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## Symposium

# Rethinking Remapping: Circuit Mechanisms of Recovery after Stroke

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Stroke is one of the most common causes of disability, and there are few treatments that can improve recovery after stroke. Therapeutic development has been hindered because of a lack of understanding of precisely how neural circuits are affected by stroke, and how these circuits change to mediate recovery. Indeed, some of the hypotheses for how the CNS changes to mediate recovery, including remapping, redundancy, and diaschisis, date to more than a century ago. Recent technological advances have enabled the interrogation of neural circuits with ever greater temporal and spatial resolution. These techniques are increasingly being applied across animal models of stroke and to human stroke survivors, and are shedding light on the molecular, structural, and functional changes that neural circuits undergo after stroke. Here we review these studies and highlight important mechanisms that underlie impairment and recovery after stroke. We begin by summarizing knowledge about changes in neural activity that occur in the peri-infarct cortex, specifically considering evidence for the functional remapping hypothesis of recovery. Next, we describe the importance of neural population dynamics, disruptions in these dynamics after stroke, and how allocation of neurons into spared circuits can restore functionality. On a more global scale, we then discuss how effects on long-range pathways, including interhemispheric interactions and corticospinal tract transmission, contribute to post-stroke impairments. Finally, we look forward and consider how a deeper understanding of neural circuit mechanisms of recovery may lead to novel treatments to reduce disability and improve recovery after stroke.

## Introduction

Stroke is one of the most common neurologic disorders and is the second leading cause of death worldwide (Vos et al., 2020; Tsao et al., 2023). Many stroke survivors are left with permanent disability; and outside of rehabilitation (physical, occupational, and speech/language), there are few therapies (e.g., vagus nerve stimulation) that can improve recovery after stroke. The trajectory of recovery after stroke is dynamic, with many patients exhibiting improvement over time, particularly early on following injury, but often extending into the chronic phase of recovery. The development of therapeutics to improve recovery has been hindered by a limited understanding of how circuits within the CNS are affected by stroke and how they change throughout

recovery. Over the years, many hypotheses have been advanced to explain how strokes lead to impairment and what CNS changes might underlie recovery. One of the most widely cited is the remapping hypothesis. This hypothesis has its origins in the late 19th century theory of “vicariation,” which suggested that, after a focal lesion, a spared part of the CNS reorganizes, and over time, subsumes the function(s) lost to damage (Finger, 2010). Some modern formulations of the remapping hypothesis extend this idea to the neuronal level, with spared neurons, typically in areas adjacent or functionally related to the damaged region, changing their activity to encode information previously encoded by those destroyed by stroke (Murphy and Corbett, 2009). In its most basic conceptualization, the remapping hypothesis implies that ischemia leads to irreversible damage, and recovery proceeds as spared circuits remap to take on new functionality (Fig. 1A).

Aside from remapping, other theories have been advanced to explain impairment and recovery after stroke, including redundancy and diaschisis. Redundancy hypotheses suggest that functions within the CNS are normally duplicated or distributed across brain regions, with stroke temporarily disrupting a particular function and the degree of recovery dictated by the extent of the redundant areas that are spared (Finger, 2010). Diaschisis, on the other hand, refers to a state of disconnection because of a

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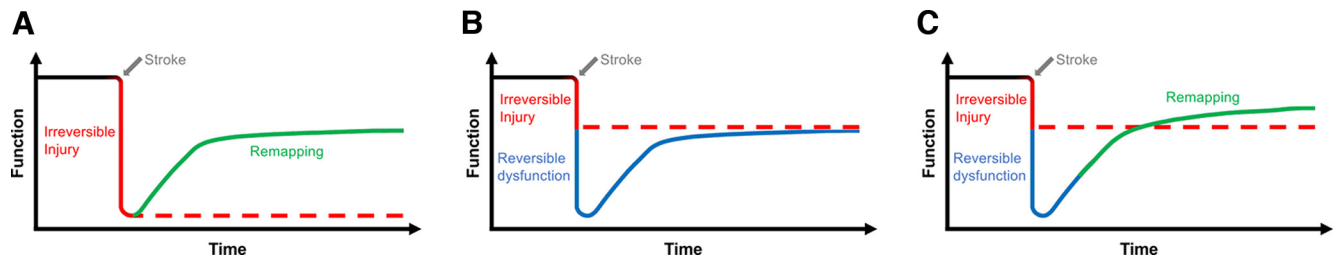
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**Figure 1.** Hypothetical models of recovery. **A**, Remapping hypothesis. Upon stroke onset, irreversible injury (in red) leads to an acute loss of function. Over time, remapping (in green) results in some recovery of function. Dotted red line indicates a complete lack of recovery in the absence of remapping. **B**, Redundancy and diaschisis hypotheses. Upon stroke onset, irreversible injury at the ischemic core is combined with reversible dysfunction in local or distant “spared” areas (in blue), leading to loss of function. Over time, restoration of function in spared areas results in some recovery, with a ceiling imposed by the irreversible injury (dotted red line). **C**, Combined models. Loss of function occurs as in **B**, with recovery attributable to restoration of function in spared areas and remapping, enabling recovery greater than predicted by the initial irreversible component of injury.

loss of long-range connections to spared areas, which leads to dysfunction in areas of the CNS distant from the stroke (Finger et al., 2004). Diaschisis may resolve, contributing to recovery, or persist, contributing to long-term impairments. Both redundancy and diaschisis suggest that the initial impairment results from a combination of irreversible focal damage because of ischemia plus dysfunction of spared areas. Recovery then proceeds as disrupted long-range connections to spared areas and/or functionality of redundant circuits are restored, with irreversible damage because of the ischemic core setting a ceiling for potential recovery (Fig. 1B). In reality, all of these mechanisms may coexist and jointly contribute to impairment and recovery (Fig. 1C).

Although the hypotheses for stroke recovery have origins decades, if not centuries ago, considerable debate still exists about precisely how neural circuits change after stroke and throughout recovery. Recent technological advances have enabled the study of neural circuits with ever greater temporal and spatial resolution, both in humans and across animal models, and it is now possible to test long-held hypotheses more directly than ever before. This review highlights work across multiple species, using diverse approaches, to understand the circuit mechanisms underlying impairment and recovery after stroke. We first consider contemporary evidence for remapping and other theories of recovery in animal models and humans, focusing on the peri-infarct cortex. Then we consider how factors such as the dynamics of neuronal ensembles and long-range connectivity, contribute to recovery. Finally, we discuss approaches for translating knowledge of neural circuit changes after stroke into treatments to reduce disability and improve recovery.

### Functional remapping in the peri-infarct cortex

Peri-infarct regions are often considered likely sites for remapping as they may contain neurons and circuits subserving a similar function, or having similar long-range connectivity, to those in the ischemic core. As such, the peri-infarct cortex has been extensively studied, with rodent models of stroke often used to investigate changes at the molecular and cellular levels. These studies have revealed evidence of changes within peri-infarct regions that could potentially support remapping. Structurally, neurons in the peri-infarct cortex undergo axonal sprouting, dendritic remodeling, and dendritic spine turnover (Jones and Schallert, 1994; Stroemer et al., 1995; Brown et al., 2007, 2010; S. Li et al., 2010; Mostany et al., 2010). These structural changes are driven by a specific transcriptional program in peri-infarct neurons after stroke (S. Li et al., 2010) and might facilitate synapse formation and circuit reorganization. Functionally, macroscopic imaging studies of intrinsic signals or voltage sensors have

demonstrated changes in cortical activity patterns after stroke that could be consistent with remapping (Winship and Murphy, 2008; Brown et al., 2009). Perhaps the most direct evidence for peri-infarct remapping, however, comes from Winship and Murphy (2008) who performed acute two-photon *in vivo* calcium imaging of sensory-evoked neuronal activity in layer 2/3 (L2/3) of the forelimb and hindlimb somatosensory (S1) cortex following photothrombotic strokes targeting the forelimb map (Winship and Murphy, 2008). In animals imaged 1–2 months after stroke, they found a small increase in the number of neurons in hindlimb S1 responding to stimulation of the contralateral forelimb compared with control animals (without stroke). These data suggest that direct remapping of neuronal function may be possible after stroke, at least in certain circumstances.

In contrast, accumulating evidence suggests against large-scale remapping of the peri-infarct cortex as a general mechanism of recovery. Zeiger et al. (2021) tested this directly using two-photon calcium imaging to longitudinally record neuronal activity in the peri-infarct S1 whisker barrel field after a photothrombotic stroke targeting a single barrel (Zeiger et al., 2021). Sensory-evoked activity was reduced in spared neurons after stroke, with gradual return to baseline, but there was no significant remapping up to 2 months after stroke. Furthermore, forced use of the whisker corresponding to the infarcted barrel led to increased reliability of sensory-evoked responses in spared neurons but still did not lead to remapping. Other recent studies have also found reduced activity in peri-infarct regions for prolonged periods after stroke (Neumann-Haefelin and Witte, 2000), including in spared pyramidal neurons (Kokinovic and Medini, 2018; He et al., 2020), interneurons (Motaharinia et al., 2021), and even excitatory thalamocortical inputs (Tennant et al., 2017). In addition, mechanisms of experience-dependent plasticity operant in the healthy brain are actually impaired in the peri-infarct cortex. For example, in the S1 whisker barrel field, whisker-trimming induced recruitment of L2/3 neurons to the spared whisker and cortical map expansion are blocked in peri-infarct cortex (Jablonka et al., 2007, 2012; Zeiger et al., 2021). Likewise, in the visual cortex (V1), visual sensory learning and ocular dominance plasticity after monocular deprivation are blocked (Greifzu et al., 2011; Akol et al., 2022). One important factor contributing to reduced activity and impaired plasticity mechanisms within the peri-infarct cortex is increased inhibition (Clarkson et al., 2010; Alia et al., 2016), which results in an imbalance between excitation and inhibition (Joy and Carmichael, 2021). Together, these data suggest that dysfunction of spared peri-infarct regions contributes to impairment after stroke, and that restoration of functionality within peri-infarct circuits, perhaps by overcoming excessive inhibition,

may lead to some recovery over time in the absence of any remapping.

The role of the peri-infarct cortex has also been investigated extensively in humans. Because this work often utilizes fMRI, it is important to consider how stroke and remapping mechanisms might manifest in the BOLD signal, which is only a proxy for neuronal activity. To ensure interpretability, it is important to evaluate the fMRI signal elicited (1) during a specific task relative to a close comparison condition and (2) with respect to activation from a healthy group. With these principles in mind, one might predict remapping to be associated with supranormal task-specific activation in peri-infarct cortex or elsewhere that exceeds that observed in a control group. In motor stroke recovery, it has been suggested that recovery relies on functional takeover by peri-infarct sensorimotor (Teasell et al., 2005) or primary motor cortices (Xerri et al., 1998; Jaillard et al., 2005). However, direct comparison to healthy individuals has found subnormal, rather than supranormal, activation in peri-infarct tissue (Cramer et al., 2006). Nevertheless, the motor stroke findings have informed models of aphasia recovery, which will be the focus of the following section. Such models stipulate that, when language tissue is damaged, alternative peri-infarct processors may become recruited to support outcomes, especially around small lesions (Heiss and Thiel, 2006; Thompson and den Ouden, 2008). A variation on this account is that upregulated peri-infarct activation may reflect spare functional capacity that is typically downregulated under healthy conditions to save energy (Stefaniak et al., 2020). In line with this idea, several studies have found increased peri-infarct activity associated with improved long-term outcomes in spontaneous stroke aphasia recovery (Heiss et al., 1999; Warburton et al., 1999; Szaflarski et al., 2011). However, these studies have not systematically considered lesion characteristics (Stefaniak et al., 2020), so heterogeneity in effects may relate to individual lesion size and location of available peri-infarct tissue. Treatment studies have also found that increased peri-infarct activity following treatment was related to performance gains (Meinzer et al., 2008; Fridriksson et al., 2012). However, because these studies have not compared patient activation to control subjects, they cannot clearly establish that increases in peri-infarct activity represent either recruitment of new tissue for language or supranormal recruitment of typical language regions because of plasticity.

Alternatively, treatment-related increases in peri-infarct activity may reflect normalization of function in language tissue that became dysfunctional because of network effects of the nearby lesion. Studies of spontaneous stroke aphasia recovery have found an acute reduction in left-hemisphere language activity, followed by subacute supranormal activity, and finally a chronic normalization of activity that is associated with good outcomes (Saur et al., 2006). DeMarco et al. (2022) recently examined predictions regarding peri-infarct plasticity by contrasting activity elicited by two independent language tasks in two different cohorts of chronic patients with left-hemisphere stroke and matched controls. Consistent with Cramer et al. (2006), peri-infarct tissue was associated with subnormal, rather than supranormal, activity. Moreover, no brain regions exhibited selectively increased activity in peri-infarct cortex, nor was peri-infarct recruitment observed around small lesions. The degree of network disruption correlated with lesion size, but notably, disrupted language activity accounted for some behavioral aphasia impairment independent of lesion size. Together, these results support an alternative interpretation of peri-infarct recruitment: strokes to the language network produce

network-wide disruptions with decreased language activity, and recovery is supported by normalization of peri-infarct activity in spared language processors. In addition to normalization of language processing, previous reports of peri-infarct plasticity may also reflect increased engagement of alternative left-hemisphere processors regardless of their proximity to the lesion. This is supported by the regional analysis finding that certain processors were engaged above control levels, but that in every case, these were either regions distant from the lesion or regions that were recruited regardless of their proximity to the lesion.

Several types of processes might underlie the recruitment measured as increases in alternative left-hemisphere processors. For instance, the increased activation might relate to compensatory plasticity (Takeuchi and Izumi, 2013), the use of compensatory strategies relying on spared ability (Saur et al., 2006), or network-specific changes, such as increased reliance on “domain general” processes (Geranmayeh et al., 2014; DeMarco et al., 2018). The finding of increased activity in posterior superior frontal lobe and parietal lobe shows consistent localization with a domain general dorsal attention/salience network (Fedorenko et al., 2013). Previous work has found increased left-hemisphere activity in patients with aphasia during language processing, but a common region exhibiting increased activation would be unlikely to be perilesional since perilesional tissue would be in different places for different individuals (Brownsett et al., 2014; Geranmayeh et al., 2014). Thus, greater activation observed in these regions might relate to compensatory increased reliance on domain-general processing for language tasks. In summary, these findings suggest that, while peri-infarct cortex activation similar to healthy individuals is an independent predictor of behavioral language performance, the mechanisms at play to support normalization and recovery may also extend throughout the relevant brain network, in this case critical language regions, and perhaps to nonlinguistic regions as well.

### Neural population dynamics and functional allocation

Thus far, we have focused primarily on the magnitude of activity in the peri-infarct cortex as a surrogate for recovery of function. However, behavior is generated by temporal patterns of activity across populations of neurons, and the dynamics thus produced encode function. This phenomenon, where population dynamics encode function, is perhaps best understood in the motor system, where neural dynamics underlying motor tasks have been extensively studied (Baker, 2007; Shenoy et al., 2013). Spiking activity (i.e., firing of action potentials) across neurons in motor circuits is time-locked to specific epochs of movement, such as movement direction, reach, and grasp, and also in planning of movements, where behavior is modulated by cofiring of task-specific neurons (Georgopoulos et al., 1982; Murthy and Fetz, 1992, 1996; Baker et al., 1997; Donoghue et al., 1998; Hatsopoulos et al., 1998; N. Li et al., 2015; Suresh et al., 2020; Ariani et al., 2022). Importantly, spatiotemporal firing patterns, driven by inputs from and to cortical (Omlor et al., 2019; Terada et al., 2022) and subcortical targets (Sauerbrei et al., 2020; Wolff et al., 2022) and the resultant dynamics are critical for task execution. Synchronization of neural activity across populations of neurons gives rise to rhythmic patterns of activity, or neural oscillations, at different frequencies. These rhythmic patterns exist during planning of movements and show characteristic changes during and after movement. For example, desynchronization of  $\beta$ -oscillations (13–30 Hz) and postmovement rebound of  $\beta$ -oscillations are well-defined features of movement in the motor cortex (M1) (Pfurtscheller et al., 1996; Baker et al., 1997, 2003; Donoghue

et al., 1998; McFarland et al., 2000; Witham et al., 2007; Little et al., 2019). These dynamics arise from, and depend on, structural and functional connectivity within motor networks.

After stroke, neuronal populations show shifting patterns in connectivity strength within the motor network that extend to different cortical (Silasi and Murphy, 2014; Siegel et al., 2016; Latifi et al., 2020) and subcortical targets (Tennant et al., 2017; Guo et al., 2021; Favaretto et al., 2022). Movement-related population dynamics are disrupted, including changes in low-frequency oscillations (<4 Hz) (Ramanathan et al., 2018; Bönstrup et al., 2019; Guo et al., 2021),  $\beta$ -oscillations (Wu et al., 2016; Espenhahn et al., 2020), and  $\gamma$ -oscillations (30–59 Hz) (Hazime et al., 2021; J. Zhou et al., 2022). Accordingly, it has also been shown that there is an initial depression in network connectivity (Grefkes et al., 2008; Lim et al., 2014), followed by either increased connectivity in certain brain regions (Bauer et al., 2014; Grefkes and Fink, 2014; Cramer et al., 2019; Bice et al., 2022) or lack of connectivity in other regions (Siegel et al., 2016; Soleimani et al., 2023). Recovery follows normalization of network activity to pre-stroke levels (Ramanathan et al., 2018; Rocha et al., 2022), and this normalization extends to spatiotemporal firing patterns, including recovery of movement-related oscillations across cortical (Nudo et al., 1996; Ramanathan et al., 2018) and subcortical targets (Tennant et al., 2017; Guo et al., 2021). In other words, restoration of function likely results not only from restoration of excitability within neuronal circuits, but more importantly, recapitulation of the dynamics of neural activity normally operant in motor circuits in the healthy brain (Ramanathan et al., 2018; Guo et al., 2021).

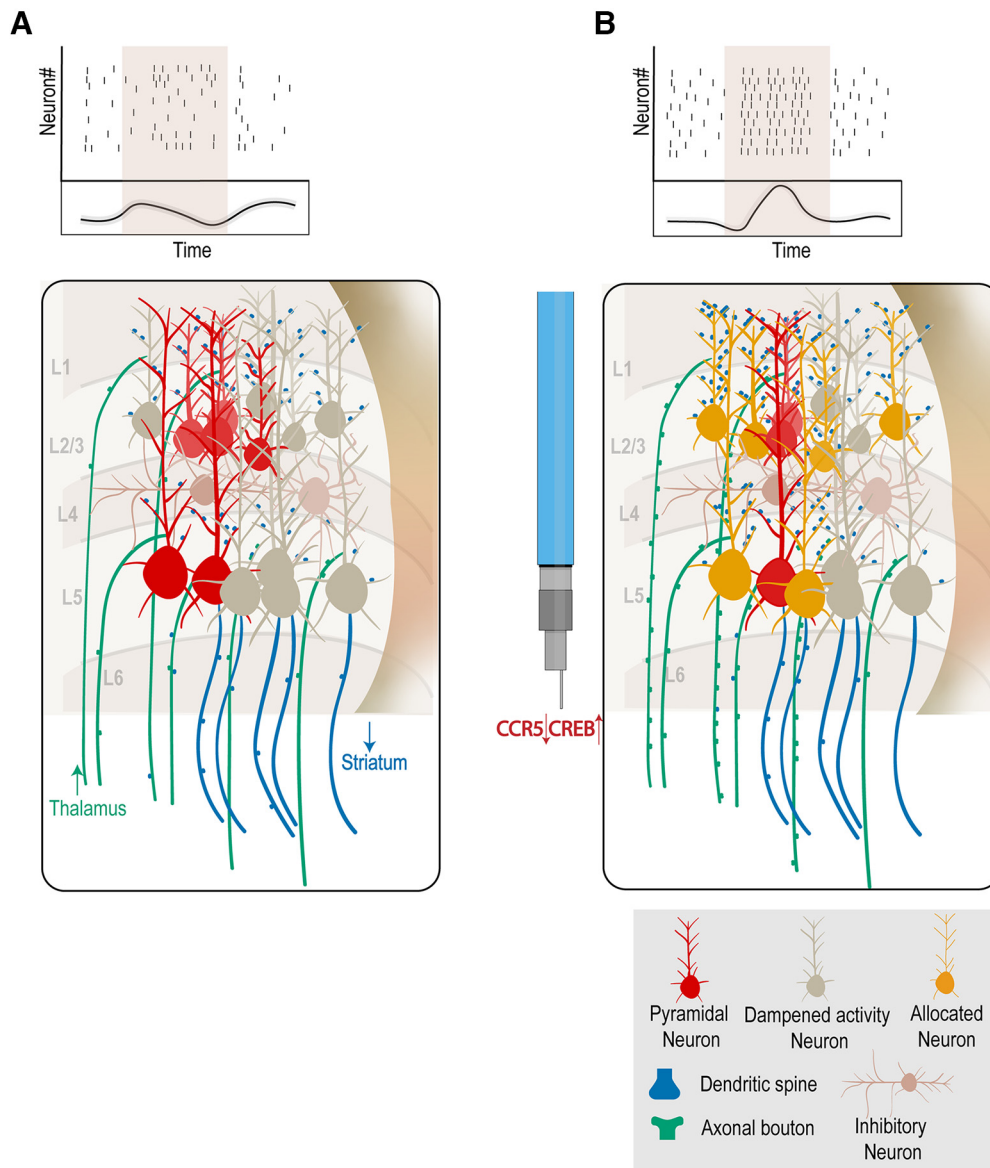
Restoration of activity, despite the loss of neurons in a network caused by stroke, suggests a restructuring of information within surviving neurons. Mechanistically, functional allocation may play an important role in this process (Fig. 2). Functional allocation refers to selective integration of a neuron into a circuit by virtue of its molecular profile or cellular excitability. Allocation has been studied in various systems of development (Lodato et al., 2011; Ye et al., 2015), sensory processing (Marshall et al., 2019; Edmondson et al., 2022), and during learning (Biane et al., 2016; Park et al., 2016; Lavi et al., 2023). Examples of allocation range from integration of inhibitory neurons into local excitatory circuits based on extrinsic cues from pyramidal neurons (Lodato et al., 2011), allocation of information to sensory (Huber et al., 2008) or visual circuits in perception (Marshall et al., 2019; Miller et al., 2022), and the selection of highly excitable neurons during formation of new memories (Park et al., 2016; Lavi et al., 2023). After stroke, loss of neurons and metabolic constraints require networks to use efficient coding (Mimica et al., 2018; Glanz et al., 2021; Koay et al., 2022), whereby neurons that maximize information transfer are selected for allocation to promote recovery. The attributes for allocation are cellular excitability and molecular programs that support excitability. Allocative processes have been implicated in spontaneous recovery after stroke, primarily arising from endogenous rewiring. Such adaptations result in reemergence of network connectivity with existing or new synaptic partners and can lead to compensated forms of motor behavior (Whishaw, 2000; Siegel et al., 2016; Jones, 2017). However, targeting allocation using the same cellular principles demonstrated in learning and memory (Josselyn and Tonegawa, 2020), namely, selective integration of neurons that efficiently encode information for a particular stimulus, could promote true recovery rather than compensation. Indeed, studies have shown that manipulation of genes that drive such

allocation in memory formation improves functional motor recovery in mice (Caracciolo et al., 2018; Joy et al., 2019). In summary, functional allocation offers a mechanism of remapping within existing stroke-disrupted networks by selective integration of excitable neurons with synchronized activity, restoring excitability and normal dynamics, resulting in recovery of function.

### Disruptions in long-range pathways after stroke

The effects of stroke are not isolated to peri-infarct regions, and changes at more distant sites, such as diaschisis, likely play an important role in post-stroke disability and recovery as well. In particular, we will focus on two well-studied long-range pathways within the CNS: interhemispheric interactions and the descending corticospinal tract (CST). The most well-studied form of interhemispheric interaction is interhemispheric inhibition (IHI). In the motor system, neural activity in one hemisphere can inhibit CST output of homologous regions in the contralateral hemisphere (Ferber et al., 1992). Such IHI is of cortical origin (Ferber et al., 1992; Di Lazzaro et al., 1999) and depends on integrity of the corpus callosum (Meyer et al., 1995). After stroke, decreased excitability of the ipsilesional motor cortex (iM1) is thought to reduce the inhibitory influence of iM1 onto the contralesional M1 (cM1), leading to cM1 hyperexcitability and increased inhibition from cM1 to iM1, thus interfering with voluntary movement of the paretic limb (Fig. 3A,B) (Boddington and Reynolds, 2017). Supporting this idea, Murase et al. (2004) reported that, in neurotypical adults, IHI transitions to excitation during the shift from movement preparation to execution. In chronic stroke survivors, this transition was absent and IHI from the cM1 to iM1 persisted during both movement preparation and execution. The magnitude of this abnormal IHI correlated with muscle weakness and finger tapping speed, suggesting that exaggerated IHI may underlie poststroke motor impairments (Murase et al., 2004). If so, then one might expect elevated IHI from the cM1 to iM1 to decrease over time, facilitating motor recovery. However, a recent longitudinal study found the opposite: IHI increased as motor recovery proceeded, and these increases correlated with behavioral markers of better motor recovery (Xu et al., 2019). These findings were reinforced by a recent study in chronic stroke survivors showing that increased IHI negatively correlated with impairment (i.e., more IHI corresponded to less impairment) (Mirdamadi et al., 2023), suggesting that abnormal IHI does not causally underlie post-stroke motor impairment. Instead, abnormal IHI may result from disuse of the paretic limb (King et al., 2022), overuse of the nonparetic limb (Avanzino et al., 2011), or maladaptive upregulation of uncrossed cortico-reticulospinal pathways (Ellis et al., 2012; Karbasforoushan et al., 2019).

In aphasia, increased right-hemisphere activation has sometimes been found in fMRI studies of people whose language was disrupted by a left-hemisphere stroke (Turkeltaub et al., 2011) or by a virtual lesion (Hartwigsen et al., 2013). As in the motor system, this contralesional hyperexcitability has been ascribed to decreased IHI from the lesioned hemisphere, and hypothesized to interfere with recovery by leading to overinhibition of perilesional tissue that might otherwise subservise language recovery (Martin et al., 2004). Evidence in favor of this hypothesis comes from studies showing associations between right-hemisphere activation and naming errors (Postman-Caucheteux et al., 2010), correlation between a reduction of right-hemisphere overactivation and aphasia treatment success (Richter et al., 2008), and beneficial effects of inhibitory stimulation to the right hemisphere on aphasia recovery (Naeser et al., 2005; Hamilton et al.,

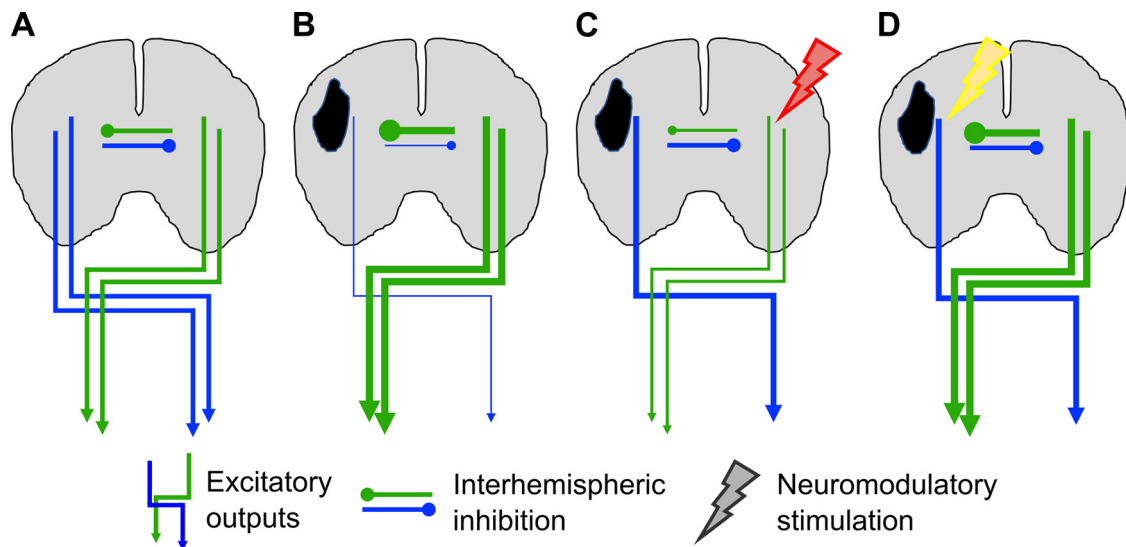


**Figure 2.** Functional allocation in neural circuits after stroke. **A**, Stroke causes loss of connectivity and reduction in spiking activity and synchronization. Shaded region represents stroke. Red represents pyramidal neurons in layers 2/3 and 5 in peri-infarct cortex. Green represents inputs from the thalamus. Blue represents output to the striatum. Gray pyramidal neurons indicate those with dampened activity after stroke from loss of structural connectivity and reduction in spine densities and axonal boutons. Time series plot above represents reduction in movement-related spiking activity (shaded region) with the trace of the population average shown below. **B**, Enhancing excitability within neuronal circuits either through neurostimulation (blue device on left) time-locked to task onset or with genetic modulations of CCR5 or CREB allows selective integration of excitable neurons into a functional motor circuit. Yellow represents allocated neurons. Functional allocation leads to restoring connectivity through increased spine densities, spiking activity, and synchronization.

2010). However, there is little direct evidence that IHI explains these findings, and there is also evidence that increased right-hemisphere activation may be compensatory and that its inhibition by experimental means or a second stroke is detrimental (Kinsbourne, 1971; Turkeltaub et al., 2012; Turkeltaub, 2015). Thus, as for motor recovery (Xu et al., 2019; Mirdamadi et al., 2023), the role of IHI in aphasia is still in question (Gainotti, 2015).

Another instance in which IHI has been proposed to play a role in stroke-induced disability is spatial neglect. Spatial neglect is characterized by asymmetric spatial performance (e.g., failure to detect or move toward stimuli on the contralesional side) that is not explained by a basic sensory or motor deficit, and it is more common, severe, and persistent after right-hemispheric injury (Stone et al., 1993; Ten Brink et al., 2017). It has been proposed that each hemisphere has a contralateral attention bias,

and that the hemispheres inhibit one another through transcallosal IHI (Kinsbourne, 1970). Unilateral lesions may produce neglect of contralateral space because the damaged hemisphere is impaired both in its ability to direct attention to the contralesional side and in its ability to inhibit the opposing hemisphere's attentional bias toward the ipsilesional side. Neglect may be less severe and persistent after left-hemisphere lesions either because of the right hemisphere's dominant role for attention (Robertson et al., 1998; Husain and Rorden, 2003) and/or because the right hemisphere can allocate attention to both sides of space, which allows it to compensate for left-hemisphere lesions (Heilman and Van Den Abell, 1980; Mesulam, 1999). Support for the IHI hypothesis of spatial neglect includes a case study in which neglect caused by a right parietal lesion resolved after a second infarct to the left frontal cortex (Vuilleumier et al., 1996), functional neuroimaging evidence for a link between normalization



**Figure 3.** Long-range pathways important for post-stroke impairment and recovery. **A**, In the healthy brain, excitatory (arrows) and inhibitory (lines with dots) outputs of the two hemispheres are balanced. **B**, After a unilateral lesion directly disrupting some of one hemisphere's excitatory and inhibitory outputs, the remaining perilesional outputs are suppressed by increased IHI from the disinhibited contralesional hemisphere. **C**, Inhibitory stimulation (red lightning bolt) of the intact hemisphere may help restore interhemispheric balance (e.g., to alleviate spatial neglect). **D**, In the motor system, excitatory stimulation (yellow lightning bolt) of CST projections from the lesioned hemisphere to alpha motoneurons in the spinal cord may upregulate remaining perilesional outputs and improve paretic motor behavior, irrespective of changes to interhemispheric balance.

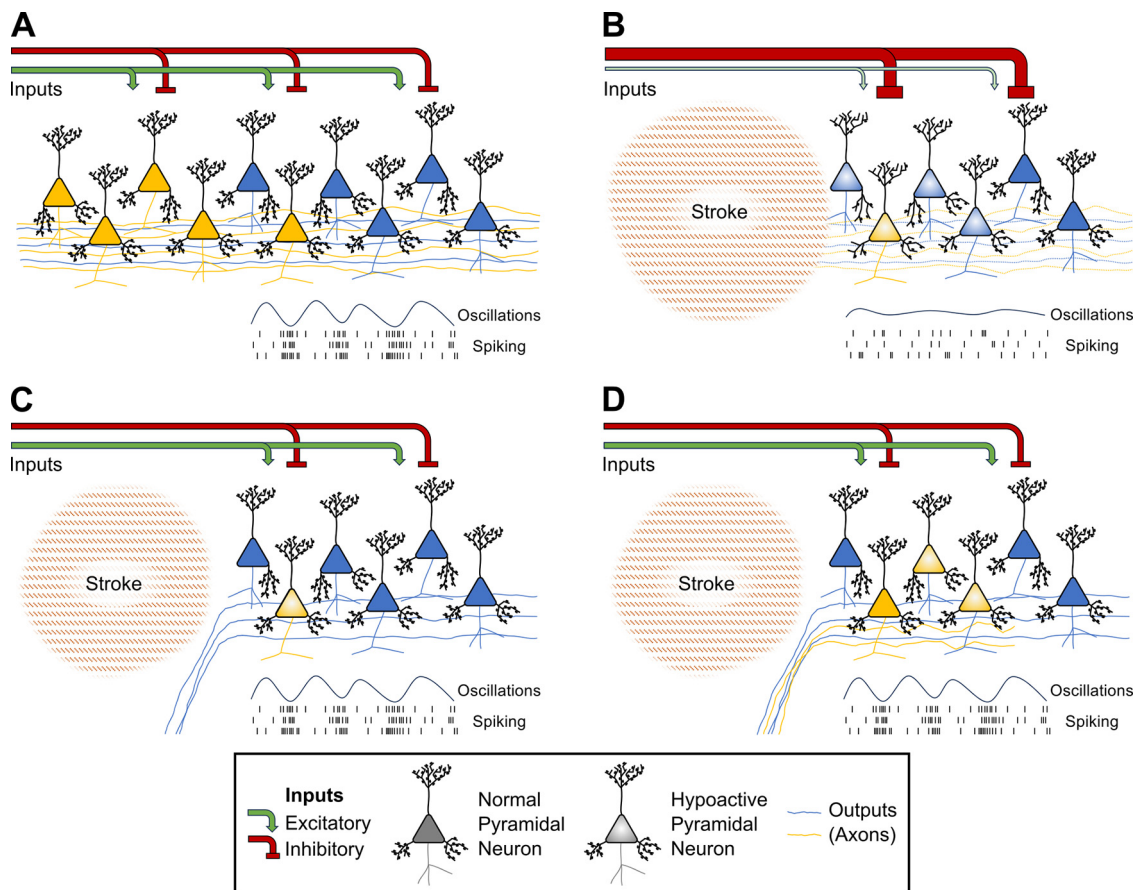
of left-hemisphere hyperactivation and spontaneous recovery from neglect (Corbetta et al., 2005), and several studies inducing a temporary shift in attention contralateral to excitatory and ipsilateral to inhibitory neurostimulation in neurologically healthy adults (Dambeck et al., 2006; Sparing et al., 2009; Giglia et al., 2011; Szczepanski and Kastner, 2013). In a cat model, neglect induced by unilateral cortical lesions temporarily resolved after deactivation of contralesional cortex or superior colliculus (Rushmore et al., 2006). Evidence regarding the use of neurostimulation to restore interhemispheric balance and treat neglect in humans is growing (Fig. 3C), albeit not unequivocal (e.g., Oliveri et al., 2001; Yi et al., 2016; Yang et al., 2017; Zebhauser et al., 2019; Veldema et al., 2020).

Outside of interhemispheric interactions, descending pathways reflect another form of long-range connectivity that is crucially involved in stroke recovery. In humans, the CST is the primary descending system responsible for voluntary, dexterous, goal-directed movements; lesions that disrupt it produce hemiparesis. In humans and nonhuman primates, the CST is highly specialized and includes monosynaptic connections between layer V pyramidal neurons in M1 and  $\alpha$  motoneurons in the spinal cord (Lemon, 2008). Stroke commonly disrupts the CST, either directly (Puig et al., 2011) or through secondary degeneration of descending axons (i.e., Wallerian degeneration) (Yu et al., 2009; DeVetten et al., 2010). However, up to 85% of stroke survivors have residual CST projections from the lesioned hemisphere to  $\alpha$  motoneuron pools innervating paretic upper extremity muscles (Stinear et al., 2017). The presence and functional integrity of these projections are a strong predictor of upper extremity motor recovery (Stinear et al., 2007, 2017), raising the possibility that improving synaptic transmission along this pathway could enhance recovery. In this way, stroke-related weakness shares a common substrate (i.e., decreased CST transmission) with incomplete spinal cord injury (Christiansen and Perez, 2018), where neurostimulation aimed at strengthening cortical-corticospinal and corticospinal-motoneuronal synaptic transmission has shown promise for promoting motor recovery (Bunday and Perez, 2012; Long

et al., 2017; Jo et al., 2023). Neurostimulation targeting cortico-spinal-motoneuronal synaptic transmission may also benefit post-stroke CST transmission and paretic hand muscle activation (Urbin et al., 2021), but large-scale trials have not yet been conducted. Future work should focus on developing a detailed mechanistic understanding of how residual CST transmission recovers after stroke and implementing targeted interventions that potentiate synaptic transmission at remaining corticospinal connections (Fig. 3D). In summary, changes in long-range pathways frequently occur after stroke and likely contribute to multiple types of post-stroke disability. Normalization of these pathways then may also be important for recovery, either alone or in conjunction with restoration or remapping of more local peri-infarct circuits.

#### Next generation approaches to restoring neural circuits to promote recovery

Mechanisms governing post-stroke impairment and recovery are clearly multifaceted, involving changes that span from individual neurons, to local neuronal ensembles, and to long-range connections affecting distributed networks. A common theme throughout this review is that dysfunction extends beyond the infarct core and contributes to post-stroke disability, and that normalization or restoration of the activity of "spared" neurons, circuits, and pathways likely contributes to recovery of function after stroke. We suggest the following simplified model summarizing these ideas. In the healthy brain, individual neurons are situated in local microcircuits, with long-range excitatory and inhibitory inputs, as well as local and long-range outputs (Fig. 4A). Proper functionality results from population dynamics, with network-wide oscillations from coordination of spiking activity of individual neurons into ensembles. After stroke, neurons in the infarct core are destroyed, connectivity is disrupted, excitation/inhibition balance shifts, network oscillations are impaired, and the activity of spared neurons in peri-infarct and more distant regions (diaschisis) is disrupted (Fig. 4B). Over time, many of these changes normalize to some extent and the function of spared neurons and circuits is restored, although often incompletely



**Figure 4.** A simplified model of neural circuit changes after stroke and during recovery. **A**, In the healthy brain, neurons subserving two distinct functions (yellow and blue triangles) are situated in local microcircuits, with long-range excitatory and inhibitory inputs (top, green and red lines, respectively), and axonal outputs (middle, thin yellow and blue lines). Neural oscillations coordinate population activity and synchronize spiking in functional ensembles. **B**, After stroke (red hatched circle), neurons in the ischemic core are lost. Spared neurons may lose synaptic connectivity (loss of dendritic spines), excitation/inhibition balance shifts, neural oscillations are disrupted, and neuronal activity is impaired (depicted as pale coloration of neurons and reduced spiking activity). **C**, During recovery, the infarct core contracts due to gliosis, and activity in spared neurons and circuits is (partially) restored, with normalization of synaptic connectivity, excitation/inhibition balance, neural oscillations, and neuronal activity. **D**, Engagement of plasticity mechanisms, either endogenously or via therapeutic interventions, may allow allocation of spared neurons (depicted as color change from blue to yellow) into networks subserving the functionality lost to stroke, resulting in remapping and better recovery.

(Fig. 4C). Structural changes and engagement of plasticity programs may allow functional allocation of spared neurons into established networks, enabling true remapping and potentiating recovery of function (Fig. 4D). This framework suggests that recovery is a dynamic process occurring across stages over time, with multiple potential avenues of intervention to promote recovery after stroke.

As summarized above, the balance between excitation and inhibition shifts after stroke, impairing the function of spared neurons and circuits. In rodents, several studies have demonstrated that shifting this balance toward greater excitation can promote restoration of neuronal activity and/or remapping. Pharmacologically, both reducing GABAergic inhibition (Clarkson et al., 2010; Alia et al., 2016) and promoting excitatory neurotransmission via AMPARs (Clarkson et al., 2011) promote recovery after stroke. Optogenetic tools have also been used to increase excitation in a cell- and region-specific manner after stroke to promote recovery, including direct stimulation of peri-infarct excitatory neurons (Cheng et al., 2014; Conti et al., 2022) and stimulation of excitatory thalamocortical inputs (Tennant et al., 2017). More recently, cell-specific chemogenetic stimulation of vasoactive intestinal peptide inhibitory interneurons was shown to improve recovery after stroke, likely through disinhibition of peri-infarct circuits (Motaharinia et al., 2021). A recent Phase 2

trial in humans tested the effects of an oral GABA<sub>A</sub>  $\alpha 5$  antagonist that reduces tonic inhibition on disability after ischemic stroke but unfortunately found no significant improvement compared with placebo (Chabriat et al., 2020). There are a number of possible explanations for this outcome, but future interventions will likely need to be more precisely targeted to manipulate the excitation/inhibition balance in the right areas of the CNS and at the right times during recovery. Proper timing will be particularly crucial to avoid exacerbating acute phase excitotoxicity (Lai et al., 2014), while capitalizing on adaptive plasticity mechanisms upregulated in the subacute phase after stroke. Optogenetic and chemogenetic approaches targeting specific neuronal subpopulations in defined regions may offer one potential avenue to do so in the future (Sahel et al., 2022), although significant work still needs to be done to translate these technologies to patients recovering from stroke.

In addition to generally promoting excitability of neurons, studies of neural population dynamics after stroke suggest that it may be important to coordinate this activity precisely as well (Ganguly et al., 2022). Noninvasively modulating oscillatory dynamics offers one potential approach (Storch et al., 2021). In nonhuman primates, electrical stimulation of peri-infarct cortex can drive changes in low-frequency oscillations and  $\gamma$ -oscillations acutely after stroke (J. Zhou et al., 2022). During recovery,



stimulation can entrain ensembles of neurons to cofire, leading to enhanced behavioral performance (Khanna et al., 2021). Likewise, stimulation of peri-infarct cortex in rodents can improve low-frequency oscillation dynamics and improve recovery (Ramanathan et al., 2018). In humans, transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation technique that can activate and induce plastic changes within neural circuits supporting motor, language, and cognitive abilities. However, these techniques produce highly variable effects, even when applied in the nonlesioned brain (Ridding and Ziemann, 2010; López-Alonso et al., 2014; Ziemann and Siebner, 2015). Such variability likely contributes to the conflicting results of recent post-stroke TMS trials (Hao et al., 2013; Müri et al., 2013; Smith and Stinear, 2016; Nyffeler et al., 2019; Lefaucheur et al., 2020). TMS interventions therefore require further optimization to reach their therapeutic potential; and delivering TMS specifically coupled to brain activity patterns, termed brain state-dependent TMS, offers one potential approach. For example, in the healthy human motor system, TMS interventions best improve CST transmission and motor learning when coupled to specific phases of EEG-defined sensorimotor rhythms that correspond to strong CST activation (Zrenner et al., 2018; Baur et al., 2020; Hussain et al., 2021). These findings have led to the initiation of a multisite clinical trial that will combine standard rehabilitation with repeated application of  $\mu$  phase-coupled iM1 TMS in subacute stroke (Lieb et al., 2023) to determine whether this dynamically informed approach to neurostimulation can improve motor recovery. However, post-stroke sensorimotor rhythm generating circuits may be disrupted in a heterogeneous manner that depends on lesion pattern, the amount of perilesional remapping, and motor impairment level (Cramer et al., 2003; Griffis et al., 2019), complicating efforts to couple neurostimulation with “normal” sensorimotor rhythms. An alternative approach involves identifying personalized whole-brain EEG activity patterns during which each stroke survivor’s residual CST is best activated (Metsomaa et al., 2021; Hussain and Quentin, 2022), and then coupling TMS interventions to these patterns (Khatri and Hussain, 2023). Translating these approaches outside of the motor system will, however, require additional work to obtain reliable readouts of TMS-induced activation of recovery-relevant circuits. With continued development, this approach may lead to personalized brain state-dependent TMS interventions that are fully customized to each stroke survivor’s pattern of brain activity, residual CST engagement, and stage of recovery.

Modulating excitability of neurons after stroke might offer one avenue to drive their functional allocation into new neuronal ensembles. However, it may also be possible to drive functional allocation genetically. There are distinct molecular programs that are activated in allocated neurons after stroke that mirror those involved in functional allocation during memory formation in the healthy brain. Supporting this idea, machine learning models applied to gene expression datasets can predict, and hence classify, samples from animals with functional motor recovery from animals with deficits (M.T.J., unpublished data) based on expression of gene sets normally expressed in functionally allocated neurons during memory formation in the healthy brain. The best studied of these genes are the transcription factor, *CREB* (cAMP Response Element Binding Protein) (Y. Zhou et al., 2009; Park et al., 2016) and the GPCR *CCR5* (C-C Chemokine Receptor-5) (M. Zhou et al., 2016; Shen et al., 2022). Gene expression profiles of neurons with *CCR5* or *CREB* perturbations after stroke show overrepresentation of gene sets that are normally expressed in neurons allocated to a memory trace

(M.T.J., unpublished data). Furthermore, both overexpression of *CREB* (Caracciolo et al., 2018; Bechay et al., 2022) or downregulation of *CCR5* (Joy et al., 2019; Wu et al., 2023) improves functional motor recovery in mouse models of stroke. Stroke patients that are carriers for a loss-of-function mutation in *CCR5* show better outcomes compared with control patients (Joy et al., 2019). Forcing allocation through *CREB* overexpression in cortical neurons in peri-infarct cortex promotes recovery (Caracciolo et al., 2018), and inactivation of the same neurons leads to a loss of recovery, demonstrating the necessity of these allocated neurons. While gene therapy approaches still face significant translational hurdles for clinical use, clinical trials targeting *CCR5* pharmacologically are already underway (clinical trial identifiers NCT04789616, NCT04966429). Thus, genetic manipulation of functional allocation (Fig. 2B) represents a novel molecular approach to restoring neural circuits and promoting recovery.

Historical hypotheses, such as remapping, redundancy, and diaschisis, have driven research into stroke recovery for over a century. In some ways, these early ideas, made in the infancy of neuroscience, have held up remarkably well and still hold relevance for current research. However, as advances in neuroscience techniques allow for the study of the structure and function of neural circuits with ever greater precision, our understanding of the complexity and dynamics of the changes that occur in the CNS after stroke has deepened as well. While this complexity does not always fit neatly into historical models, it does offer promising new avenues for investigation and, more importantly, suggests novel next generation approaches toward reducing disability and improving recovery after stroke.

## References

- Alia C, Spalletti C, Lai S, Panarese A, Micera S, Caleo M (2016) Reducing GABAA-mediated inhibition improves forelimb motor function after focal cortical stroke in mice. *Sci Rep* 6:37823.
- Akol I, Kalogeraki E, Pielecka-Fortuna J, Fricke M, Löwel S (2022) MMP2 and MMP9 activity is crucial for adult visual cortex plasticity in healthy and stroke-affected mice. *J Neurosci* 42:16–32.
- Ariani G, Pruszynski JA, Diedrichsen J (2022) Motor planning brings human primary somatosensory cortex into action-specific preparatory states. *Elife* 11:e69517.
- Avanzino L, Bassolino M, Pozzo T, Bove M (2011) Use-dependent hemispheric balance. *J Neurosci* 31:3423–3428.
- Baker SN (2007) Oscillatory interactions between sensorimotor cortex and the periphery. *Curr Opin Neurobiol* 17:649–655.
- Baker SN, Olivier E, Lemon RN (1997) Coherent oscillations in monkey motor cortex and hand muscle EMG show task-dependent modulation. *J Physiol* 501:225–241.
- Baker SN, Pinches EM, Lemon RN (2003) Synchronization in monkey motor cortex during a precision grip task: II. Effect of oscillatory activity on corticospinal output. *J Neurophysiol* 89:1941–1953.
- Bauer AQ, Kraft AW, Wright PW, Snyder AZ, Lee JM, Culver JP (2014) Optical imaging of disrupted functional connectivity following ischemic stroke in mice. *Neuroimage* 99:388–401.
- Baur D, Galevska D, Hussain S, Cohen LG, Ziemann U, Zrenner C (2020) Induction of LTD-like corticospinal plasticity by low-frequency rTMS depends on pre-stimulus phase of sensorimotor  $\mu$ -rhythm. *Brain Stimul* 13:1580–1587.
- Bechay KR, Abduljawad N, Latifi S, Suzuki K, Iwashita H, Carmichael ST (2022) PDE2A inhibition enhances axonal sprouting, functional connectivity, and recovery after stroke. *J Neurosci* 42:8225–8236.
- Biane JS, Takashima Y, Scanziani M, Conner JM, Tuszynski MH (2016) Thalamocortical projections onto behaviorally relevant neurons exhibit plasticity during adult motor learning. *Neuron* 89:1173–1179.
- Bice AR, Xiao Q, Kong J, Yan P, Rosenthal ZP, Kraft AW, Smith KP, Wieloch T, Lee JM, Culver JP, Bauer AQ (2022) Homotopic

- contralateral excitation suppresses spontaneous circuit repair and global network reconnections following ischemic stroke. *Elife* 11:e68852.
- Boddington LJ, Reynolds JN (2017) Targeting interhemispheric inhibition with neuromodulation to enhance stroke rehabilitation. *Brain Stimul* 10:214–222.
- Bönstrup M, Krawinkel L, Schulz R, Cheng B, Feldheim J, Thomalla G, Cohen LG, Gerloff C (2019) Low-frequency brain oscillations track motor recovery in human stroke. *Ann Neurol* 86:853–865.
- Brown CE, Li P, Boyd JD, Delaney KR, Murphy TH (2007) Extensive turnover of dendritic spines and vascular remodeling in cortical tissues recovering from stroke. *J Neurosci* 27:4101–4109.
- Brown CE, Aminoltejeri K, Erb H, Winship IR, Murphy TH (2009) In vivo voltage-sensitive dye imaging in adult mice reveals that somatosensory maps lost to stroke are replaced over weeks by new structural and functional circuits with prolonged modes of activation within both the peri-infarct zone and distant sites. *J Neurosci* 29:1719–1734.
- Brown CE, Boyd JD, Murphy TH (2010) Longitudinal in vivo imaging reveals balanced and branch-specific remodeling of mature cortical pyramidal dendritic arbors after stroke. *J Cereb Blood Flow Metab* 30:783–791.
- Brownset SL, Warren JE, Geranmayeh F, Woodhead Z, Leech R, Wise RJ (2014) Cognitive control and its impact on recovery from aphasic stroke. *Brain* 137:242–254.
- Bunday KL, Perez MA (2012) Motor recovery after spinal cord injury enhanced by strengthening corticospinal synaptic transmission. *Curr Biol* 22:2355–2361.
- Caracciolo L, Marosi M, Mazzitelli J, Latifi S, Sano Y, Galvan L, Kawaguchi R, Holley S, Levine MS, Coppola G, Portera-Cailliau C, Silva AJ, Carmichael ST (2018) CREB controls cortical circuit plasticity and functional recovery after stroke. *Nat Commun* 9:2250.
- Chabriat H, Bassetti CL, Marx U, Audoli-Inthavong ML, Sors A, Lambert E, Watzte M, Hermann DM, RESTORE BRAIN Study Investigators (2020) Safety and efficacy of GABAA  $\alpha$ 5 antagonist S44819 in patients with ischaemic stroke: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Neurol* 19:226–233.
- Cheng MY, Wang EH, Woodson WJ, Wang S, Sun G, Lee AG, Arac A, Fenno LE, Deisseroth K, Steinberg GK (2014) Optogenetic neuronal stimulation promotes functional recovery after stroke. *Proc Natl Acad Sci USA* 111:12913–12918.
- Christiansen L, Perez MA (2018) Targeted-plasticity in the corticospinal tract after human spinal cord injury. *Neurotherapeutics* 15:618–627.
- Clarkson AN, Huang BS, Macisaac SE, Mody I, Carmichael ST (2010) Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. *Nature* 468:305–309.
- Clarkson AN, Overman JJ, Zhong S, Mueller R, Lynch G, Carmichael ST (2011) AMPA receptor-induced local brain-derived neurotrophic factor signaling mediates motor recovery after stroke. *J Neurosci* 31:3766–3775.
- Conti E, Scaglione A, de Vito G, Calugi F, Pasquini M, Pizzorusso T, Micera S, Allegra Mascaro AL, Pavone FS (2022) Combining optogenetic stimulation and motor training improves functional recovery and perilesional cortical activity. *Neurorehabil Neural Repair* 36:107–118.
- Corbetta M, Kincade MJ, Lewis C, Snyder AZ, Sapir A (2005) Neural basis and recovery of spatial attention deficits in spatial neglect. *Nat Neurosci* 8:1603–1610.
- Cramer JV, Gesierich B, Roth S, Dichgans M, Düring M, Liesz A (2019) In vivo widefield calcium imaging of the mouse cortex for analysis of network connectivity in health and brain disease. *Neuroimage* 199:570–584.
- Cramer SC, Benson RR, Burra VC, Himes D, Crafton KR, Janowsky JS, Brown JA, Lutsep HL (2003) Mapping individual brains to guide restorative therapy after stroke: rationale and pilot studies. *Neuro Res* 25:811–814.
- Cramer SC, Shah R, Juranek J, Crafton KR, Le V (2006) Activity in the peri-infarct rim in relation to recovery from stroke. *Stroke* 37:111–115.
- Dambeck N, Sparing R, Meister IG, Wienemann M, Weidemann J, Topper R, Boroojerdi B (2006) Interhemispheric imbalance during visuospatial attention investigated by unilateral and bilateral TMS over human parietal cortices. *Brain Res* 1072:194–199.
- DeMarco AT, Wilson SM, Rising K, Rapcsak SZ, Beeson PM (2018) The neural substrates of improved phonological processing following successful treatment in a case of phonological alexia and agraphia. *Neurocase* 24:31–40.
- DeMarco AT, van der Stelt C, Paul S, Dvorak E, Lacey E, Snider S, Turkeltaub PE (2022) Absence of perilesional neuroplastic recruitment in chronic poststroke aphasia. *Neurology* 99:e119–e128.
- DeVetten G, Coutts SB, Hill MD, Goyal M, Eesa M, O'Brien B, Demchuk AM, Kirton A, MONITOR and VISION Study Groups (2010) Acute corticospinal tract Wallerian degeneration is associated with stroke outcome. *Stroke* 41:751–756.
- Di Lazzaro V, Oliviero A, Profice P, Insaola A, Mazzone P, Tonali P, Rothwell JC (1999) Direct demonstration of interhemispheric inhibition of the human motor cortex produced by transcranial magnetic stimulation. *Exp Brain Res* 124:520–524.
- Donoghue JP, Sanes JN, Hatsopoulos NG, Gaál G (1998) Neural discharge and local field potential oscillations in primate motor cortex during voluntary movements. *J Neurophysiol* 79:159–173.
- Edmondson LR, Jiménez Rodríguez A, Saal HP (2022) Expansion and contraction of resource allocation in sensory bottlenecks. *Elife* 11:e70777.
- Ellis MD, Drogos J, Carmona C, Keller T, Dewald JP (2012) Neck rotation modulates flexion synergy torques, indicating an ipsilateral reticulospinal source for impairment in stroke. *J Neurophysiol* 108:3096–3104.
- Espenhahn S, Rossiter HE, van Wijk BC, Redman N, Rondina JM, Diedrichsen J, Ward NS (2020) Sensorimotor cortex beta oscillations reflect motor skill learning ability after stroke. *Brain Commun* 2:fcaa161.
- Favaretto C, Allegra M, Deco G, Metcalf NV, Griffis JC, Shulman GL, Brovelli A, Corbetta M (2022) Subcortical-cortical dynamical states of the human brain and their breakdown in stroke. *Nat Commun* 13:5069.
- Fedorenko E, Duncan J, Kanwisher N (2013) Broad domain generality in focal regions of frontal and parietal cortex. *Proc Natl Acad Sci USA* 110:16616–16621.
- Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992) Interhemispheric inhibition of the human motor cortex. *J Physiol* 453:525–546.
- Finger S (2010) Chapter 51: recovery of function: redundancy and vicariation theories. *Handb Clin Neurol* 95:833–841.
- Finger S, Koehler PJ, Jagella C (2004) The Monakow concept of diaschisis: origins and perspectives. *Arch Neurol* 61:283–288.
- Fridriksson J, Richardson JD, Fillmore P, Cai B (2012) Left hemisphere plasticity and aphasia recovery. *Neuroimage* 60:854–863.
- Gainotti G (2015) Contrasting opinions on the role of the right hemisphere in the recovery of language: a critical survey. *Aphasiology* 29:1020–1037.
- Ganguly K, Khanna P, Morecraft RJ, Lin DJ (2022) Modulation of neural co-firing to enhance network transmission and improve motor function after stroke. *Neuron* 110:2363–2385.
- Georgopoulos AP, Kalaska JF, Caminiti R, Massey JT (1982) On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. *J Neurosci* 2:1527–1537.
- Geranmayeh F, Brownset SL, Wise RJ (2014) Task-induced brain activity in aphasic stroke patients: what is driving recovery? *Brain* 137:2632–2648.
- Giglia G, Mattaliano P, Puma A, Rizzo S, Fierro B, Brighina F (2011) Neglect-like effects induced by tDCS modulation of posterior parietal cortices in healthy subjects. *Brain Stimul* 4:294–299.
- Glanz RM, Dooley JC, Sokoloff G, Blumberg MS (2021) Sensory coding of limb kinematics in motor cortex across a key developmental transition. *J Neurosci* 41:6905–6918.
- Grefkes C, Fink GR (2014) Connectivity-based approaches in stroke and recovery of function. *Lancet Neurol* 13:206–216.
- Grefkes C, Nowak DA, Eickhoff SB, Dafotakis M, Küst J, Karbe H, Fink GR (2008) Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. *Ann Neurol* 63:236–246.
- Greifzu F, Schmidt S, Schmidt K-F, Kreikemeier K, Witte OW, Löwel S (2011) Global impairment and therapeutic restoration of visual plasticity mechanisms after a localized cortical stroke. *Proc Natl Acad Sci U S A* 108:15450–15455.
- Griffis JC, Metcalf NV, Corbetta M, Shulman GL (2019) Structural disconnections explain brain network dysfunction after stroke. *Cell Rep* 28:2527–2540.e9.
- Guo L, Kondapavulur S, Lemke SM, Won SJ, Ganguly K (2021) Coordinated increase of reliable cortical and striatal ensemble activations during recovery after stroke. *Cell Rep* 36:109370.
- Hamilton RH, Sanders L, Benson J, Faseyitan O, Norise C, Naeser M, Martin P, Coslett HB (2010) Stimulating conversation: enhancement of elicited propositional speech in a patient with chronic non-fluent aphasia following transcranial magnetic stimulation. *Brain Lang* 113:45–50.

- Hao Z, Wang D, Zeng Y, Liu M (2013) Repetitive transcranial magnetic stimulation for improving function after stroke. *Cochrane Database Syst Rev* 2013:CD008862.
- Hartwigsen G, Saur D, Price CJ, Ulmer S, Baumgaertner A, Siebner HR (2013) Perturbation of the left inferior frontal gyrus triggers adaptive plasticity in the right homologous area during speech production. *Proc Natl Acad Sci USA* 110:16402–16407.
- Hatsopoulos NG, Ojakangas CL, Paninski L, Donoghue JP (1998) Information about movement direction obtained from synchronous activity of motor cortical neurons. *Proc Natl Acad Sci USA* 95:15706–15711.
- Hazime M, Alasoadura M, Lamtahri R, Quilichini P, Leprince J, Vaudry D, Chuquet J (2021) Prolonged deficit of low gamma oscillations in the peri-infarct cortex of mice after stroke. *Exp Neurol* 341:113696.
- He F, Sullender CT, Zhu H, Williamson MR, Li X, Zhao Z, Jones TA, Xie C, Dunn AK, Luan L (2020) Multimodal mapping of neural activity and cerebral blood flow reveals long-lasting neurovascular dissociations after small-scale strokes. *Sci Adv* 6:aba1933.
- Heilman KM, Van Den Abell T (1980) Right hemisphere dominance for attention: the mechanism underlying hemispheric asymmetries of inattention (neglect). *Neurology* 30:327–330.
- Heiss WD, Kessler J, Thiel A, Ghaemi M, Karbe H (1999) Differential capacity of left and right hemispheric areas for compensation of post-stroke aphasia. *Ann Neurol* 45:430–438.
- Heiss WD, Thiel A (2006) A proposed regional hierarchy in recovery of post-stroke aphasia. *Brain Lang* 98:118–123.
- Huber D, Petreanu L, Ghilani N, Ranade S, Hromádka T, Mainen Z, Svoboda K (2008) Sparse optical microstimulation in barrel cortex drives learned behaviour in freely moving mice. *Nature* 451:61–64.
- Hussain SJ, Quentin R (2022) Decoding personalized motor cortical excitability states from human electroencephalography. *Sci Rep* 12:6323.
- Husain M, Rorden C (2003) Non-spatially lateralized mechanisms in hemispatial neglect. *Nat Rev Neurosci* 4:26–36.
- Hussain SJ, Vollmer MK, Stimely J, Norato G, Zrenner C, Ziemann U, Buch ER, Cohen LG (2021) Phase-dependent offline enhancement of human motor memory. *Brain Stimul* 14:873–883.
- Jablonka JA, Witte OW, Kossut M (2007) Photothrombotic infarct impairs experience-dependent plasticity in neighboring cortex. *Neuroreport* 18:165–169.
- Jablonka JA, Kossut M, Witte OW, Liguz-Leczna M (2012) Experience-dependent brain plasticity after stroke: effect of ibuprofen and poststroke delay. *Eur J Neurosci* 36:2632–2639.
- Jaillard A, Martin CD, Garambois K, Lebas JF, Hommel M (2005) Vicarious function within the human primary motor cortex? *Brain* 128:1122–1138.
- Jo HJ, Kizziar E, Sangari S, Chen D, Kessler A, Kim K, Anshel A, Heinemann AW, Mensh BD, Awadalla S, Lieber RL, Oudega M, Perez MA (2023) Multisite Hebbian plasticity restores function in humans with spinal cord injury. *Ann Neurol* 93:1198–1213.
- Jones TA (2017) Motor compensation and its effects on neural reorganization after stroke. *Nat Rev Neurosci* 18:267–280.
- Jones TA, Schallert T (1994) Use-dependent growth of pyramidal neurons after neocortical damage. *J Neurosci* 14:2140–2152.
- Josselyn SA, Tonegawa S (2020) Memory engrams: recalling the past and imagining the future. *Science* 367:eaaaw4325.
- Joy MT, Ben Assayag E, Shabashov-Stone D, Liraz-Zaltsman S, Mazzitelli J, Arenas M, Abduljawad N, Kliper E, Korczyn AD, Thareja NS, Kesner EL, Zhou M, Huang S, Silva TK, Katz N, Bornstein NM, Silva AJ, Shohami E, Carmichael ST (2019) CCR5 is a therapeutic target for recovery after stroke and traumatic brain injury. *Cell* 176:1143–1157.e13.
- Joy MT, Carmichael ST (2021) Encouraging an excitable brain state: mechanisms of brain repair in stroke. *Nat Rev Neurosci* 22:38–53.
- Karbasforoushan H, Cohen-Adad J, Dewald JP (2019) Brainstem and spinal cord MRI identifies altered sensorimotor pathways post-stroke. *Nat Commun* 10:3524.
- Khanna P, Totten D, Novik L, Roberts J, Morecraft RJ, Ganguly K (2021) Low-frequency stimulation enhances ensemble co-firing and dexterity after stroke. *Cell* 184:912–930.e20.
- Khatru U, Hussain SJ (2023) Personalized whole-brain activity patterns predict corticospinal tract activation in real-time [abstract]. Annual Meeting of the American Society for Neurorehabilitation, Charleston, SC.
- King EM, Edwards LL, Borich MR (2022) Short-term arm immobilization modulates excitability of inhibitory circuits within, and between, primary motor cortices. *Physiol Rep* 10:e15359.
- Kinsbourne M (1970) A model for the mechanism of unilateral neglect of space. *Trans Am Neurol Assoc* 95:143–146.
- Kinsbourne M (1971) The minor cerebral hemisphere as a source of aphasic speech. *Arch Neurol* 25:302–306.
- Koay SA, Charles AS, Thiberge SY, Brody CD, Tank DW (2022) Sequential and efficient neural-population coding of complex task information. *Neuron* 110:328–349.e11.
- Kokinovic B, Medini P (2018) Loss of GABAB-mediated interhemispheric synaptic inhibition in stroke periphery. *J Physiol* 596:1949–1964.
- Lai TW, Zhang S, Wang YT (2014) Excitotoxicity and stroke: identifying novel targets for neuroprotection. *Prog Neurobiol* 115:157–188.
- Latifi S, Mitchell S, Habibey R, Hosseini F, Donzis E, Estrada-Sánchez AM, Nejad HR, Levine M, Golshani P, Carmichael ST (2020) Neuronal network topology indicates distinct recovery processes after stroke. *Cereb Cortex* 30:6363–6375.
- Lavi A, Sehgal M, de Sousa AF, Ter-Mkrtychyan D, Sisan F, Luchetti A, Okabe A, Bear C, Silva AJ (2023) Local memory allocation recruits memory ensembles across brain regions. *Neuron* 111:470–480.e5.
- Lefaucheur JP, et al. (2020) Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). *Clin Neurophysiol* 131:474–528.
- Lemon RN (2008) Descending pathways in motor control. *Annu Rev Neurosci* 31:195–218.
- Li N, Chen TW, Guo ZV, Gerfen CR, Svoboda K (2015) A motor cortex circuit for motor planning and movement. *Nature* 519:51–56.
- Li S, Overman JJ, Katsman D, Kozlov SV, Donnelly CJ, Twiss JL, Giger RJ, Coppola G, Geschwind DH, Carmichael ST (2010) An age-related sprouting transcriptome provides molecular control of axonal sprouting after stroke. *Nat Neurosci* 13:1496–1504.
- Lieb A, Zrenner B, Zrenner C, Kozák G, Martus P, Grefkes C, Ziemann U (2023) Brain-oscillation-synchronized stimulation to enhance motor recovery in early subacute stroke: a randomized controlled double-blind three-arm parallel-group exploratory trial comparing personalized, non-personalized and sham repetitive transcranial magnetic stimulation (Acronym: BOSS-STROKE). *BMC Neurol* 23:204.
- Lim DH, LeDue JM, Mohajerani MH, Murphy TH (2014) Optogenetic mapping after stroke reveals network-wide scaling of functional connections and heterogeneous recovery of the peri-infarct. *J Neurosci* 34:16455–16466.
- Little S, Bonaiuto J, Barnes G, Bestmann S (2019) Human motor cortical beta bursts relate to movement planning and response errors. *PLoS Biol* 17:e3000479.
- Lodato S, Rouaux C, Quast KB, Jantrachotechatchawan C, Studer M, Hensch TK, Arlotta P (2011) Excitatory projection neuron subtypes control the distribution of local inhibitory interneurons in the cerebral cortex. *Neuron* 69:763–779.
- Long J, Federico P, Perez MA (2017) A novel cortical target to enhance hand motor output in humans with spinal cord injury. *Brain* 140:1619–1632.
- López-Alonso V, Cheeran B, Río-Rodríguez D, Fernández-Del-Olmo M (2014) Inter-individual variability in response to non-invasive brain stimulation paradigms. *Brain Stimul* 7:372–380.
- Marshall JH, Kim YS, Machado TA, Quirin S, Benson B, Kadmon J, Raja C, Chibukhchyan A, Ramakrishnan C, Inoue M, Shane JC, McKnight DJ, Yoshizawa S, Kato HE, Ganguli S, Deisseroth K (2019) Cortical layer-specific critical dynamics triggering perception. *Science* 365:eaaaw5202.
- Martin PI, Naeser MA, Theoret H, Tormos JM, Nicholas M, Kurland J, Fregni F, Seekins H, Doron K, Pascual-Leone A (2004) Transcranial magnetic stimulation as a complementary treatment for aphasia. *Semin Speech Lang* 25:181–191.
- McFarland DJ, Miner LA, Vaughan TM, Wolpaw JR (2000) Mu and beta rhythm topographies during motor imagery and actual movements. *Brain Topogr* 12:177–186.
- Meinzer M, Flaisch T, Breitenstein C, Wienbruch C, Elbert T, Rockstroh B (2008) Functional re-recruitment of dysfunctional brain areas predicts language recovery in chronic aphasia. *Neuroimage* 39:2038–2046.
- Mesulam MM (1999) Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. *Philos Trans R Soc Lond B Biol Sci* 354:1325–1346.

- Metsomaa J, Belardinelli P, Ermolova M, Ziemann U, Zrenner C (2021) Causal decoding of individual cortical excitability states. *Neuroimage* 245:118652.
- Meyer BU, Röricht S, Gräfin von Einsiedel H, Kruggel F, Weindl A (1995) Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. *Brain* 118:429–440.
- Miller JE, Miller BR, O'Neil DA, Yuste R (2022) An increase in spontaneous activity mediates visual habituation. *Cell Rep* 39:110751.
- Mimica B, Dunn BA, Tombaz T, Bojja V, Whitlock JR (2018) Efficient cortical coding of 3D posture in freely behaving rats. *Science* 362:584–589.
- Mirdamadi JL, Xu J, Arevalo-Alas KM, Kam LK, Borich MR (2023) State-dependent interhemispheric inhibition reveals individual differences in motor behavior in chronic stroke. *Clin Neurophysiol* 149:157–167.
- Mostany R, Chowdhury TG, Johnston DG, Portonovo SA, Carmichael ST, Portera-Cailliau C (2010) Local hemodynamics dictate long-term dendritic plasticity in peri-infarct cortex. *J Neurosci* 30:14116–14126.
- Motaharinia M, Gerrow K, Boghazian R, White E, Choi SE, Delaney KR, Brown CE (2021) Longitudinal functional imaging of VIP interneurons reveals sup-population specific effects of stroke that are rescued with chemogenetic therapy. *Nat Commun* 12:6112.
- Murase N, Duque J, Mazzocchio R, Cohen LG (2004) Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol* 55:400–409.
- Müri RM, Cazzoli D, Nef T, Mosimann UP, Hopfner S, Nyffeler T (2013) Non-invasive brain stimulation in neglect rehabilitation: an update. *Front Hum Neurosci* 7:248.
- Murphy TH, Corbett D (2009) Plasticity during stroke recovery: from synapse to behaviour. *Nat Rev Neurosci* 10:861–872.
- Murthy VN, Fetz EE (1992) Coherent 25- to 35-Hz oscillations in the sensorimotor cortex of awake behaving monkeys. *Proc Natl Acad Sci USA* 89:5670–5674.
- Murthy VN, Fetz EE (1996) Synchronization of neurons during local field potential oscillations in sensorimotor cortex of awake monkeys. *J Neurophysiol* 76:3968–3982.
- Naeser MA, Martin PI, Nicholas M, Baker EH, Seekins H, Kobayashi M, Theoret H, Fregni F, Maria-Tormos J, Kurland J, Doron KW, Pascual-Leone A (2005) Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study. *Brain Lang* 93:95–105.
- Neumann-Haefelin T, Witte OW (2000) Perinfarct and remote excitability changes after transient middle cerebral artery occlusion. *J Cereb Blood Flow Metab* 20:45–52.
- Nudo RJ, Wise BM, SiFuentes F, Milliken GW (1996) Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science* 272:1791–1794.
- Nyffeler T, Vanbellingen T, Kaufmann BC, Pflugshaupt T, Bauer D, Frey J, Chechlacz M, Bohlhalter S, Müri RM, Nef T, Cazzoli D (2019) Theta burst stimulation in neglect after stroke: functional outcome and response variability origins. *Brain* 142:992–1008.
- Oliveri M, Bisiach E, Brighina F, Piazza A, Bua VL, Buffa D, Fierro B (2001) rTMS of the unaffected hemisphere transiently reduces contralesional visuospatial hemineglect. *Neurology* 57:1338–1340.
- Omlor W, Wahl AS, Sipilä P, Lütcke H, Laurenczy B, Chen IW, Sumanovski LT, van 't Hoff M, Bethge P, Voigt FF, Schwab ME, Helmchen F (2019) Context-dependent limb movement encoding in neuronal populations of motor cortex. *Nat Commun* 10:4812.
- Park S, Kramer EE, Mercaldo V, Rashid AJ, Insel N, Frankland PW, Josselyn SA (2016) Neuronal allocation to a hippocampal engram. *Neuropsychopharmacology* 41:2987–2993.
- Pfurtscheller G, Stancák A, Neuper C (1996) Post-movement beta synchronization: a correlate of an idling motor area? *Electroencephalogr Clin Neurophysiol* 98:281–293.
- Postman-Caucheteux WA, Birn RM, Pursley RH, Butman JA, Solomon JM, Picchioni D, McArdle J, Braun AR (2010) Single-trial fMRI shows contralesional activity linked to overt naming errors in chronic aphasic patients. *J Cogn Neurosci* 22:1299–1318.
- Puig J, Pedraza S, Blasco G, Daunis-I-Estadella J, Prados F, Remollo S, Prats-Galino A, Soria G, Boada I, Castellanos M, Serena J (2011) Acute damage to the posterior limb of the internal capsule on diffusion tensor tractography as an early imaging predictor of motor outcome after stroke. *AJNR Am J Neuroradiol* 32:857–863.
- Ramanathan DS, Guo L, Gulati T, Davidson G, Hishinuma AK, Won SJ, Knight RT, Chang EF, Swanson RA, Ganguly K (2018) Low-frequency cortical activity is a neuromodulatory target that tracks recovery after stroke. *Nat Med* 24:1257–1267.
- Richter M, Miltner WH, Straube T (2008) Association between therapy outcome and right-hemispheric activation in chronic aphasia. *Brain* 131:1391–1401.
- Ridding MC, Ziemann U (2010) Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. *J Physiol* 588:2291–2304.
- Robertson IH, Mattingley JB, Rorden C, Driver J (1998) Phasic alerting of neglect patients overcomes their spatial deficit in visual awareness. *Nature* 395:169–172.
- Rocha RP, Koçillari L, Suweis S, De Filippo De Grazia M, de Schotten MT, Zorzi M, Corbetta M (2022) Recovery of neural dynamics criticality in personalized whole-brain models of stroke. *Nat Commun* 13:3683.
- Rushmore RJ, Valero-Cabre A, Lomber SG, Hilgetag CC, Payne BR (2006) Functional circuitry underlying visual neglect. *Brain* 129:1803–1821.
- Sahel JA, Audo IS, Boulanger-Scemama E, Pagot C, Arleo A, Martel JN, Degli Esposti S, Delaux A, de Saint Aubert JB, de Montleau C, Gutman E, Duebel J, Picaud S, Dalkara D, Taeli M, Roska B (2022) Optogenetics in the clinic: safety and efficacy updates on the phase 1/2 clinical trial PIONEER. *Invest Ophthalmol Vis Sci* 63:1106.
- Sauerbrey BA, Guo JZ, Cohen JD, Mischiati M, Guo W, Kabra M, Verma N, Mensh B, Branson K, Hantman AW (2020) Cortical pattern generation during dexterous movement is input-driven. *Nature* 577:386–391.
- Saur D, Lange R, Baumgaertner A, Schraknepper V, Willmes K, Rijntjes M, Weiller C (2006) Dynamics of language reorganization after stroke. *Brain* 129:1371–1384.
- Shen Y, et al. (2022) CCR5 closes the temporal window for memory linking. *Nature* 606:146–152.
- Shenoy KV, Sahani M, Churchland MM (2013) Cortical control of arm movements: a dynamical systems perspective. *Annu Rev Neurosci* 36:337–359.
- Siegel JS, Ramsey LE, Snyder AZ, Metcalf NV, Chacko RV, Weinberger K, Baldassarre A, Hacker CD, Shulman GL, Corbetta M (2016) Disruptions of network connectivity predict impairment in multiple behavioral domains after stroke. *Proc Natl Acad Sci USA* 113:E4367–E4376.
- Silasi G, Murphy TH (2014) Stroke and the connectome: how connectivity guides therapeutic intervention. *Neuron* 83:1354–1368.
- Smith MC, Stinear CM (2016) Transcranial magnetic stimulation (TMS) in stroke: ready for clinical practice? *J Clin Neurosci* 31:10–14.
- Soleimani B, Dallasta I, Das P, Kulasingham JP, Girgenti S, Simon JZ, Babadi B, Marsh EB (2023) Altered directional functional connectivity underlies post-stroke cognitive recovery. *Brain Commun* 5:fcad149.
- Sparing R, Thimm M, Hesse MD, Küst J, Karbe H, Fink GR (2009) Bidirectional alterations of interhemispheric parietal balance by non-invasive cortical stimulation. *Brain* 132:3011–3020.
- Stefaniak JD, Halai AD, Lambon Ralph MA (2020) The neural and neuro-computational bases of recovery from post-stroke aphasia. *Nat Rev Neurol* 16:43–55.
- Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD (2007) Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain* 130:170–180.
- Stinear CM, Byblow WD, Ackerley SJ, Smith MC, Borges VM, Barber PA (2017) PREP2: a biomarker-based algorithm for predicting upper limb function after stroke. *Ann Clin Transl Neurol* 4:811–820.
- Stone SP, Halligan PW, Greenwood RJ (1993) The incidence of neglect phenomena and related disorders in patients with an acute right or left hemisphere stroke. *Age Ageing* 22:46–52.
- Storch S, Samantzi M, Balbi M (2021) Driving oscillatory dynamics: neuro-modulation for recovery after stroke. *Front Syst Neurosci* 15:712664.
- Stroemer RP, Kent TA, Hulsebosch CE (1995) Neocortical neural sprouting, synaptogenesis, and behavioral recovery after neocortical infarction in rats. *Stroke* 26:2135–2144.
- Suresh AK, Goodman JM, Okorokova EV, Kaufman M, Hatsopoulos NG, Bensmaia SJ (2020) Neural population dynamics in motor cortex are different for reach and grasp. *Elife* 9:e58848.
- Szaflarski JP, Eaton K, Ball AL, Banks C, Vannest J, Allendorfer JB, Page S, Holland SK (2011) Post-stroke aphasia recovery assessed with fMRI and a picture identification task. *J Stroke Cerebrovasc Dis* 20:336–345.

- Szczepanski SM, Kastner S (2013) Shifting attentional priorities: control of spatial attention through hemispheric competition. *J Neurosci* 33:5411–5421.
- Takeuchi N, Izumi S-I (2013) Rehabilitation with poststroke motor recovery: a review with a focus on neural plasticity. *Stroke Res Treat* 2013:128641.
- Teasell R, Bayona NA, Bitensky J (2005) Plasticity and reorganization of the brain post stroke. *Top Stroke Rehabil* 12:11–26.
- Ten Brink AF, Verwer JH, Biesbroek JM, Visser-Meily JM, Nijboer TC (2017) Differences between left- and right-sided neglect revisited: a large cohort study across multiple domains. *J Clin Exp Neuropsychol* 39:707–723.
- Tennant KA, Taylor SL, White ER, Brown CE (2017) Optogenetic rewiring of thalamocortical circuits to restore function in the stroke injured brain. *Nat Commun* 8:15879.
- Terada SI, Kobayashi K, Matsuzaki M (2022) Transition of distinct context-dependent ensembles from secondary to primary motor cortex in skilled motor performance. *Cell Rep* 41:111494.
- Thompson CK, den Ouden DB (2008) Neuroimaging and recovery of language in aphasia. *Curr Neurol Neurosci Rep* 8:475–483.
- Tsao CW, et al., American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee (2023) Heart disease and stroke statistics—2023 update: a report from the American Heart Association. *Circulation* 147:e93–e621.
- Turkeltaub PE (2015) Brain stimulation and the role of the right hemisphere in aphasia recovery. *Curr Neurol Neurosci Rep* 15:72.
- Turkeltaub PE, Messing S, Norise C, Hamilton RH (2011) Are networks for residual language function and recovery consistent across aphasic patients? *Neurology* 76:1726–1734.
- Turkeltaub PE, Coslett HB, Thomas AL, Faseyitan O, Benson J, Norise C, Hamilton RH (2012) The right hemisphere is not unitary in its role in aphasia recovery. *Cortex* 48:1179–1186.
- Urbán MA, Collinger JL, Wittenberg GF (2021) Corticospinal recruitment of spinal motor neurons in human stroke survivors. *J Physiol* 599:4357–4373.
- Veldema J, Bösl K, Neumann G, Verheyden G, Nowak DA (2020) Noninvasive brain stimulation in rehabilitation of hemispatial neglect after stroke. *CNS Spectr* 25:38–49.
- Vos T, et al. (2020) Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 396:1204–1222.
- Vuilleumier P, Hester D, Assal G, Regli F (1996) Unilateral spatial neglect recovery after sequential strokes. *Neurology* 46:184–189.
- Warburton E, Price CJ, Swinburn K, Wise RJ (1999) Mechanisms of recovery from aphasia: evidence from positron emission tomography studies. *J Neurol Neurosurg Psychiatry* 66:155–161.
- Whishaw IQ (2000) Loss of the innate cortical engram for action patterns used in skilled reaching and the development of behavioral compensation following motor cortex lesions in the rat. *Neuropharmacology* 39:788–805.
- Winship IR, Murphy TH (2008) In vivo calcium imaging reveals functional rewiring of single somatosensory neurons after stroke. *J Neurosci* 28:6592–6606.
- Witham CL, Wang M, Baker SN (2007) Cells in somatosensory areas show synchrony with beta oscillations in monkey motor cortex. *Eur J Neurosci* 26:2677–2686.
- Wolff SB, Ko R, Ölveczky BP (2022) Distinct roles for motor cortical and thalamic inputs to striatum during motor skill learning and execution. *Sci Adv* 8:eabk0231.
- Wu J, Srinivasan R, Burke Quinlan E, Solodkin A, Small SL, Cramer SC (2016) Utility of EEG measures of brain function in patients with acute stroke. *J Neurophysiol* 115:2399–2405.
- Wu QL, Cui LY, Ma WY, Wang SS, Zhang Z, Feng ZP, Sun HS, Chu SF, He WB, Chen NH (2023) A novel small-molecular CCR5 antagonist promotes neural repair after stroke. *Acta Pharmacol Sin*. Advance online publication. Retrieved May 17, 2023. <https://doi.org/10.1038/s41401-023-01100-y>.
- Xerri C, Merzenich MM, Peterson BE, Jenkins W (1998) Plasticity of primary somatosensory cortex paralleling sensorimotor skill recovery from stroke in adult monkeys. *J Neurophysiol* 79:2119–2148.
- Xu J, Branscheidt M, Schambra H, Steiner L, Widmer M, Diedrichsen J, Goldsmith J, Lindquist M, Kitago T, Luft AR, Krakauer JW, Celnik PA, SMARTS Study Group (2019) Rethinking interhemispheric imbalance as a target for stroke neurorehabilitation. *Ann Neurol* 85:502–513.
- Yang NY, Fong KN, Li-Tsang CW, Zhou D (2017) Effects of repetitive transcranial magnetic stimulation combined with sensory cueing on unilateral neglect in subacute patients with right hemispheric stroke: a randomized controlled study. *Clin Rehabil* 31:1154–1163.
- Ye Z, Mostajo-Radji MA, Brown JR, Rouaux C, Tomassy GS, Hensch TK, Arlotta P (2015) Instructing perisomatic inhibition by direct lineage reprogramming of neocortical projection neurons. *Neuron* 88:475–483.
- Yi YG, Chun MH, Do KH, Sung EJ, Kwon YG, Kim DY (2016) The effect of transcranial direct current stimulation on neglect syndrome in stroke patients. *Ann Rehabil Med* 40:223–229.
- Yu C, Zhu C, Zhang Y, Chen H, Qin W, Wang M, Li K (2009) A longitudinal diffusion tensor imaging study on Wallerian degeneration of corticospinal tract after motor pathway stroke. *Neuroimage* 47:451–458.
- Zebhauser PT, Vernet M, Unterburger E, Brem AK (2019) Visuospatial neglect: a theory-informed overview of current and emerging strategies and a systematic review on the therapeutic use of non-invasive brain stimulation. *Neuropsychol Rev* 29:397–420.
- Zeiger WA, Marosi M, Saggi S, Noble N, Samad I, Portera-Cailliau C (2021) Barrel cortex plasticity after photothrombotic stroke involves potentiating responses of pre-existing circuits but not functional remapping to new circuits. *Nat Commun* 12:3972.
- Zhou J, Khateeb K, Gala A, Rahimi M, Griggs DJ, Ip Z, Yazdan-Shahmorad A (2022) Neuroprotective effects of electrical stimulation following ischemic stroke in non-human primates. *Annu Int Conf IEEE Eng Med Biol Soc* 2022:3085–3088.
- Zhou M, Greenhill S, Huang S, Silva TK, Sano Y, Wu S, Cai Y, Nagaoka Y, Sehgal M, Cai DJ, Lee YS, Fox K, Silva AJ (2016) CCR5 is a suppressor for cortical plasticity and hippocampal learning and memory. *Elife* 5:e20985.
- Zhou Y, Won J, Karlsson MG, Zhou M, Rogerson T, Balaji J, Neve R, Poirazi P, Silva AJ (2009) CREB regulates excitability and the allocation of memory to subsets of neurons in the amygdala. *Nat Neurosci* 12:1438–1443.
- Ziemann U, Siebner HR (2015) Inter-subject and inter-session variability of plasticity induction by non-invasive brain stimulation: boon or bane? *Brain Stimul* 8:662–663.
- Zrenner C, Desideri D, Belardinelli P, Ziemann U (2018) Real-time EEG-defined excitability states determine efficacy of TMS-induced plasticity in human motor cortex. *Brain Stimul* 11:374–389.