Multimodal Brain Mapping in Patients with Early Brain Lesions

11

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11.1 Introduction

The developing human brain possesses a superior potential of functional reorganization after lesions compared with the adult brain. Because of such reorganizational processes, children with early brain lesions often show abnormally located cortical representations of certain brain functions, e.g. of motor representations (Carr et al. 1993; Staudt et al. 2002a, 2004a) or of language functions (Rasmussen and Milner 1977; Staudt et al. 2002b). Nowadays, these abnormally located representations can be identified non-invasively using techniques such as functional MRI (fMRI), transcranial magnetic stimulation (TMS) or magnetoencephalography (MEG). Thus, these techniques not only can contribute to our general understanding of the processes involved in the reorganization of the developing human brain but can also be used clinically in the pre-surgical evaluation of children who have to undergo brain surgery, e.g. for the relief of pharmaco-refractory epilepsies originating from their lesions (Hertz-Pannier et al. 2001; Staudt et al. 2001, 2004a, b; Liégeois et al. 2006).

The clinical application of these mapping techniques in this context is particularly challenging: first, most of these patients are children, often with various degrees of cognitive impairments so that their ability to comply with the experimental requirements is often reduced; second, the brain lesions often destroy or distort anatomical landmarks, which can normally be used for the identification of eloquent brain regions; and third, the cortical representations of brain functions may have shifted because of reorganizational processes following lesions acquired during ongoing brain development. This chapter gives typical examples of examinations of children, mostly in the pre-surgical evaluation before epilepsy surgery, highlighting a number of important aspects.

11.2 Example 1

A 3-year-old boy suffered from therapy-refractory focal seizures originating from a cortical dysplasia (yellow arrows in Fig. 11.1) in the central (Rolandic) region of the right hemisphere. On clinical examination, left-hand function was normal. Prior to possible epilepsy surgery, fMRI during a simple active hand motor task (repetitive squeezing of a toy) was used to visualize the spatial relation between the dysplasia and the primary sensorimotor representation of the contralateral hand.

Based on these findings of fMRI activation in the immediate vicinity of the dysplasia, no total resection of the dysplasia was performed.

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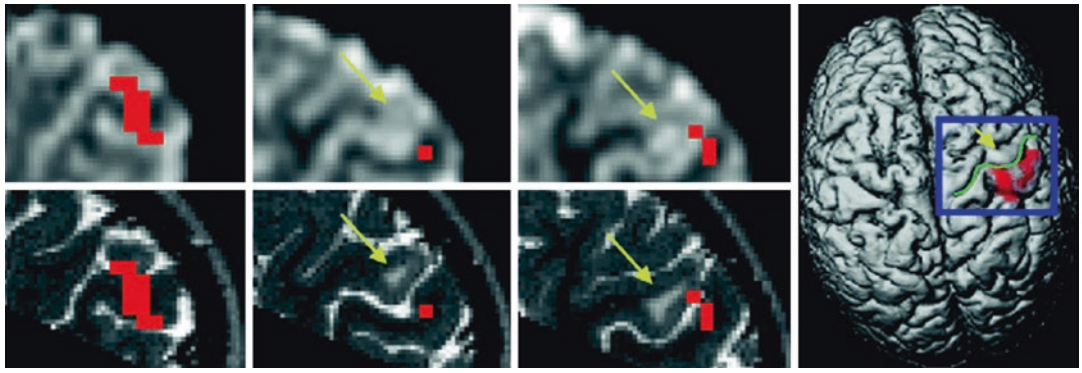

Fig. 11.1 fMRI during active left-hand movement in a 3-year-old boy with a focal cortical dysplasia (hyperintense on T2, *yellow arrows*) of the right central (Rolandic) region. The fMRI activation (in *red*) is superimposed directly on the (functional) EPI images (yielding the most reliable topographical localization since no coregistration is involved, *upper row*) after co-registration, to high-resolution structural T2-weighted images acquired in general anaesthesia during a separate session (*lower row*, courtesy of Prof. Winkler, Schön Klinik Vogtareuth), as well as onto a 3D surface reconstruction (*right*). *Green line* = central sulcus, *blue rectangle* = position of the enlarged details on the *left*

fMRI can be used even in pre-school children to localize the primary sensorimotor region (S1M1) in the vicinity of epileptogenic lesions.

11.3 Example 2

A 16-year-old girl with congenital hemiparesis due to a perinatally acquired cortico-subcortical infarct in the territory of the middle cerebral artery (MCA) showed a striking discrepancy between a large cystic lesion and relatively well-preserved sensorimotor functions (preserved grasp) of the contralateral (paretic) hand (Staudt et al. 2006b). On neurophysiological examination, TMS revealed preserved crossed cortico-spinal projections from the affected hemisphere to the paretic hand, and MEG identified the first cortical response to repetitive tactile stimulation of the paretic thumb (N20m) in the affected hemisphere, indicating the presence of preserved crossed spino-thalamocortical somatosensory projections. Accordingly, diffusion tensor imaging (DTI) tractography with a seed region positioned in the small bridge of preserved white matter between the enlarged lateral ventricle and the cystic lesion visualized extensive connectivity provided by this area (Fig. 11.2).

Small areas of preserved white matter can provide surprisingly extensive connectivity in patients with early brain lesions. Such projections can be visualized by DTI tractography.

11.4 Example 3

A 20-year-old young man with congenital right hemiparesis due to a large polymicrogyria in the left frontoparietal region shows partially preserved sensorimotor functions (preserved individual finger movements) of the contralateral (paretic) right hand (Staudt et al. 2004b). On neurophysiological examination, TMS revealed preserved crossed cortico-spinal projections from the affected hemisphere to the paretic hand. Accordingly, fMRI during a simple active hand motor task (repetitive opening/closing of the paretic hand) revealed activation in the polymicrogyric cortex. Thus, both TMS and fMRI demonstrate that, in this patient, the polymicrogyric cortex harbours the primary motor representation of the paretic hand (Fig. 11.3).

Dysgenic cortex (here: polymicrogyria) can fulfil primary motor functions, with normal descending corticospinal motor projections. This can be confirmed by a combination of fMRI and TMS.

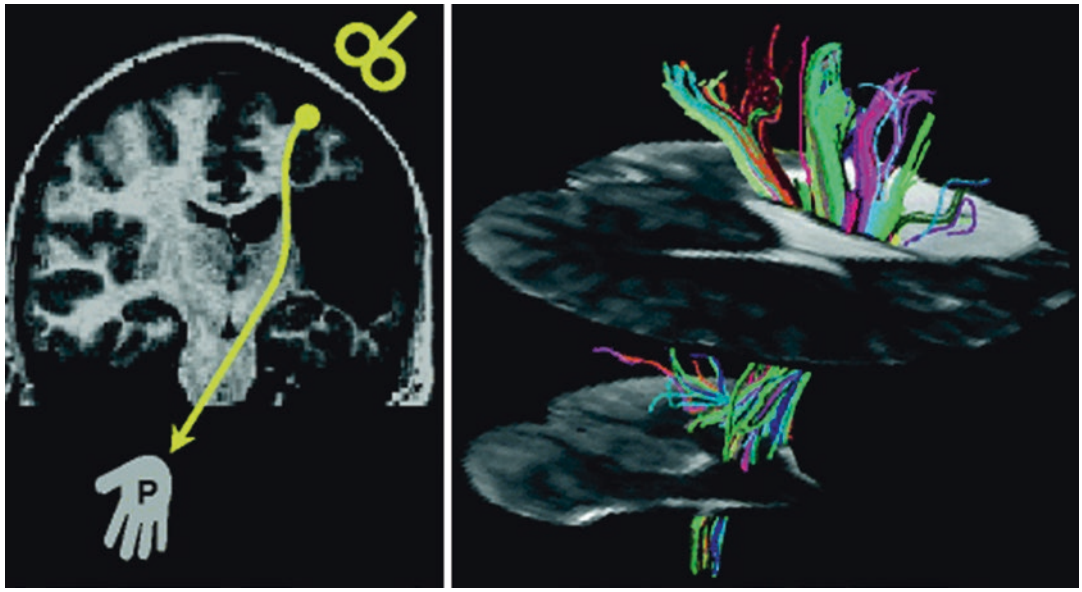

Fig. 11.2 MRI and TMS findings of a 16-year-old girl with congenital hemiparesis due to a large cortico-subcortical infarct. *Left*: coronal T1-weighted image depicting the cystic lesion. TMS (indicated by the *yellow figure-eight-coil symbol*) of the affected hemisphere elicited normal motor-evoked potentials in the paretic hand (P), confirming the presence of preserved crossed cortico-spinal projections (*yellow arrow*). *Right*: MR diffusion tensor tractography (in random colours on unweighted diffusion images; tilted axial planes, anterior-lateral-superior view) visualized numerous fibre trajectories passing through the small bridge of preserved white matter between the cystic lesion and the lateral ventricle. (Adapted from Staudt et al. (2006b) with permission)

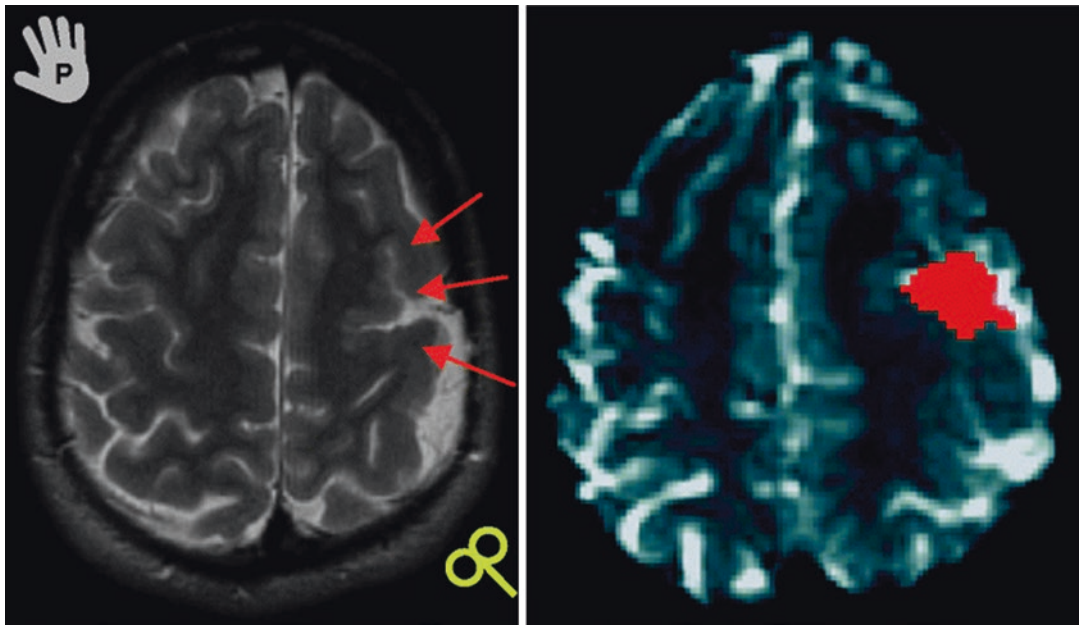

Fig. 11.3 MRI and TMS findings of a 20-year-old man with congenital hemiparesis due to a large polymicrogyria. *Top*: axial T2-weighted image depicting the polymicrogyria in the left frontoparietal region (*red arrows*). TMS (indicated by the *yellow figure-eight-coil symbol*) of the affected hemisphere elicited normal motor-evoked potentials in the paretic hand (P), confirming the presence of preserved crossed cortico-spinal projections. *Bottom*: fMRI activation (in *red*, superimposed on the functional EPI) during active movement of the paretic hand revealed activation in the polymicrogyria, approximately opposing the Rolandic region in the contra-lesional hemisphere

11.5 Example 4

A 6-year-old boy with congenital right hemiparesis due to a complex hemispheric malformation suffered from pharmaco-refractory seizures (Staudt et al. 2001). Clinical examination showed preserved individual finger movements in the paretic hand and massive mirror movements during voluntary movements of both the paretic and the non-paretic hand. Prior to epilepsy surgery, fMRI and TMS were performed to identify the primary motor representation of the paretic hand. TMS of the affected hemisphere did not elicit any response, whereas TMS of the contra-lesional hemisphere elicited bilateral responses with similar latencies. This indicated the presence of fast-conducting ipsilateral cortico-spinal projections, allowing the contra-lesional hemisphere to exert motor control over the paretic hand. Accordingly, fMRI during a simple active hand motor task (repetitive opening/closing of the paretic hand) revealed activation in the 'hand knob' area of the contra-lesional hemisphere, not different from the fMRI activation elicited by movements of the non-paretic hand. Active grasping was still possible after functional hemispherectomy (Fig. 11.4).

Early brain lesions (malformations but also defective lesions) can induce shifting of the primary motor representation (M1) of the paretic hand to the contra-lesional hemisphere (with ipsilateral cortico-spinal tracts).

11.6 Example 5

A 19-year-old woman with congenital right hemiparesis due to a large unilateral periventricular brain lesion showed preserved individual finger movements in the paretic hand and massive mirror movements during voluntary movements of both the paretic and the non-paretic hand (Staudt et al. 2006a). As in the patient in Example 4, TMS of the affected hemisphere did not elicit any response, but TMS of the contra-lesional hemisphere elicited bilateral responses with similar latencies. This indicated the presence of ipsilateral cortico-spinal projections, allowing the contra-lesional hemisphere to exert

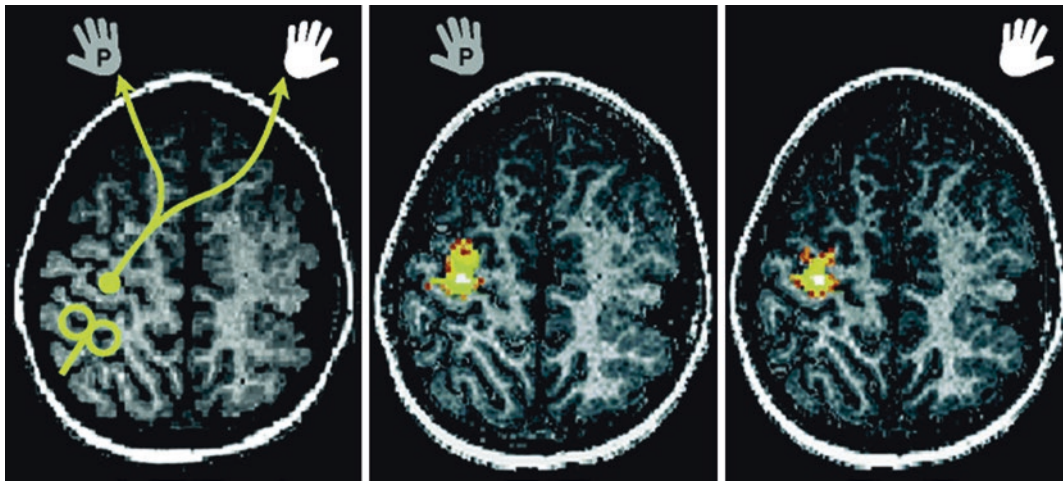

Fig. 11.4 MRI and TMS findings of a 6-year-old boy with congenital hemiparesis due to a complex hemispheric malformation. *Left*: axial T1-weighted image depicting the malformation of almost the entire hemisphere. TMS (indicated by the *yellow figure-eight-coil symbol*) of the contra-lesional hemisphere elicited not only the normal contralateral responses in the non-paretic hand but also ipsilateral motor-evoked potentials in the paretic hand (P), demonstrating the presence of ipsilateral cortico-spinal projections. fMRI during active movement of the paretic hand (*middle*) revealed activation in the hand knob area of the contra-lesional (ipsilateral) hemisphere, not different from the activation elicited by active movement of the non-paretic hand (*right*)

motor control over the paretic hand. Accordingly, fMRI during a simple active hand motor task (*active* opening/closing of the paretic hand) revealed not only activation in the 'hand knob' area of the contra-lesional hemisphere but also activation in the contralateral Rolandic region, an area from which no motor-evoked potentials could be elicited by TMS. fMRI during *passive* hand movement also elicited activation in the contralateral Rolandic region (i.e. of the affected hemisphere), suggesting preserved somatosensory functions in this region. And indeed, MEG recorded the first cortical response to repetitive tactile stimulation of the paretic thumb (N20m) in the contralateral Rolandic region, confirming this region to harbour the primary somatosensory representation (S1) of the paretic hand. Finally, DTI with a seed region in the dorsal brainstem (tegmentum pontis) visualized ascending spino-thalamocortical projections bypassing the lesion on their way to this preserved somatosensory representation of the paretic hand. This observation can be explained by the fact that developing thalamocortical somatosensory projections had not yet reached their cortical target areas by the time of the insult (the early third trimester of pregnancy; Kostovic and Judas 2002) so that these outgrowing fibres could find an alternative route in the preserved tissue, thus forming 'axonal bypasses' around the defective areas (Staudt et al. 2006a).

This example and similar cases (Thickbroom et al. 2001; Staudt et al. 2006a) teach important lessons for the application of non-invasive imaging techniques in children with early brain lesions:

1. Different mechanisms are available for the reorganization of primary motor and primary somatosensory representations (shifting to the contra-lesional hemisphere for motor functions, forming axonal bypasses around a lesion for somatosensory functions).
2. This can lead to a 'hemispheric dissociation' between the primary motor (M1) and the primary somatosensory (S1) representations of a paretic hand.
3. fMRI of passive hand movement alone is not suited to identify the 'sensorimotor representation' of a paretic hand (see Fig. 11.5); the reorganization of the primary motor representation in Example 5 would have been missed with the 'normal-looking' result for passive hand movement!

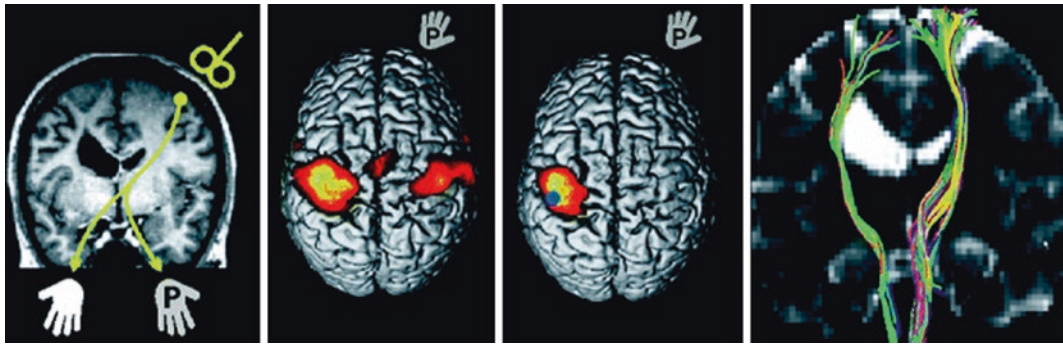

Fig. 11.5 MRI, TMS, fMRI, MEG and DTI tractography findings of a 19-year-old female with congenital hemiparesis due to a unilateral periventricular brain lesion. *Left*: coronal T1-weighted image depicting the periventricular lesion. TMS (indicated by the *yellow figure-eight-coil symbol*) of the contra-lesional hemisphere elicited not only the normal contralateral responses in the non-paretic hand but also ipsilateral motor-evoked potentials in the paretic hand (P), demonstrating the presence of ipsilateral cortico-spinal projections. *Middle*: fMRI during active (*middle left*) and passive (*middle right*) movement of the paretic hand. The *blue circle* indicates the position of the dipole reconstruction from MEG recording of the first cortical response to tactile stimulation of the paretic thumb. *Right*: diffusion tensor imaging (DTI) tractography of ascending spino-thalamocortical projections, with seed regions in the dorsal brainstem (tegmentum pontis) and in the subcortical Rolandic white matter of both hemispheres. (From Staudt et al. (2006a) with permission)

11.7 Example 6

A 7-year-old girl with right-hemispheric polymicrogyria showed congenital hemiparesis (with preserved grasp function of the paretic hand) and pharmaco-refractory epilepsy, so that a surgical disconnection of the malformed right hemisphere (hemispherotomy) for the relief of the epilepsy was considered. TMS and fMRI showed exactly the same constellation as in the patient in Example 5, so that the phenomenon of 'M1-S1-dissociation' was apparently present in this girl as well, with a reorganized primary motor (M1) representation of the paretic hand in the contra-lesional (ipsilateral) hemisphere and a contralateral primary somatosensory representation (S1) of the paretic hand in the polymicrogyria. Accordingly, color-coded fractional anisotropy (DTI) of the pons revealed symmetrical ascending tracts in the tegmentum (including the medial lemniscus carrying the somatosensory projections), while in the basis pontis, cortico-spinal projections were only seen in the contra-lesional side of the brainstem. And as predicted by this pattern (Küpper et al. 2016), when hemispherotomy was performed, the girl showed preserved grasp function but reduced tactile discrimination with her paretic hand.

11.8 Conclusions

Non-invasive mapping techniques such as fMRI, TMS, MEG and DTI tractography are useful techniques in the pre-surgical diagnostic workup of children with early brain lesions. These situations often require a combined use of complementary techniques.

The combination of fMRI (during active movements) and TMS is well suited to identify motor representations, with TMS being specific for areas from where cortico-spinal projections originate and fMRI visualizing the entire sensorimotor network with a high spatial resolution in three dimensions (Thickbroom et al. 2001; Staudt et al. 2002a, 2004a, b). This is important for the identification of (a) the spatial relation between M1 and an epileptogenic lesion (as in Example 1; Fig. 11.1), (b) a preserved M1 in dysgenic cortex (as in Example 3; Fig. 11.3) and (c) a reorganization of M1 into the contra-lesional hemisphere (as in Examples 4, 5, and 6; Figs. 11.4, 11.5 and 11.6). In this respect, patients with a 'hemispheric dissociation' between M1 and S1 (Thickbroom et al. 2001; Staudt et al. 2006a) are particularly challenging since, here, fMRI of active hand movements typically yields bilateral Rolandic activation.

The combination of fMRI (during passive movements) and MEG is well suited to identify somatosensory representations, with MEG (due to its high temporal resolution) being specific for primary somatosensory representations (i.e. the cortical projection areas of somatosensory fibres) and fMRI visualizing the somatosensory network with a high spatial resolution in three dimensions (Staudt et al. 2006a; Wilke et al. 2008). Similar to the motor system, this combination can identify (a) preserved somatosensory projections in preserved white-matter bridges (as in Example 2; Fig. 11.2), (b) a preserved S1 in Rolandic cortex overlying even large lesions (as in Example 5; Fig. 11.5) and (c) a preserved S1 in dysgenic cortex (as in example 6; Fig. 11.6).

DTI tractography can visualize preserved projections in the vicinity of a lesion (as in Example 2; Fig. 11.2) or 'axonal bypasses' around a lesion (as in Example 5; Fig. 11.5). Because of the uncertainties involved in this new technique, we still recommend to use such information only when additional evidence (e.g. neurophysiological evidence from TMS or MEG) for the existence of such projections is available. Finally, DTI fractional anisotropy maps of the brainstem, when showing marked asymmetries of the cortico-spinal tracts in the basis pontis, help to predict preserved grasp function of the paretic hand after hemispherotomies (Küpper et al. 2016).

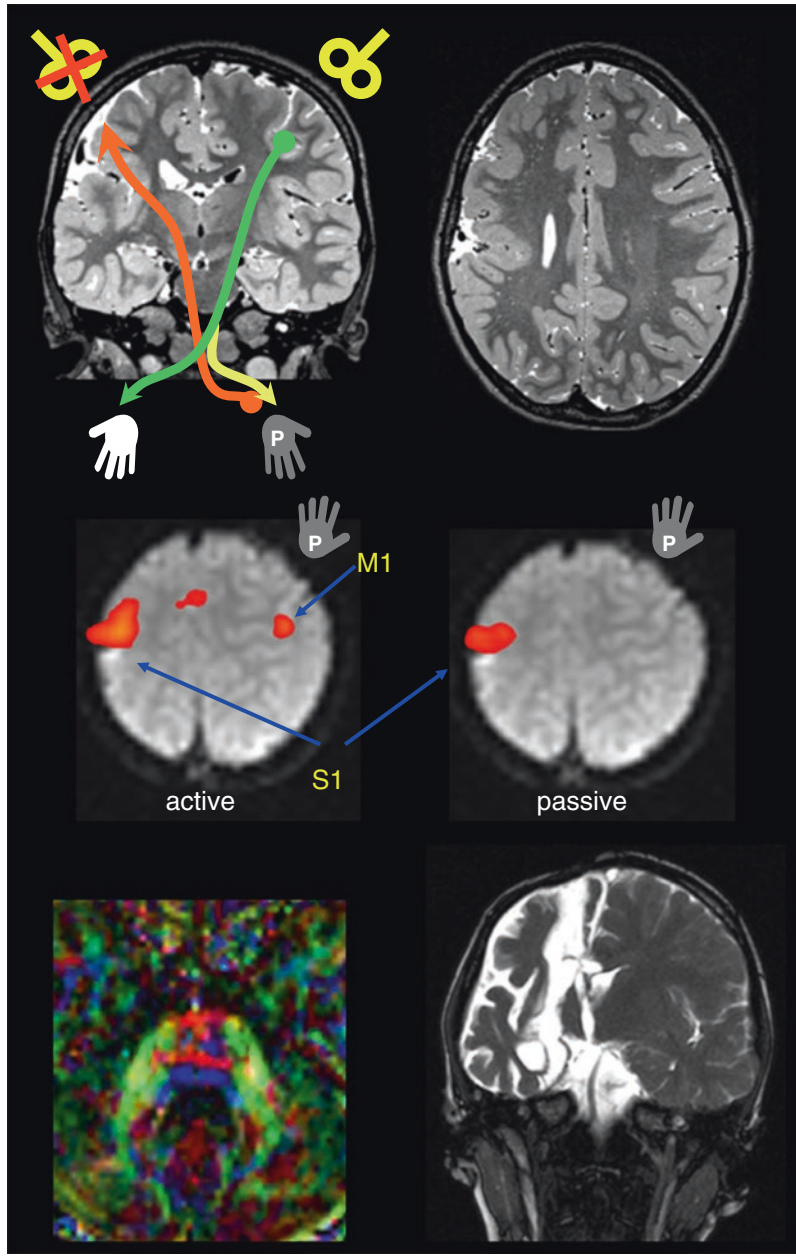

Fig. 11.6 MRI, TMS, fMRI and color-coded DTI (fractional anisotropy map) findings of a 7-year-old girl with congenital hemiparesis and pharmaco-refractory epilepsy due to polymicrogyria of the right hemisphere. *Top*: coronal (*left)* and axial (*right*) T2-weighted images depicting the polymicrogyria. TMS (indicated by the *yellow figure-eight-coil symbol*) of the contra-lesional hemisphere elicited not only the normal contralateral responses in the non-paretic hand (*green arrow*) but also ipsilateral motor-evoked potentials in the paretic hand (P), demonstrating the presence of ipsilateral cortico-spinal projections (*yellow arrow*). The *orange arrow* symbolizes crossed ascending somatosensory projections to the primary somatosensory representation of the paretic hand in the polymicrogyria (*see below*). *Middle*: fMRI during active (*middle left*) and passive (*middle right*) movement of the paretic hand. *Bottom left*: axial diffusion tensor imaging (DTI) fractional anisotropy map of the brainstem, depicting symmetrical ascending fibres in the tegmentum pontis, whereas the basis pontis shows cortico-spinal projections only in the left (healthy) side (*all coded in blue*). *Bottom right*: post-operative MRI (coronal T2 weighted) shows the vertical parasagittal hemispherotomy. (Performed by M. Kudernatsch, Schön Klinik Vogtareuth)

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