The role of ipsilateral primary motor cortex in movement control and recovery from brain damage

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The role of ipsilateral motor areas for movement control is not yet fully understood. The relevance of these areas to the recovery of motor function following a brain lesion is a matter of dispute. It has recently been stated that increased ipsilateral activation following brain damage is maladaptive and hindering the process of recovery. Others have presented evidence that ipsilateral motor areas subserve motor recovery. A recent study published in Experimental Neurology [Lotze, M., Sauseng, P., Staudt, M., 2009. Functional relevance of ipsilateral motor activation in congenital hemiparesis as tested by fMRI-navigated TMS. Exp. Neurol., 217, 440-443.] on patients with congenital hemiparesis presents evidence for the importance of ipsilateral primary motor cortex and dorsal premotor cortex to movement control even in the absence of direct ipsilateral descending output in this special set of patients. This comment briefly summarizes the relevant findings supporting both views and discusses potential causes for the prima facie contradictory findings.

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patients with congenital hemiparesis and persistent motor deficits often show abnormal brain organization with the paretic hand being controlled by ipsilateral corticospinal projections (Benecke et al., 1991; Staudt et al., 2002). In a recent paper, Lotze et al. (2009) investigate a homogeneous group of young adults with congenital hemiparesis due to small lesions acquired in the first trimester of pregnancy, who presented with well recovered hand function. In these patients there was no evidence from TMS for functionally relevant ipsilateral projections. Contralesional projections were shown to be at least partially intact with normal latencies. Nevertheless, these patients showed prominent ipsilateral activation in primary motor cortex (MI), dorsal premotor cortex (dPMC) and the superior parietal lobe (SPL) during a sequential finger movement task using fMRI. Ipsilateral MI and dPMC were shown to be functionally relevant for the execution of externally cued sequential finger movements. Trains of TMS pulses over both areas significantly slowed responses as compared to baseline without TMS and in comparison to ipsilateral TMS interference in healthy controls.

The findings of Lotze et al. (2009) are in line with previous findings in patients with brain lesions acquired later in life (Johansen-Berg et al., 2002; Lotze et al., 2006). During the acute period following the incidence a general overactivity of the brain can be observed not only locally but throughout the affected distributed network. Although activation refocuses with time and progressive recovery (Feydy et al., 2002; Ward et al., 2003) ipsilateral activation has consistently been shown in several areas related to motor function in subacute and chronic stroke patients (e.g. Weiller et al., 1992; Seitz et al., 1998; Bütefisch et al., 2005; Lotze et al., 2006; Nair et al., 2006; Schaechter and Perdue, 2008). However, the functional relevance of these areas to motor recovery has been questioned.

As prominent ipsilateral activation is mainly observed in the more impaired patients, it has been taken as a marker for poor recovery (Ward et al., 2003). Mirror movements are occasionally observed in the acute stage following stroke. Bilateral activation patterns could, therefore, be evoked by covert mirror movements (Weiller et al., 1993; Wittenberg et al., 2000). However, the most important dispute evolved around the proposition that contralesional activation might indeed represent a maladaptive rather than a functionally relevant process. The underlying hypothesis states that activation in the contralesional hemisphere is increased due to reduced interhemispheric inhibition from the lesioned to the unlesioned hemisphere (Boroojerdi et al., 1996; Schimizu et al., 2002). This increased activity does in turn lead to increased inhibition from the unlesioned to the lesioned hemisphere, which hinders the recovery process and is therefore maladaptive (Murase et al., 2004). Evidence for this hypothesis comes from a number of studies showing that inhibitory repetitive TMS (rTMS) or inhibitory transcranial direct current stimulation (tDCS) over motor areas of the intact hemisphere improves motor performance of the affected hand (for review see Nowak et al., 2009). On the other hand, there are also studies providing evidence for the functional relevance of ipsilateral motor areas to movement execution in stroke patients (Johansen-Berg et al., 2002; Lotze et al., 2006).
In the context of this debate, the study of Lotze et al. (2009) in congenital hemiparesis is a very valuable contribution because it is bare of some of the criticisms brought forward against the investigation of stroke patients: (1) as the patients of Lotze et al. (2009) show excellent recovery, it is unlikely that motor related activation seen in the unlesioned ipsilateral hemisphere represents a maladaptive process. Even if the equilibrium of transcortical inhibition were permanently changed this does not seem to have a hindering effect on bilateral hand motor function. (2) Potential pitfalls when investigating patients close in time to the insult such as changed properties of the vascular autoregulation and neurovascular coupling (Sette et al., 1989; Pineiro et al., 2002; Binkofski and Seitz, 2004) underlying functional imaging can be excluded in congenitally damaged adult patients.

One aspect that is not well discussed by Lotze et al. (2009) is the potential contribution of ipsilateral descending pathways on motor control even in the absence of measurable MEPs. To better understand the relevance of the ipsilateral hemisphere for motor function in the intact brain and its potential to support motor recovery in the lesioned brain we will first review the evidence for either direct or indirect ipsilateral corticospinal projections in the healthy adult brain. We will then address the question, whether these projections could become functionally relevant for the recovery of motor function following brain damage. Ipsilateral motor areas could furthermore support motor recovery by their functional connectivity to the lesioned hemisphere. In this context the involvement of bilateral motor areas in more complex tasks will be discussed. We will then review the evidence that ipsilateral motor activation is either epiphenomenal or dysfunctional in patients. Finally, we will summarize potential factors underlying the at least partially controversial findings across studies.

**Ipsilateral descending pathways in the adult brain.** Ipsilateral corticospinal projections have been shown for at least nine frontal and posterior areas including M1 and dPMC in the adult brain of nonhuman primates (Galea and Darian-Smith, 1994). Although the ipsilateral projections are small in number (Brodal, 1969; Wiesenfeld-Hallin et al., 2003) the 8% of the contralateral projections reported by Galea and Darian-Smith, 1994) these fibers seem to gain functional relevance when the brain is lesioned early in life (Benecke et al., 1991; Staudt et al., 2002). Ipsilateral corticospinal projections are normally detectable via TMS in healthy children until the age of ~10 years (Rocca et al., 2005). Mirror movements disappear around the same age with progressive neural maturation (Connolly and Schimizu, 1968). During this process, ipsilateral descending pathways get masked rather than degenerate. Indeed, ipsilateral MEPs with close to normal latencies can be elicited in severely affected stroke patients with poor recovery (Netz et al., 1997) and have also exceptionally been observed in healthy subjects using high stimulation intensities (e.g. Wassermann et al., 1994). However, there is also a number of oligosynaptic descending pathways. MEPs elicited via these pathways usually show smaller amplitudes and longer latencies (Benecke et al., 1991). In this context it seems also important to mention the role of ipsilateral excitatory and inhibitory descending pathways in mediating contralateral corticospinal excitability (Chen et al., 2003).

So the ipsilateral descending pathways present in the infant do not degenerate during maturation. They could - in principal - subserve function recovery after contralateral damage.

**The functional relevance of ipsilateral descending pathways in motor recovery.** As mentioned before patients who suffer from congenital hemiparesis master movement control through vast reorganization and/or abnormal organization of the immature brain. In patients with large early lesions and with more severe motor impairment movement control appears to be taken over by ipsilateral (contral- sional) fibers (Benecke et al., 1991; Staudt et al., 2002). In these patients MEPs with normal latencies can be evoked from ipsilateral M1 and they show increased ipsilateral activation of motor areas in fMRI (Staudt et al., 2002). However, in contrast to patients with smaller lesions and no ipsilateral MEPs these patients maintain a moderate motor impairment and show persistent mirror movements. Recovery based on ipsilateral pathways is, therefore, incomplete. However, given the fact that hemispherectomy (Benecke et al., 1991) or large congenital lesions affect the entire contralateral corticospinal tract (Staudt et al., 2002) the functional relevance of ipsilateral projections to movement control is beyond doubt in these patients.

The role of ipsilateral descending fibers originating in dPMC in severely affected stroke patients with poor outcome has been demonstrated and discussed by Johansen-Berg et al. (2002). As these connections are more relevant for the control of proximal movements recovery based on dPMC projections will also remain incomplete.

In small congenital lesions and lesions acquired later in life the potential relevance of ipsilateral motor projections seems to lie rather differently. It has been suggested that (oligosynaptic) ipsilateral descending projections contribute to increased contralateral corticospinal excitability, thereby supporting the recovery of the contra- lateral corticospinal pathways (Nair et al., 2006). Support for this view stems from a study by Bütefisch et al. (2008) reporting unusual decreased interhemispheric inhibition with an interstimulus interval of 2 ms in patients with hemiparetic stroke. The authors argue that 2 ms appear too short for the effect being mediated by transcallosal fibers (compare Ferbert et al., 1992). Instead they suggest that the facilitatory effect was mediated via the uncrossed contralesional corticospinal tract.

To summarize this section, ipsilateral descending fibers contribute directly to movement control in large congenital lesions or following hemispherectomy. However, motor deficits persist in these cases. In patients with an at least partially spared corticospinal tract ipsilateral projections might increase corticospinal excitability thereby supporting the recovery process of the primary pathways.

**Ipsilateral motor areas and task complexity.** Besides the potential contribution of their descending output ipsilateral motor areas might also contribute to motor recovery via their transcortical connections. In healthy subjects, increased bilateral motor activation has been shown with more complex motor tasks (e.g. Catalan et al., 1998; Ehrsson et al., 2002). Using TMS interference Chen et al. (1997) and Gerloff et al. (1998) both demonstrated that contralateral and ipsilateral M1 contribute to the processing of motor sequence complexity. Here, the cortico-cortical connections seem to be important to cope with the higher computational demand of complex movements.

In this context it is interesting to note, that the differences in activation patterns between patients and controls are more pronounced, when more complex tasks are employed (Schaechter and Perdue, 2008). Persistent contralesional M1 activation in well-recovered patients might therefore indicate altered intracortical and transcortical interactions (Nair et al., 2006). Such changes might occur as for paretic stroke patients even basic movements might appear “complex” as movement control is compromised by reduced connectivity of the lesioned corticospinal tract (Gerloff et al., 2006; Schaechter and Perdue, 2008). It is therefore reasonable to suggest, that in stroke patients ipsilateral motor areas already contribute to the control of simple movements via their intra- and intercortical connectivity. Connectivity of motor areas is indeed increased in the hemisphere contralateral to the lesion, while it is reduced on the damaged side (Gerloff et al., 2006).

The potential relevance of ipsilateral premotor cortex for the recovery of motor functions in hemiparetic stroke was demonstrated for the first time by Seitz et al. (1998). Evidence for the functional relevance of ipsilateral motor areas for motor control in patients with acquired lesions mainly stems from three studies: Johansen-Berg et al. (2002) described an interfering effect of single pulse TMS over
ipsilateral dPMC when patients had to perform a simple reaction time paradigm. These authors failed to demonstrate a similar effect when stimulating ipsilateral M1. Most interestingly, the effect was not shown in healthy control subjects and was correlated with the degree of impairment, i.e. was more pronounced in those patients experiencing the task as more “complex.” Thus, on the one hand recruitment of ipsilateral areas seemed to be related to poor outcome, on the other hand recruitment of ipsilateral areas might be particularly relevant for functional recovery in the more affected patients.

Using a more complex task, Lotze et al. (2006) showed interference effects for TMS over ipsilateral dPMC, M1 and SPL in chronic patients with good recovery. There is indeed evidence that even in well-recovered chronic stroke patients a larger network of ipsilateral areas is involved in the performance of complex (“unskilled”) movements as compared to simple (“skilled”) movements (Schaechter and Perdue, 2008). Indirect evidence stems from an earlier study by Schaechter et al. (2002) showing that constraint-induced movement therapy with associated improved motor function goes along with increased ipsilateral activation in chronic stroke patients. Please note that constraint-induced therapy led to increased contralateral (ipsilesional) excitability and activation in patients with congenital hemiparesis (Walther et al., 2009).

Why bilateral activation persists in some patients but not in others is still an open question. Ward et al. (2003) suggest that in patients with subcortical stroke and good outcome motor related brain activation is refocusing on areas underlying motor function in the healthy throughout recovery. They observe that bilateral activation persists in those subcortical stroke patients with poor outcome as “the greatest reorganization occurs in those with the greatest need”. They suggest that persistent bilateral activation despite good outcome can be observed in patients with cortical involvement (Feydy et al., 2002; Seitz et al., 1998). However, Gerloff et al. (2006) report persistent bilateral activation and increased contralesional connectivity in patients with subcortical lesions and good outcome.

When trying to reconcile these findings we face the problem that the “degree of the outcome” is not very well defined as it is based on different measures across studies. However, it seems unlikely that this is the only underlying cause for inconsistencies of an otherwise well-understood phenomenon. It is more likely that other factors such as different task complexities contribute to the confusion. As more complex tasks evoke more bilateral activation and the degree of complexity is furthermore subjectively experienced depending on the degree of impairment, we are facing interactions between at least these two variables. Furthermore, it is not obvious how best to control for task difficulty—either by trying to keep the task identical across all participants (Schaechter and Perdue, 2008) or the effort to accomplish it (Ward et al., 2003).

In this section, we suggested that simple motor tasks are perceived as complex by paretic stroke patients, leading to more bilateral activation as seen in healthy subjects performing complex motor tasks. We presented evidence for the functional relevance of ipsilateral motor areas such as ipsilateral dPMC and MI, to movement recovery. We discussed the contradictory findings concerning the relationship of bilateral activation patterns and outcome and potential causes.

Is ipsilateral motor activation either epiphenomenal or dysfunctional in patients? Despite the presented evidence for the functional relevance of ipsilateral motor areas following paretic stroke, doubts are continuously raised. While extensive bilateral activation during the acute phase following stroke has been interpreted as a more general (physiological) phenomenon related to the incidence but not to the recovery of function, persistent ipsilateral activation is suggested to be caused by a “release of inhibition” of the intact hemisphere from the damaged hemisphere (Boroojerdi et al., 1996; Schimizu et al., 2002).

Indeed, motor related activations are initially more extensive throughout both hemispheres but become more focused during the process of recovery (Feydy et al., 2002). Patients with more severe impairments show more wide-spread activations (Ward et al., 2003). In the latter study patients with good outcome showed an activation pattern that was not different from that in normal control subjects. As this could not be related to an initially only mild impairment, authors attribute good recovery to the reestablishment of normal activation patterns. However, even in those cases where extensive bilateral activation disappears with function recovery, this activation is not necessarily epiphenomenal. Some areas might be temporarily relevant to movement execution until lesioned structures have regained their function. Homologous areas of the undamaged hemisphere might also subserve the retrieval of motor associated programs. This hypothesis still remains to be tested, as studies demonstrating the functional relevance of ipsilateral motor areas for motor function using TMS interference have been focusing on chronic patients.

The release-of-inhibition hypothesis states that the transcallosal inhibition usually balanced between the two hemispheres in the healthy brain is interrupted by the lesion. This would result in reduced inhibition from the lesioned to the unlesioned hemisphere and—as a consequence—increased inhibition from the unlesioned to the lesioned side. Such increased inhibition of the damaged side would represent a maladaptive process hindering recovery of function (e.g. Nowak et al., 2009).

To test this hypothesis, contralesional M1 was inhibited using either 1 Hz rTMS (e.g. Takeuchi et al., 2005) or cathodal tDCS (e.g. Fregni et al., 2005) in patients having suffered from paretic stroke in a number of studies. Patients generally showed improved performance in a range of motor parameters, such as pinch acceleration, reaction times, and more complex motor function scores. This has been taken as evidence that contralesional hemisphere inhibits the lesioned hemisphere and hinders recovery of ipsilesional motor areas.

It has to be noted that the underlying hypothesis (increased inhibition of the lesioned side) might turn out to be wrong. In a carefully designed study Bütefisch et al. (2008) demonstrate that excitability is increased in both the unlesioned and lesioned hemisphere despite decreased inhibition on the unlesioned side. Therefore, although the unlesioned side appeared released from inhibition this does not necessarily result in increased inhibition of the affected side. In fact, inhibition from the unlesioned to the lesioned side remained normal. Furthermore, increased excitability of contralesional M1 was shown to be correlated with good recovery (Manganotti et al., 2002; Bütefisch et al., 2003).

How can these findings be reconciled with the positive effect demonstrated for inhibitory stimulation of the unlesioned hemisphere? The beneficial effect of contralesional rTMS has mainly been reported for chronic patients (with potential nonuse of the affected limb) who were not any more in the process of recovery. Improved motor function of the ipsilesional hand after 1 Hz rTMS has also been shown in healthy subjects (Kobayashi et al., 2004). It seems reasonable to assume that the effect seen in patients is mediated by the same processes as in healthy subjects rather than representing recovery-related changes.

When trying to integrate different findings across studies, lesion localization is a factor readily at hand to explain different results. Lesion localization will not only have a strong influence on the outcome but also on the pattern of compensatory recruitment throughout recovery. The integrity of the pyramidal tract is known to be one of the major determinants of motor recovery after hemiparetic stroke (Binkofski et al., 1996). The reliance on alternative corticospinal pathways including ipsilateral output will depend on the amount of lost cortico-motoneuronal projections. Transcallosal fibers on the other hand will be more affected in cortical stroke. It is intriguing to assume that contralesional inhibition, as assumed by the release-of-inhibition hypothesis, is more effective in this type of patients. While improved performance following a contralesional inhibitory intervention was
observed both in cortical and subcortical patients, the number of cortical patients across studies is still too small to come to any clear conclusion (N = 8, based on the review by Nowak et al., 2009).

Given the limited therapeutic options in stroke, the clinical relevance of contralesional rTMS/tDCS interventions has to be considered even if the underlying processes are not yet fully understood. However, the effects of single interventions are short-lasting and any carry-over to more complex tasks still has to be proven. Effects are somewhat more stable with repetitive interventions (Nowak et al., 2009). The advantage of inhibitory contralesional stimulation compared to more easily applied measures such as constrained-induced movement therapy or the potentially beneficial combination of both still has to be explored.

Overall, the attractiveness of the release-of-inhibition hypothesis seems to lie mainly with its (over-) simplicity. It is reasonable to assume that patients would recruit their contralateral motor areas to accomplish a given task if it were not for the lesion. Ipsilateral activation might be a marker for poor recovery (although it has also been related to functional improvement, compare Schaechter et al., 2002). It is certainly not suitable as an explanation for poor outcome. Purely ipsilesional reorganization might not be sufficient for maximal recovery in many patients, who then benefit from bilateral recruitment.

Concluding remarks. We have to conclude that there is not yet any unifying concept for the reorganization of motor function following damage. It seems likely that recovery relies on different mechanisms depending on lesion localization and extent, age of the patient and recovery stage (acute vs. chronic). Task complexity has been considered as one factor underlying different findings but its potential to reconcile seemingly contradictory results still has to be explored. Furthermore, we have to be cautious when comparing congenital lesions with damage acquired later in life as it is a well-known fact, that the immature organism has superior capacities for reorganization (Kennard, 1936). On the other hand it is tempting to assume similar mechanisms underlying similar outcomes for congenital brain lesions as compared to brain damage acquired later in life given the obvious similarities between previous research in stroke patients (Johansen-Berg et al., 2002; Lotze et al., 2006) and the findings of Lotze et al. (2009).

References


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