structure in the long term. However, there is strong evidence that the strength of the link between structure and function is domain-dependent. The findings of Siegel, Ramsey and colleagues (2017) suggest that function is tightly coupled to structure in the motor and visual domains, while the two are more decoupled for "higher order" domains such as memory. These findings have been echoed in Preti & Van De Ville's work (2019), which found that brain regions responsible for "low level sensory function" tend to exhibit strong structural-functional coupling, and vice versa.

The present study aspires to bolster our understanding of mechanics underlying multiple-domain deficits by providing a multi-modal and multi-domain evaluation of stroke patients longitudinally during the first year after the stroke. This research intends to investigate the different behavioral profiles and their dynamics in stroke patients, not only looking at the motor domain but undergoing a holistic approach coupled with neuro-imaging and electrophysiological parameters. Therefore, the originality of the project lies in the multiplicity of the approaches undertaken that will allow a very detailed picture of the recovery and the reorganization in the brain following stroke. Structural, diffusion-weighted and functional MRI will provide the opportunity to study network dysfunctions as well as the complex interactions between brain function and structure. In addition, simultaneous EEG recording during TMS is a promising approach that will enable to explore brain connectivity and recovery pattern for functional networks after stroke by providing a direct measure of the cortical activity induced by TMS. By combining modalities with different advantages (such as either excellent spatial or temporal resolution, structural versus functional information) and by following patients along the first year post-stroke, we will provide a complete dataset allowing to integrate multimodal information in statistical and computational models. The overall goal is to determine interactions between the different parameters as well as factors usable as biomarkers for phenotyping patients in regard of the course and the degree of recovery.

Identifying such biomarkers might help (1) to predict the course of recovery, i.e. to early detect patients that will spontaneously recover and those who will not and, consequently, (2) to personalize the therapeutic strategies in order to meet the individual needs of each patient and to maximize the treatment benefits. Therefore, this work will serve as a basis for improving existing treatments or developing novel and innovative ones tailored to the individual patients' characteristics by providing a better understanding of neural mechanisms underlying successful recovery. For

instance, non-invasive brain stimulation (NIBS) are neuro-technologies that are more and more used in stroke rehabilitation to promote motor recovery (32,74,75) due to their noninvasiveness, relatively low cost and limited side effects. However, there is a high heterogeneity in the outcomes (30,31,66,76,77): effects of NIBS are still limited, which can be partly explained by the use of non-personalized approaches (32,78). Some biomarkers have already been identified to stratify patients in order to assess the individual recovery potential, for instance the cortico-spinal tract integrity as measured by presence or absence of MEP (79). However there is still a lack of fundamental knowledge on the topic especially considering the longitudinal changes in brain dynamics following stroke (23). The detailed phenotyping based on the dataset from the present study might further help to provide extra layers of stratifications allowing more precise predictions about treatment outcomes in order to reduce the number of non-responders (66). Therefore, some potential perspectives are to further design interventional studies to analyze the efficacy of neurotechnologies-based treatment personalized thanks to clustering and stratifying algorithms arising from this research.

## Challenges and limitations

Since this work involves plural and extensive multi-modal assessments, it is worthwhile to emphasize that the patients need to be physically and mentally capable of undergoing such multiple recordings. Plus, as the patients need to understand what the project entails, severe language deficits prevent possible participants to be enrolled because they do not have the ability to consent while being transparently informed. Furthermore, the presence of TMS recordings is associated with a consistent list of exclusion criteria related to medication, epilepsy or implants (metallic or electronic) that could interact with the stimulation. These aspects might cause a bias in the recruitment of patients that we need to consider when interpreting the results. Plus, we decided to include both first-ever and recurrent stroke patients to obtain a cohort that is representative of the stroke population. Although we are interested in the brain dynamics following the latest ictal event, we might carefully take this in caution in the analyses, as some residual impairments may be related to previous lesions in patients with a recurrent stroke. In addition, the presence of an upper-limb motor deficits is an inclusion criterion as the initial purpose of the project is to investigate post-stroke motor recovery. The investigation of interactions between cognitive and motor domains might be biased as we do not explore these interactions in patients with cognitive deficits but no motor impairment. We nevertheless aim to recruit a cohort as heterogeneous as possible to cluster patients and identify specific patterns of recovery and brain reorganization. Therefore, we still expect to observe varying degrees of motor impairment, from very slight to severe, which can reduce the risk of biased interpretations concerning the relationships between cognitive and motor domains.

Other challenges relate to the longitudinal aspect of the project. First, the four timepoints might be insufficient to capture some fine temporal changes in brain connectivity and behavior. However, the extensive and multi-modal nature of the study requires many resources and represent a large amount of time testing per patient.

Although the current protocol is feasible thanks to the physical location of the laboratory close to the hospital and the rehabilitation clinics (for details, see Appendix n°4), adding more timepoints would have seem unrealistic. Second, drop-outs are common for this type of study and we expect some missing datapoints Specifically, there is a higher chance of loss for the most impaired patients as the drop-outs are likely to be related to bad medical condition for example or a lack of motivation. This needs to be carefully considered in the choose of the statistical tools and in the interpretations of results. Still, efforts will be maintained to avoid drop-outs, e.g. by maintaining contact with the patients between timepoints and by facilitating their visits during the follow-up (see Appendix n°4)

Finally, it is crucial to emphasize the observational aspect of the study. For example, the post-stroke changes in brain connectivity observed through neural measurements could be due to effects of the lesion which are not related to recovery. Alternatively, they can be related to reactive changes associated with recovery but that do not directly cause it. It is of great importance to consider these aspects when investigating biomarkers of post-stroke recovery.

## Summary and conclusions

A better understanding of the neuronal mechanisms associated with recovery-related plasticity and reorganization of the brain networks after a stroke is needed to enhance the understanding of the recovery process, and to predict the outcome and course of recovery. This knowledge will enable to develop and apply interventional strategies in a personalized way to enhance the effects of the treatments for each individual patient. The TiMeS project is a longitudinal, multimodal, and multidomain study of a large, representative cohort of patients during the first year after the stroke, including structural and functional neuro-imaging, electrophysiological and extensive behavioral evaluations. This exploratory research will provide the opportunity to integrate and combine multidimensional data from neuroscience systems methods together with detailed behavioral outcomes to identify specific biomarkers of recovery. This phenotyping will serve as a basis to tailor current rehabilitation strategies according to each patient’s individual needs and to develop innovative personalized neuro-technologies based treatment like NIBS, beyond a one-fits-all approach. Overall, the knowledge gained from this study will pave the way for establishing a close link between basic neuroscience and the development of novel treatments into clinical routine towards precision medicine in stroke, which is highly promising to reduce the burden of the disease.

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**Supplement 1 – Neuropsychological evaluation**

Motor and cognitive tests

The battery of tests includes 14 tests assessing the sensory and motor functions, and 26 tests assessing the cognitive functions (see Table 1). It covers the neurocognitive domains described in the DSM-V (Sachdev et al., 2014), i.e. complex attention, language, learning and memory, executive functions, social cognition, perceptual-motor functions, with the latter divided into perceptual and motor functions.

The DSM-V does not name any proprietary tests to objectively assess these functions. Therefore, we selected the tests and questionnaires on the basis of their validity and reproducibility as well as the existence of normative data in the literature. We chose several tests per neurocognitive domain to have an extensive and detailed evaluation, and also to have data that are representative of the several subdomains for each neurocognitive domain.

We use the same battery for each timepoint, excluding a few tests that are skipped during the first timepoint in order to reduce the total time of the evaluation as patients are in general highly fatigable during the first week after the stroke. When possible, versioning was used to reduce learning effects.

The entire evaluation is divided into at least two sessions of 2 to 3 hours per timepoint, depending on the patients' state and availability. Breaks are imposed to the patients during the session to maintain their attention and concentration, but they are also able to take some rest at any time. The order of the tests is pre-defined to reduce the possible interferences between the different tests, but the examinator keeps to possibility to adjust if this is needed regarding the patients' state. In any case, the final tests' order for each evaluation is recorded on the patient's file.

Specific materials and licenses were acquired for each test. The evaluation is conducted by a neuropsychologist with a relevant clinical experience who follows rigorously the instructions provided by the authors of each test. The instructions of the tests are given, in French, Italian, or German, depending on the patients' first language. When possible, the version of the tests is adapted to the language used, especially for memory tests for which there are French, Italian, English, and Portuguese versions.

Questionnaires

In addition, 16 questionnaires assess daily life aspects of patients, including physical and mental activity, functional level of dependance and level of reintegration, mental state, fatigue, sleep; etc (see Table 1). The questionnaires are filled by the patients themselves when they are able to, and checked by the neuropsychologist. If needed, the neuropsychologist helps the patients by reading and filling the questionnaires for them. These questionnaires are used at each timepoint plus an additional time between the third and the fourth time points.

| Test | Function assessed | Reference |
|---|---|---|
| ***Clinical evaluation*** | | |
| NIHSS | Neurological examination | Brott et al., 1989 |
| ***General cognitive screening*** | | |
| Montreal Cognitive Assessment | All cognitive functions – general screening | Nasreddine et al., 2005 |
| ***Attention*** | | |
| Test of Attention Performance – Phasic alert test | Alertness, intensity of attention | Zimmermann & Fimm, 2016 |
| Test of Attention Performance – Divided attention test | Attentional selectivity, focused attention | Zimmermann & Fimm, 2016 |
| D2-R | Sustained and focused attention | Brickenkamp, 2015 |
| ***Social cognition*** | | |
| Geneva Emotions Recognition Test – Short* | Emotion recognition ability | Schlegel et al., 2016 |
| ***Executive functions*** | | |
| Frontal Assessment Battery | Executive functions | Dubois et al., 2000 |
| Stroop Victoria | Flexibility, inhibition, information processing speed | Spreen & Strauss, 1991; Bayard et al., 2007 |
| Bimanual coordination | Planification, programmation | Dolivo & Assal, ,1985 |
| Apraxia Screen of Test for Upper-Limb Apraxia | Planification, programmation | Vanbellingen et al., 2010 |
| CERAD Constructional Praxis | Planification, programmation | Morris et al., 1989; Roussel & Godefroy, 2016 – GRECOGVASC |

| | | |
|---|---|---|
| Color Trail Test | Planification, programmation, information processing speed | D'Elia et al., 1996 |
| Bisiach anosognosia scale | Self-awareness | Bisiach et al., 1986 |
| Somatoparaphrenia test | Self-awareness | Ronchi et al., adapted |
| 5-points tests* | Flexibility | Strauss & Knapp, 1982 |
| ***Language*** | | |
| LAST | Repetition, denomination, comprehension | Flamand-Roze et al., 2011; Koenig-Bruhin et al., 2016 |
| Ardila's language test* | Denomination | Ardila, 2007 |
| Token Test* | Comprehension | De Renzi & Vignolo, 1962 |
| Phonological verbal fluency | Fluency | Roussel & Godefroy, 2016 - GRECOGVASC battery |
| Semantic verbal fluency | Fluency | Roussel & Godefroy, 2016 - GRECOGVASC battery |
| ***Learning and Memory*** | | |
| Hopkins Verbal Learning Test – revised* | Verbal episodic memory | Brandt, 1990 |
| Doors test* | Visual episodic memory | Roussel & Godefroy, 2016 - GRECOGVASC battery |
| Digit span | Verbal short-term memory | Wechsler, 2008 - Wechsler Adult Intelligence Scale |
| Corsi-Kessels | Visual short-term memory | Kessels et al., 2000 |
| ***Motor functioning*** | | |
| Fugl-Meyer | Upper limb function | Fugl-Meyer, 1980 |
| Pinch&Grip | Hand strength | Mathiowetz et al., 1984 |
| Medical Research Council muscle strength testing | Upper limb strength | Ciesla et al., 2011, Hislop & Montgomery; 2007 |
| Nine-Hole Peg Test | Fine manual dexterity | Mathiowetz et al., 1985 |
| Box and Blocks test | Gross manual dexterity | Mathiowetz et al., 1985 |

| | | |
|---|---|---|
| Purdue Pegboard Test | Fine manual dexterity, bimanual coordination | Tiffin & Asher, 1948 |
| Action Research Arm Test* | Upper limb function | Lyle, 1981 |
| Modified Ashworth Scale | Spasticities | Bohannon & Smith, 1987 |
| 2 minutes walk test* | Gait | Butland et al., 1982 |
| 10 meters walk test* | Gait | van Hedel et al., 2005 |
| Time Up and Go test* | Gait, balance, functional ability | Podsiadlo & Richardson, 1991 |
| Berg Balance Scale | Balance | Berg, 1992 |
| ***Sensory*** | | |
| Rivermead Assessment of Sensory performance | Face, hands, feet sensitivity | Winward & Halligan, 2002 |
| ***Perceptual function*** | | |
| Overlapping figures test | Gnosis, neglect | Unilateral neglect assessment battery of the GEREN, 2002 |
| Bisection line test | Neglect | Unilateral neglect assessment battery of the GEREN, 2002 |
| Bells cancellation test | Neglect | Unilateral neglect assessment battery of the GEREN, 2002 |
| ***Questionnaires*** | | |
| Stroke Impact Scale (SIS) | General recovery | Duncan et al., 2003 |
| Hospital Anxiety and Depression Scale (HADS) | Anxiety and depression | Zigmond & Snaith, 1983 |
| State/Trait Anxiety Inventory for adults (STAI) | | Spielberger, 1983 |
| Fear and stress scale | Fear and stress | Carmen Sandi's version |
| Medical Outcome Study Short Form 12 | Reintegration | Ware & Sherbourne, 1992; Hurst et al., 1998 |

| | | |
|---|---|---|
| Modified Reintegration to Normal Living Index | | Wood-Dauphinee et al., 1988 |
| Social Comparison Scale | Social comparison | Allan & Gilbert, 1995 |
| Generalized Self Efficacy Scale | Efficacy | Scharzer & Jerusalem, 1995 |
| Pittsburgh Sleep Quality Index | Sleep and Fatigue | Buysse et al., 1989 |
| Multidimensional Fatigue Inventory | | Smets et al., 1995 |
| Feeling of foreigness questionnaire | Disembodiement | |
| Neurobehavioral questionnaire | | |
| Barthel index | Functional indexes | Mahoney & Barthel, 1965 |
| mRS modified Rankin Scale | | van Swieten et al., 1988 |
| FAC functional ambulation category | | Holden et al., 1984 |
| FIM functional independance | | Kidd et al., 1995 |
| Edinburgh handedness inventory | Handedness | Oldfield, 1971 |

**Table legend** - The table 1. lists all the tests and questionnaires used in TiMeS, with the main function(s) assessed by the tool. The latter information is not exhaustive as some tests could assess functions in multiple neurocognitive domains (for instance, the Color Trail Test mainly assesses some executive functions but could also give information about the sustained attention capacity). The third column indicates the authors / owners of the tests.

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**Supplement 2 – Neuroimaging recordings**

**Data acquisition**

Structural, functional, diffusion-weighted and susceptibility-weighted imaging data are acquired using a 3T MAGNETOM Prisma scanner (Siemens, Erlangen, Germany) with a 64-channel head and neck coil.

Diffusion-weighted imaging (DWI)

Diffusion-weighted images are acquired using pulsed gradient spin echo technique (TR = 5000 ms; TE = 77 ms; slices = 84; FOV = 234x234 mm; voxel resolution = 1.6 × 1.6 × 1.6 $mm^3$; readout bandwidth = 1630 Hz/pixels; GRAPPA acceleration factor = 3). Seven T2-weighted images without diffusion weighting (b = 0 $s/mm^2$) are acquired, including one in opposite phase encoded direction. Further, 101 images with noncollinear diffusion gradient directions distributed uniformly over the half-sphere covering 5 diffusion gradient strengths are measured (b-values = [300, 700, 1000, 2000, 3000] $s/mm^2$; shell-samples = [3, 7, 16, 29, 46]). Total acquisition time is 11:06 min.

T1-weighted image

A T1-weighted image is acquired using a 3D Magnetization-Prepared Rapid Gradient-Echo sequence (MPRAGE, TR = 2300 ms; TE = 2.96 ms; flip angle = 9°; slices = 192; voxel size =1 × 1 × 1 mm, FOV 256 × 256 mm, acquisition time = 5:12min).

multi-echo GRASE

A multi-echo $T_2$ GRASE sequence supporting CAIPIRINHA parallel imaging (Piredda et al., 2021) is used for myelin water fraction and multi-compartment T2 imaging (in-plane resolution 1.6mm x 1.6mm; slice thickness 1.6mm; 84 slices; acquisition time = 10:30min)..

Blood oxygenation-level dependent (BOLD) MRI / functional MRI (fMRI)

Resting-state BOLD data (with fixation cross) is acquired using a multi-band echo-planar imaging (EPI) sequence. In total, 385 functional volumes are acquired and every volume comprises 75 axial slices covering the whole brain (in-plane resolution = 2 mm x 2 mm; slice thickness 2 mm; no gap, FOV = 256mm, TE = 32 ms, TR=1250 ms, flip angle = 58°, Accel. Factor slice = 5, acquisition time = 8:13min).

GRE field mapping

GRE field mapping is acquired covering the whole brain (75 axial slices), using the following imaging parameters: in-plane resolution = 2mm x 2mm; slice thickness = 2mm; FOV = 224 x 224 $mm^2$, TR = 704 mm TE1 = 4.92 ms, TE2 = 7.38 ms , flip angle = 60°, acquisition time = 2:41min.

mp2rage

3D T1-weighted Magnetization-Prepared 2 Rapid Gradient-Echo (MP2RAGE) sequence (INV1 or TI1 = 700 ms, flip angle = 4° and INV2 or TI2 = 2500 ms, flip angle = 5°, TE = 2.98 ms, TR = 5000 ms, acquisition time = 8:22min) with an isotropic voxel resolution of 1 $mm^3$.

Susceptibility-weighted imaging (SWI)

We are using a susceptibility-weighed imaging sequence with a TR of 28 ms, a TE of 20ms, FOV = 230 x 230 $mm^2$, FOV phase = 78.1%, in-plane resolution of 0.6mm x 0.6mm, slice thickness = 1.2mm, flip angle = 15°, acquisition time = 4:07min.

**Image Analysis**

Lesion segmentation

All the lesion masks were hand-drawn using mrview from MRtrix3 (Tournier et al., 2019) and subsequently verified by a neurologist.

Multi-echo $T_2$ imaging

The multi-echo $T_2$ data is filtered using a 3D total variation algorithm before fitting (denoise-tv-chambolle function of the scikit-image python toolbox (Walt et al., 2014). The data is then registered to the T1-weighted image using using FSL FLIRT (Jenkinson and Smith, 2001) and FNIRT (Andersson et al., 2007; Jenkinson et al., 2012) methods. The myelin water fraction and multi-compartment $T_2$ maps are obtained using the L-curve-I method (Canales-Rodríguez et al., 2021) available at https://github.com/ejcanalesr/multicomponent-T2-toolbox.

Diffusion-weighted imaging

The diffusion-weighted images are preprocessed using MRtrix3 (Tournier et al., 2019), FSL (Smith et al., 2004), and Dipy (Garyfallidis et al., 2014). First, Gibbs ringing artefacts are removed from the data (Kellner et al., 2016), then motion artefact reduction, as well as field inhomogeneity, susceptibility-induced off-resonance field and eddy currents correction are performed using FSL TOPUP and EDDY (Andersson et al., 2003; Andersson & Sotiropoulos, 2016). Diffusion-weighted images were then corrected for spatial intensity variations (Zhang et al., 2001). Multi-shell multi-tissue constrained spherical deconvolution (Jeurissen et al., 2014) is used to estimate the fibre orientation distributions within each voxel. Whole-brain probabilistic tractography is performed using the MRtrix3 second-order integration over fibre orientation distribution (iFOD2) algorithm, initiating streamlines in all voxels of the white matter. For each dataset, 1 million streamlines are selected with both endpoints in the individual cortical or subcortical mask using the Dipy software package (Garyfallidis et al., 2014). The obtained tractograms are weighted fitting the underlying diffusion compartment model using a Stick-Ball-Zeppelin model based on COMMIT (Daducci et al., 2015). The stick compartment models the intra-axonal water with parallel diffusivity of 1.7 $\mu m^2/ms$ and no perpendicular diffusivity. The Ball compartment models the extra-axonal water with isotropic diffusivity of 1.7 $\mu m^2/ms$ and free water with diffusivity of 3.0 $\mu m^2/ms$ (Alexander, 2008; Scholz et al., 2009). The Zeppelin compartment models of the extra-axonal water with parallel diffusivity of 1.7 $\mu m^2/ms$ and perpendicular diffusivity of 0.51 $\mu m^2/ms$ (Alexander, 2008). Tissue partial volume estimates are obtained from the T1-weighted image using the FSL FAST (Zhang et al., 2001) and BET (Smith, 2002) methods. The T1-weighted image is registered to the average b0 image using FSL FLIRT (Jenkinson & Smith, 2001) and FNIRT (Andersson et al., 2007; Jenkinson et al., 2012) methods.

For the cortical parcellation, we choose either the Destrieux (74 areas per hemisphere) (Destrieux et al., 2010) or the Glasser atlas (180 areas per hemisphere) (Glasser et

al., 2016) using FreeSurfer (Fischl, 2012; Fischl et al., 2004). To the Destrieux parcellation, we add subcortical areas (thalamus, caudate, putamen. hippocampus, amygdala), the cerebellum ) and a subdivision of the brainstem (midbrain, pons, medulla), totalizing 163 cortical and subcortical areas using the Destrieux cortical parcellation. The parcellations are performed on the T1-weighted image. For stroke patients, the voxels corresponding to the lesion are stamped out and replaced by the mirrored voxels of the contralateral side. For each participant, a structural connectome (SC) is built with 163 (Destrieux atlas), respectively 360 (Glasser atlas), pairs of areas obtained through the parcellation.

Functional (BOLD) Imaging

All preprocessing and statistical analyses are conducted using the SPM12 package (Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm) running on MATLAB (v2020b, Mathworks, The MathWorks, Massachusetts, http://www.mathworks.ch). Functional images are realigned to the mean functional image. Then, the anatomical image is co-registered to the mean functional image. The anatomical image is segmented into tissue maps based on tissue probability maps of SPM12 (for patients, voxels corresponding to the lesion are not considered). The resulting forward deformation field is used to warp both the anatomical and functional images into MNI space. Finally, the functional images are smoothed using a Gaussian kernel (FWHM = 6 mm). The first 10 volumes are discarded so that the fMRI signal achieves steady-state magnetization, resulting in 375 functional volumes.

Using the conn toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012), voxel fMRI time courses are detrended and nuisance variables are regressed out (6 head motion parameters, average cerebrospinal fluid and white matter signal). Finally, a band-pass filter is applied (0.01-0.15Hz) to improve signal-to-noise ratio. The average timeseries is then extracted for every ROI of the Glasser parcellation and a functional connectome is obtained by computing the Pearson correlation between timeseries.

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**Supplement 3 – Electrophysiological recordings**

Electrophysiological recordings (resting-state EEG and TMS-EEG coupling) are performed at each time point post stroke: within a week, three weeks, three months, and one year after the ictal event; not for all patients the 4 timepoints are available.

Electroencephalography (EEG)

EEG recordings are acquired using a 64 passive electrodes EEG BrainCap-MR compatible with TMS (Brain Vision LLC, North Carolina, USA) with the reference electrode at FCz and the ground at AFz. The data is recorded with the help of BrainVision Recorder (Brain Vision LLC, North Carolina, USA). The experiment is performed in a faraday cage (IAC Acoustics, Illinois, USA) to limit power line interference. Each electrode is brought to an impedance below 5 kOhm or as low as possible. Impedance levels are recorded at the beginning and end of the session. Data are recorded using DC mode, a resolution of 0.5 µV and a low-pass filter (cutoff frequency of 1 kHz) at a sampling rate of 5 kHz.

Electromyography (EMG)

The EMG activity is recorded using pairs of disposable Ag-AgCl electrodes on 7 muscles in the affected side (First Dorsal Interossei, FDI; Abductor Digiti Minimi, ADM; Abductor Pollicis Brevis, APB; Flexor Carpi Ulnaris, FCU; Flexor Carpi Radialis, FCR; Extensor Carpi Radialis, ECR; Extensor Carpi Ulnaris, ECU) and 1 muscle on the non-affected one (FDI). The signal is amplified and sampled at 3 kHz using a Noraxon DTS Receiver (Scottasdale, Arizona, United States) using a band-pass filter from 10 Hz to

1000 Hz, and finally fed to the Signal software (Cambridge Electronic Design Limited, Cambridge, UK) for further processing.

Transcranial Magnetic Stimulation

Neuronavigated TMS is applied using a MagPro X100 stimulator connected to an MC-B70 coil (Magventure, Farum, Denmark). A neuronavigation system (Localite GmbH, Bonn, Germany) is used throughout the experiment to track and record the position of the stimulation coil in respect to the patient's individual anatomy, using T1-weighted images (see supp. 2). EEG channel coordinates are also recorded using the neuronavigation system. Biphasic pulses inducing a posterior to anterior current direction are delivered over the first dorsal intraosseous (FDI) hotspot of the affected arm. The stimulation intensity is adjusted to produce MEPs presenting a peak-to-peak amplitude between 0.5 to 1 mV. If no visible MEP (50 µV) can be elicited at maximal stimulator output, the intensity is set similarly on the unaffected hemisphere. The resting motor threshold (rMT) is defined as the lowest intensity necessary to evoke MEPs higher than 50 µV in at least 5 out of 10 trials. Two types of stimulation are applied: a single pulse at the supra-motor threshold intensity fixed earlier or a double pulse (Short-interval Cortical Inhibition; SICI) comprised of a conditioning pulse at 80% rMT followed by a test pulse at the supra-motor threshold intensity, with an inter-stimulus interval of 3 ms.

In order to reduce electromagnetic and acoustic interference resulting from the TMS, electrodes wires are oriented perpendicular to the magnetic field, athin layer of foam is applied between the coil and the scalp and white noise is played through earplugs at a volume covering the sound of the TMS or as loud as tolerated (ter Braack et al., 2015; Veniero et al., 2009).

Data processing

EMG: EMG data are exported to Matlab files to be used with a custom graphical interface for pre-processing. Rejection criteria are as follows: trials with muscle pre-activation exceeding ± 25 µV from baseline less than 100 ms before TMS onset (Delorme & Makeig, 2004) and/or ± 100 µV from baseline 500–100 ms before the pulse are rejected. Trials containing artefacts or with documented suboptimal coil placement are rejected from further analysis. The main features of interest consist of MEP peak-to-peak amplitudes and latencies.

EEG: EEG data are analyzed on Matlab (MathWorks, Massachusetts, USA) using the Fieldtrip (Oostenveld et al., 2011), Brainstorm (Tadel et al., 2011), EEGLAB (Delorme & Makeig, 2004) and TESA (Rogasch et al., 2017) toolboxes. Resting-state EEG recording are preprocessed following international standards (Babiloni et al., 2020) that were successfully used in previous studies on stroke patients (Snyder et al., 2021). First, the continuous data are epoched in non-overlapping 2 s time windows. After removing bad channels and trials, an ICA is performed in order to filter out any remaining ocular, muscular or electrical artifacts. Data are finally re-referenced (average reference), and time-frequency maps are drawn from them by means of multitaper frequency transformation within the 1-50 Hz frequency bandwidth. The asymmetry indices (Snyder et al., 2021) and the brain oscillatory modes drawn from

tensor decomposition methods (Tangwiriyasakul et al., 2019) are the main outcomes of interest for this analysis.

Regarding TMS-EEG recordings, the preprocessing pipeline is similar to the one defined by Rogasch et al. (2017) and consists of: epoching, removing data corrupted by the TMS pulse [-5,+20ms], removing bad trials and channels after a visual inspection, removing the remaining TMS artefact and others artefacts such as eye blinks or large muscle artefacts using two rounds of ICA,and finally re-referencing to the average reference. TMS evoked potentials (TEPs) and induced oscillations are then computed by averaging the signal in the time and time-frequency domains respectively. These features allow for the study of both local properties of the stimulated tissue, such as cortical excitability (Raffin et al., 2020), and large-scale properties of the stimulated brain, such as functional and effective connectivity (Tremblay et al., 2019).

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**Supplement 4 – Study organization**

The proposed multi-modal and longitudinal protocol entails a large and time-consuming number of recordings (see Figure 1). Although this project is highly challenging especially with severely impaired patients, the protocol is feasible thanks to several aspects. The MRI facilities as well as our laboratory are in close vicinity of the acute hospital (HVS) and the rehabilitation clinic (CRR), see figure 2. This facilitates the recruitment, but also the evaluations and recordings, especially during the acute and subacute phase (T1 and T2). In addition, we established an excellent relationship with the medical staff of the hospitals which facilitates the integration of the testing into the clinical work and rehabilitation schedule. We also have materials for neuropsychological testing in the laboratory, at the hospital, and at both clinics and specific rooms dedicated to test the patients directly in the hospital/clinic, while keeping a high reproducibility. Another aspect is that we have good access to transportations facilities through a partnership with local transportations companies and associations to offer the patient the possibility to easily come to the laboratory. As we recruit from the local regional hospital, most patients live in a close vicinity to the laboratory. Noticeably, a member of the staff entirely work to the whole organization of patients visits, including contact with patients or relatives, medical staff, and transportations facilities.

In addition, we established a hierarchy in the different modalities of assessments (e.g., the order of the MRI sequences performed, importance of the behavioral scales). Therefore, we could adjust to the patients 'needs and schedules optimally. Concerning the behavioral evaluations for example, two sessions are initially planned but can be divided into more if the state or the rehabilitation schedule of the patient require to do so.

All these organizational aspects allow to facilitate the recruitment and the longitudinal follow-up of the patients with flexibility in regard to their personal schedule and state.

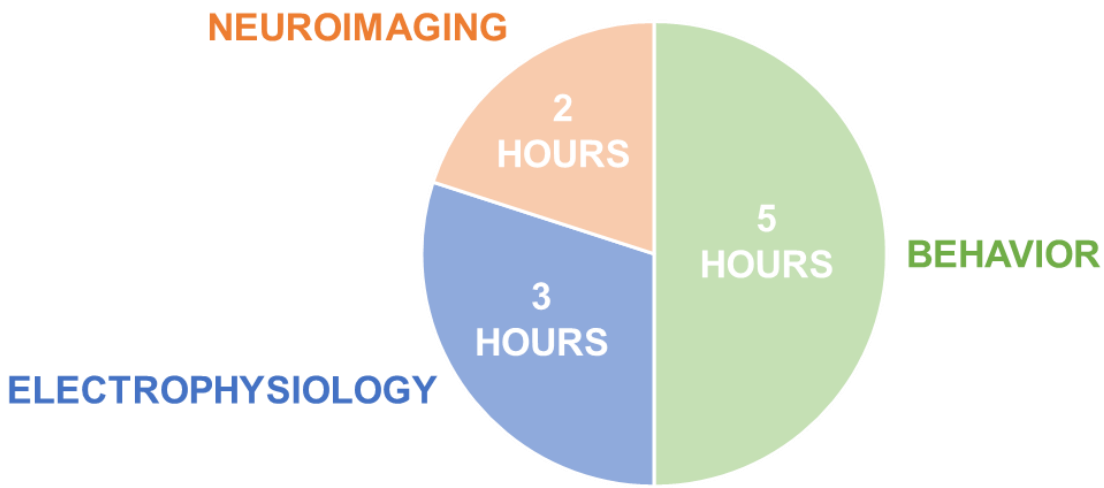


Figure 14 - Hours of testing per timepoint

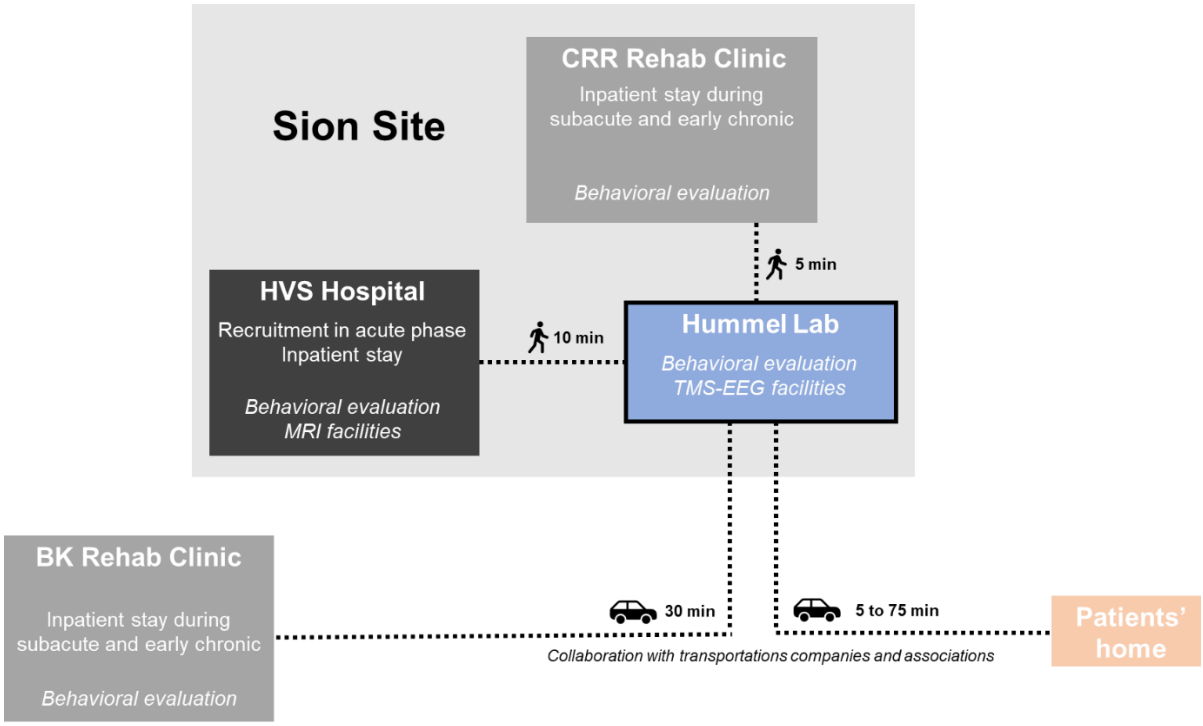


Figure 15 - Organization between the different structures and sites

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# 7. Curriculum Vitae


**Andéol Cadic-Melchior**

29 years old
Driving licence

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Switzerland

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## LANGUAGES

- FRENCH
- ENGLISH
- GERMAN

## SKILLS

- Matlab
- Python
- Office suite
- Adobe Illustrator

## HOBBIES

## WORK EXPERIENCE

**2018 - 2022 | PHD IN NEUROSCIENCE (5 YEARS)**
Laboratory of Prof. Hummel - Swiss Federal Institute of Technology Lausanne (EPFL), Switzerland
Title : Longitudinal evaluation of the mechanisms supporting post-stroke motor recovery using TMS-EEG coupling
Methods : Transcranial magnetic stimulation and surface electroencephalography

**2017 - 2017 | INTERNSHIP (5 MONTHS)**
Laboratory Neuropain - Neuroscience Research Center Lyon (CRNL), France
Title : Pre-stimulus cerebral activity predicts reaction to nociceptive stimuli during sleep
Methods : Intracranial electroencephalography

**2016 - 2016 | INTERNSHIP (6 WEEKS)**
Laboratory of Neuroeconomy and decision making - Cognitive Neurosciences Center Lyon (CNC), France
Title : Performances modulation by the audience effect : personality impact
Methods : Psychocognitive tests and visual task

**2015 - 2015 | INTERNSHIP (2 MONTHS)**
Gentner Lab - University of California, San Diego (UCSD), USA
Title : Perception and recognition of audio sequences on Starling birds
Methods : Animal behaviour task and intracranial recordings

**2015 - 2015 | INTERNSHIP (6 WEEKS)**
Neuropediatric service - Antwerp UZA Hospital, Belgium
Title : Epileptic activity characterization by EEG analysis of young sleeping and awake patients
Methods : Surface electroencephalography

## EDUCATION

**2016 - 2017 | MASTER 2 - FONDAMENTAL AND CLINICAL NEUROSCIENCES**
University Claude Bernard Lyon 1 (France)
Grade : 15.95/20
Rank : 2/34

**2015 - 2016 | MASTER 1 - INTEGRATIVE BIOLOGY, PHYSIOLOGY AND NEUROSCIENCES**
University Claude Bernard Lyon 1 (France)
Grade : 12.75/20
Rank : 19/78

**2014 - 2015 | ERASMUS : MASTER 1 NEUROSCIENCES (RESEARCH)**
University of Antwerp (Belgium)
Grade : 11.7/20
Rank : Unknown

**2013 - 2014 | BACHELOR - ANIMAL PHYSIOLOGY AND NEUROSCIENCES**
University of Montpellier 2 (France)
Grade : 13.59/20
Rank : 16/113

## CERTIFICATES

**2017 | MASTER NEUROSCIENCES**
Distinction : Bien

**2014 | BACHELOR BIOLOGY**
Distinction : Assez Bien

**2011 | BACCALAURÉAT**
Distinction : Très Bien

**2017 | ENGLISH TOEIC CERTIFICATE**
Score : 990/990

**2010 | SCIENTIFIC POPULARIZATION TRAINING**
Associtation Les Petits Débrouillards - Planète Science

## ORAL COMMUNICATIONS

**2022 | 8TH EUROPEAN STROKE ORGANISATION CONFERENCE**
Title : The role of ipsilesional motor cortical excitability and upper limb function after a stroke – a TMS-EEG coupling study

**2017 | SLEEP-CONSCIOUSNESS DAY CNRL**
Title : Pre-stimulus cortical activity predicts reaction to nociceptive stimuli during sleep

# 8. List of publications

Stroke recovery related changes in brain reactivity based on modulation of intracortical inhibition

**Andéol Cadic-Melchior***, Sylvain Harquel*, Takuya Morishita, Lisa Fleury, Adrien Witon, Martino Ceroni, Julia Brügger, Nathalie Meyer, Giorgia G. Evangelista, Philip Egger, Elena Beanato, Pauline Menoud, Dimitri Van de Ville, Silvestro Micera, Olaf Blanke, Bertrand Léger, Jan Adolphsen, Caroline Jagella, Christophe Constantin, Vincent Alvarez, Philippe Vuadens, Joseph-André Ghika, Jean-Luc Turlan, Andreas Mühl, Diego San Millán, Christophe Bonvin, Philipp J. Koch, Maximilian J. Wessel, Friedhelm C. Hummel

* These authors contributed equally to this work

Submitted

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Brain oscillatory modes as a proxy of stroke recovery

Sylvain Harquel*, **Andéol Cadic-Melchior***, Takuya Morishita, Lisa Fleury, Martino Ceroni, Pauline Menoud, Julia Brügger, Elena Beanato, Nathalie Meyer, Giorgia G. Evangelista, Philip Egger, Dimitri Van de Ville, Olaf Blanke, Silvestro Micera, Bertrand Léger, Jan Adolphsen, Caroline Jagella, Andreas Mühl, Christophe Constantin, Vincent Alvarez, Philippe Vuadens, Jean-Luc Turlan, Diego San Millán, Christophe Bonvin, Philipp J. Koch, Maximilian J. Wessel and Friedhelm C. Hummel

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Submitted

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Differential impact of brain network efficiency on post-stroke motor and attentional deficits

Giorgia G. Evangelista, Philip Egger, Julia Brügger, Elena Beanato, Philipp J. Koch, Martino Ceroni, Lisa Fleury, **Andéol Cadic-Melchior**, Nathalie Meyer, Diego de León Rodríguez, Gabriel Girard, Bertrand Léger, Jean-Luc Turlan, Andreas Mühl, Philippe Vuadens, Jan Adolphsen, Caroline Jagella, Christophe Constantin, Vincent Alvarez, Joseph-André Ghika, Diego San Millán, Christophe Bonvin, Takuya Morishita, Maximilian J. Wessel, Dimitri Van de Ville, Friedhelm C. Hummel

Submitted

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Optimization of phase prediction for brain-state dependent stimulation: a grid-search approach

Claudia Bigoni; **Andéol Cadic-Melchior**; Takuya Morishita; Friedhelm C. Hummel

Submitted

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Toward individualized medicine in stroke-The TiMeS project: Protocol of longitudinal, multi-modal, multi-domain study in stroke

Lisa Fleury, Philipp J, Maximilian J Wessel, Christophe Bonvin, Diego San Millan, Christophe Constantin, Philippe Vuadens, Jan Adolphsen, **Andéol Cadic Melchior**, Julia Brügger, Elena Beanato, Martino Ceroni, Pauline Menoud, Diego De Leon Rodriguez, Valérie Zufferey,

Nathalie H Meyer, Philip Egger, Sylvain Harquel, Traian Popa, Estelle Raffin, Gabriel Girard, Jean-Philippe Thiran, Claude Vaney, Vincent Alvarez, Jean-Luc Turlan, Andreas Mühl, Bertrand Léger, Takuya Morishita, Silvestro Micera, Olaf Blanke, Dimitri Van De Ville, Friedhelm C Hummel
Front Neurol. 2022 Sep 26;13:939640.doi: 10.3389/fneur.2022.939640.

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An automatized method to determine latencies of motor-evoked potentials under physiological and pathophysiological conditions
Claudia Bigoni, **Andéol Cadic-Melchior**, Pierre Vassiliadis, Takuya Morishita and Friedhelm C. Hummel
Journal of Neural Engineering, 2022, Volume 19, Number 2, DOI 10.1088/1741-2552/ac636c

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Evaluating reproducibility and subject-specificity of microstructure-informed connectivity
Philipp J. Koch, Gabriel Girard, Julia Brügger, **Andéol G. Cadic-Melchior**, Elena Beanato, Chang-Hyun Park, Takuya Morishita, Maximilian J. Wessel, Marco Pizzolato, Erick J. Canales-Rodríguez, Elda Fischi-Gomez, Simona Schiavi, Alessandro Daducci, Gian Franco Piredda, Tom Hilbert, Tobias Kober, Jean-Philippe Thiran, Friedhelm C. Hummel
NeuroImage, Volume 258, 2022, 119356, ISSN 1053-8119,
https://doi.org/10.1016/j.neuroimage.2022.119356.

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Variability and reproducibility of multi-echo T2 relaxometry: Insights from multi-site, multi-session and multi-subject MRI acquisitions
Fischi Gomez, Elda ; Girard, Gabriel ; Koch, Philipp Johannes ; Yu, Thomas ; Pizzolato, Marco ; Brügger, Julia ; Piredda, Gian Franco ; Hilbert, Tom **; Cadic-Melchior, Andéol Geoffroy** ; Beanato, Elena ; Park, Chang-Hyun ; Morishita, Takuya ; Wessel, Maximilian Jonas ; Schiavi, Simona ; Daducci, Alessandro ; Kober, Tobias ; Canales Rodriguez, Erick Jorge ; Hummel, Friedhelm C. ; Thiran, Jean-Philippe
Frontiers in Radiology, 2022, DOI 10.3389/fradi.2022.930666

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Intracortical Functional Connectivity Predicts Arousal to Noxious Stimuli during Sleep in Humans
Hélène Bastuji, **Andéol Cadic-Melchior**, Michel Magnin, Luis Garcia-Larrea
Journal of Neuroscience 9 June 2021, 41 (23) 5115-5123; DOI: 10.1523/JNEUROSCI.2935-20.2021

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Towards an Adaptive Upper Limb Rehabilitation Game with Tangible Robots
Arzu Guneysu Ozgur; Louis P. Faucon; Pablo Maceira-Elvira; Maximilian J. Wessel; Wafa Johal; Ayberk Özgür; **Andéol Cadic-Melchior**; Friedhelm C. Hummel; Pierre Dillenbourg
2019 IEEE 16th International Conference on Rehabilitation Robotics (ICORR), 2019, pp. 294-299, doi: 10.1109/ICORR.2019.8779429.