ARE WE ABLE TO PREDICT RESULTS OF REHABILITATION OF STROKE PATIENTS USING fMRI?

Petr Hluštík[1,2], Michal Mayer[3], Martin Köcher[2], Petr Kaňovský[1], Jaroslav Opavský[3]

Over the past 10 years, the noninvasive functional magnetic resonance imaging (fMRI) has been used to map the functional neuroanatomy of the motor system in patients after hemiparetic cerebrovascular stroke, both in a cross-sectional and longitudinal design. Longitudinal studies in patients through poor as well as successful recovery identified a number of brain areas where activation evolution over time correlated with good recovery, such as the ipsilesional premotor cortex, secondary somatosensory area and the cerebellum. Early overactivation in motor association areas decreasing over time has been observed, as well. However, the early motor activation networks did not significantly differ in those who were going to recover well versus poorly. Therefore, we have to conclude that the available fMRI data does not provide any clear markers of the future progress of rehabilitation and recovery from hemiparesis due to cerebrovascular stroke.

Key words: *cerebrovascular stroke, functional magnetic resonance imaging, recovery, rehabilitation, motor cortex*

Departments of [1]Neurology and [2]Radiology, Faculty of Medicine, [3]Department of Physiotherapy, Faculty of Physical Culture, Palacký University, Olomouc, Czech Republic

Background and Introduction

Recently developed functional magnetic resonance imaging (fMRI) and other non-invasive brain mapping methods provide a novel opportunity to visualize cerebral networks active during external stimulation or motor and cognitive processing in human subjects as well as patients. Functional magnetic resonance imaging indirectly observes changes in neuronal activity through a succession of local changes in the activated gray matter: Increased synaptic activity increases regional cerebral metabolic rate of glucose, causes local vasodilation and local increase in regional cerebral blood flow. As oxygen extraction in activated gray matter increases much less than regional cerebral blood flow, local microscopic vessels carry more highly oxygenated blood than those in an inactive tissue. The increase in blood oxygenation decreases the ratio of deoxygenated (paramagnetic) to oxygenated (diamagnetic) hemoglobin, decreases the inhomogeneity of the local magnetic field, and increases the apparent transverse relaxation time (T_2*), leading to a higher MRI signal in T_2*-weighted MR images for more highly activated tissue. This blood oxygen level-dependent (BOLD) contrast method requires no exogenous contrast agent and has been used for human functional brain mapping since 1992 (Ogawa *et al.*, 1992).

An fMRI examination includes both morphological (structural, anatomical) and functional images, takes 40 – 90 minutes and is feasible on common clinical MRI scanners (at least 1.5 Tesla) equipped with the BOLD MRI sequence. Because of the non-invasive nature of the methodology, which involves no radioactive tracers or contrast agents, functional MRI is also well suited to longitudinal studies, such as to uncover the functional neuroanatomical correlates of skill learning or stroke recovery.

Functional MRI has revealed cerebral motor networks that participate in control of normal voluntary movement (e.g., Solodkin *et al.*, 2001; e.g., Hluštík *et al.*, 2002) as well as in performance of

movement impaired due to a central or peripheral lesion in the human motor system. In neurological diseases associated with motor impairment, such as stroke or multiple sclerosis, deviations from the normal motor pattern have been described in multiple brain regions, such as primary motor cortex contralateral to the major lesion, premotor cortex, supplementary motor area or the cerebellum (e.g., Chollet *et al.*, 1991; Weiller *et al.*, 1993; Small *et al.*, 2002).

This contribution reviews the use of functional MRI during performance of normal movement and of movement impaired in cerebrovascular stroke and discusses the possible use of this technique early after hemiparetic stroke with the goal to predict recovery and the success of rehabilitation.

Cerebral motor networks after cerebrovascular stroke

As has been known from experiments in monkeys, lesions in the primary motor or sensory cortices lead to functional reorganization in areas surrounding the lesion or in contralateral homologous regions. Changes in human motor circuits of the brain after stroke have been lately studied with non-invasive methods, such as positron emission tomography (PET), transcranial magnetic stimulation (TMS) - magnetic motor evoked potentials, and for the last 10 years, increasingly more with functional magnetic resonance imaging (fMRI). These methods reveal that even simple movement of the stroke-affected upper extremity activates brain in a pattern that is multifocal and bilateral, encompassing more extensive networks than the "core" circuit containing the primary motor cortex and thalamus contralateral to the moving hand and ipsilateral cerebellum, as seen when the same simple movement is performed by healthy individuals. The activations seen in stroke patients resemble rather networks associated in healthy humans with performance of complex and sequential movements, involving the ipsilateral (to the hand) primary sensorimotor cortex, dorsolateral premotor cortex (PMd),

ventrolateral premotor cortex (PMv), supplementary motor area (SMA), cingulate motor areas (CMA), parietal cortex, insula cortex and cerebellum (see Rijntjes and Weiller, 2002 for more extensive reviews; see Baron *et al.*, 2004).

The roles of different regions active after stroke, especially those, whose activation deviates from the normal pattern, are unclear. For instance, the uninjured primary motor cortex is often overactive early as well as late in the course of motor recovery – does this activity enhance neural plasticity and reparation of the surviving part of the "normal" motor network contributing to good prognosis? Perhaps it means that a compensatory network is being recruited, which is also associated with good prognosis. Or does it simply indicate that the normal networks are dysfunctional and therefore the prognosis is poor? For example, this can reflect the appearance of mirror movements.

Similarly, the activation of a more extensive network of bilateral premotor areas may reflect a nonspecific increase in effort or attention because the given task is more difficult for the post-stroke patient. The medial premotor areas (supplementary and cingulate motor areas) and both cerebellar hemispheres may be more prominently active because they are located outside the most frequently affected middle cerebral artery distribution. Moreover, contribution of the lateral premotor areas is more difficult to assess as the demarcation of primary motor and lateral premotor cortices is not trivial.

Imaging alone cannot provide answers to these questions (Baron *et al.*, 2004). Some insight has been gained from comparison of better and worse-recovered chronic stroke patients. Patients with more pronounced chronic motor deficit exhibit greater recruitment in ipsilesional primary motor cortex (M1) (see, e.g., Johansen-Berg, Rushworth *et al.*, 2002; Ward *et al.*, 2003) as well as in secondary motor areas bilaterally (Ward *et al.*, 2003), when compared to controls and patients who recovered well.

The early functional imaging studies in stroke recovery have studied well-recovered patients or have been cross-sectional. Hence, it was not known how brain activation related to behavioural change over the time course of recovery.

In a study where one of us (PH) participated, we used functional MRI (fMRI) to study 12 patients longitudinally over the first 6 months of stroke recovery. All subjects had acute stroke causing unilateral arm weakness and had some ability to move the impaired hand within 1 month. Each patient had both motor testing and fMRI during finger and wrist movements at four points during the observed period - 1, 2, 3, and 6 months after stroke. Patients were subdivided post-hoc into two groups of six patients each - one group showed good motor recovery, whereas the other did not. The functional imaging results support a role for the cerebellum in mediating functional recovery from stroke: Patients with better recovery had progressive increase in the activation volume of the cerebellar hemisphere opposite the injured corticospinal tract. Patients with poor recovery did not show these changes in cerebellar activation. No other brain region had a significant correlation with recovery, although there was a trend ($P = 0.08$) for the ipsilesional premotor cortex. Interestingly, activation in the cerebellum ipsilateral to the injury increases transiently after stroke, independently of the success of recovery. The results suggest a possible link between cerebellar activation and behavioral recovery from hand weakness from stroke. The underlying mechanism is not known, but it could relate to hemodynamic changes such as diaschisis or to the postulated role of the cerebellum in motor skill learning. (Small *et al.*, 2002).

Some of the subsequent fMRI studies that followed patients longitudinally through the course of recovery (Ward *et al.*, 2003; Nhan *et al.*, 2004) or rehabilitation (Johansen-Berg, Dawes *et al.*, 2002) verified the role of the cerebellum and ipsilesional premotor cortex (Johansen-Berg, Dawes *et al.*, 2002) or described other regions, where increased activation correlated with motor improvement, such as ipsilesional

(Johansen-Berg, Dawes *et al.*, 2002) or bilateral (Nhan *et al.*, 2004) secondary somatosensory cortex. On the other hand, Ward et al. (2003) described predominantly recovery-related decreases rather than increases in a number of areas, which has been interpreted as convergence of the patient data towards a more normal pattern upon recovery. Even though a number of the areas active early showed negative correlation of activation magnitude with early performance, no prediction of subsequent recovery was made (Ward *et al.*, 2003).

A different approach at uncovering the role of different areas that functional neuroimaging recognized as active upon recovery has relied on a transient non-destructive disruption of an area with repetitive TMS to see whether this functional lesion will be associated with worsening the functional deficit, i.e., loss of the re-gained motor function.

Contralesional M1 was one obvious target: surprisingly for some, TMS-induced functional lesion of this area does not affect movements of the stroke-impaired limb (Johansen-Berg, Rushworth *et al.*, 2002; Werhahn *et al.*, 2003). This suggests that activity of this recruited region does not simply act to replace the function of the damaged corticospinal system. In contrast, disruption of ipsilesional PMd (Fridman *et al.*, 2004) and contralesional PMd (Johansen-Berg, Rushworth *et al.*, 2002) by TMS increases motor reaction times in chronic stroke patients but not controls, suggesting PMd in both hemispheres contributes to recovery. Furthermore, there seem to be differential effects of TMS-induced functional lesions in patients with different outcomes. TMS to ipsilesional PMd was most disruptive in patients with smallest residual deficit (Fridman *et al.*, 2004), suggesting it may be capable of supporting good recovery. TMS to contralesional PMd, however, was most disruptive in patients with greater motor impairment (Johansen-Berg, Rushworth *et al.*, 2002), suggesting functionally relevant recruitment of contralesional PMd in those with greatest need. To summarize these results, motor areas of the unaffected hemisphere do not seem to “take

over" the functions lost with stroke in any simple and direct way (Baron *et al.*, 2004).

Prognosis of recovery and successful rehabilitation

As seen in the previous text, although there is now a wealth of functional imaging data related to stroke recovery, the relevance of different imaging results for the success of recovery has been more difficult to uncover. Can we inspect functional imaging data obtained early after stroke in patients whose recovery was studied over the next few weeks (Binkofski *et al.*, 1996) or months (Small *et al.*, 2002; Ward *et al.*, 2003; Nhan *et al.*, 2004) and search for imaging markers predictive of good recovery? Unfortunately, such retrospective examination typically does not reveal any systematic differences between the early brain maps of patients who later recovered well and of those who did not. One notable exception has been the correlation of early thalamic hypometabolism of glucose detected by PET with subsequent poor recovery (Binkofski *et al.*, 1996).

This prompted researchers to look at the results from other methods searching to find structural or functional parameters assessed early after stroke and to predict subsequent recovery. In middle cerebral artery stroke with hemiparesis, lesion size alone is not a good predictor of future recovery, although large strokes do associate with poor outcome (Šaňák *et al.*, 2005). Lesion location appears more significant, e.g., lesion of premotor cortex (Seitz *et al.*, 1998) or more extensive damage to subcortical white matter (Shelton and Reding, 2001) will prevent successful recovery. Functional assessment of the integrity of efferent and afferent tracts and motor cortex with evoked potentials (TMS - MEP and SEP) demonstrated that their lesions are associated with worse outcome, independent of the severity of the initial deficit (La Joie *et al.*, 1982; Bartoušek *et al.*, 1993; Heald *et al.*, 1993; Cruz Martinez *et al.*, 1999; Vang *et al.*, 1999; Palliyath, 2000).

Conclusion

Although available functional imaging data provides some indications which motor areas are associated with good recovery, functional MRI early after stroke does not presently seem to provide clear markers predicting future recovery, even though areas correlated with good recovery are already seen active. Other parameters, such as the structural and functional integrity of the corticospinal tract seem to have more prognostic value.

Acknowledgment

This work was supported by U.S. National Institutes of Health grants NS-37195 and MH-01916 and by the Internal Grant Agency, Ministry of Health, Czech Republic, grant NR8367–3/2005.

Literature

1. Baron J.C., Cohen L.G., Cramer S.C. et al. 2004. Neuroimaging in stroke recovery: position paper from the First International Workshop on Neuroimaging and Stroke Recovery. Cerebrovasc Dis.; 18: 260-7.
2. Bartoušek J., Beranová M., Grenarová O. et al. 1993. Transkraniální magnetická stimulace u CMP [Abstrakt]. In: 40th Annual Meeting of the Czech and Slovak Neurophysiological Society. Brno.
3. Binkofski F., Seitz R.J., Arnold S. et al. 1996. Thalamic metabolism and corticospinal tract integrity determine motor recovery in stroke. Ann Neurol.; 39: 460-70.
4. Cruz Martinez A., Tejada J., Diez Tejedor E. 1999. Motor hand recovery after stroke. Prognostic yield of early transcranial magnetic stimulation. Electromyogr Clin Neurophysiol.; 39: 405-10.
5. Fridman E.A., Hanakawa T., Chung M. et al. 2004. Reorganization of the human ipsilesional premotor cortex after stroke. Brain; 127: 747-58.

6. Heald A., Bates D., Cartlidge N.E. et al. 1993. Longitudinal study of central motor conduction time following stroke. 2. Central motor conduction measured within 72 h after stroke as a predictor of functional outcome at 12 months. Brain; 116: 1371-85.
7. Hluštík P., Solodkin A., Gullapalli R.P. et al. 2002. Functional lateralization of the human premotor cortex during sequential movements. Brain Cogn.; 49: 54-62.
8. Chollet F., DiPiero V., Wise R.J. et al. 1991. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. Ann Neurol.; 29: 63-71.
9. Johansen-Berg H., Dawes H., Guy C. et al. 2002. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. Brain; 125: 2731-42.
10. Johansen-Berg H., Rushworth M.F., Bogdanovic M.D. et al. 2002. The role of ipsilateral premotor cortex in hand movement after stroke. Proc Natl Acad Sci USA; 99: 14518-23.
11. La Joie W.J., Reddy N.M., Melvin J.L. 1982. Somatosensory evoked potentials: their predictive value in right hemiplegia. Arch Phys Med Rehabil.; 63: 223-6.
12. Nhan H., Barquist K., Bell K. et al. 2004. Brain function early after stroke in relation to subsequent recovery. J Cereb Blood Flow Metab.; 24: 756-63.
13. Ogawa S., Tank D.W., Menon R. et al. 1992. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci USA; 89: 5951-5.
14. Palliyath S. 2000. Role of central conduction time and motor evoked response amplitude in predicting stroke outcome. Electromyogr Clin Neurophysiol.; 40: 315-20.
15. Rijntjes M., Weiller C. 2002. Recovery of motor and language abilities after stroke: the contribution of functional imaging [Review]. Prog Neurobiol.; 66: 109-22.

16. Seitz R.J., Hoflich P., Binkofski F. et al. 1998. Role of the premotor cortex in recovery from middle cerebral artery infarction. Arch Neurol.; 55: 1081-8.
17. Shelton F.N., Reding M.J. 2001. Effect of lesion location on upper limb motor recovery after stroke. Stroke; 32: 107-12.
18. Small S.L., Hluštík P., Noll D.C. et al. 2002. Cerebellar hemispheric activation ipsilateral to the paretic hand correlates with functional recovery after stroke. Brain; 125: 1544-57.
19. Solodkin A., Hluštík P., Noll D.C. et al. 2001. Lateralization of motor circuits and handedness during finger movements. Eur J Neurol.; 8: 425-34.
20. Šaňák D., Horák D., Nosál V. et al. 2005. Impact of initial cerebral infarction volume measured in diffusion-weighted MRI on clinical outcome in acute stroke patients: a pilot study. J Neurol Sci.; 41: 439.
21. Vang C., Dunbabin D., Kilpatrick D. 1999. Correlation between functional and electrophysiological recovery in acute ischemic stroke. Stroke; 30: 2126-30.
22. Ward N.S., Brown M.M., Thompson A.J. et al. 2003. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain; 126: 2476-96.
23. N.S., Brown M.M., Thompson A.J. et al. 2003. Neural correlates of outcome after stroke: cross-sectional fMRI study. Brain; 126: 1430-48.
24. Weiller C., Ramsay S.C., Wise R.J. et al. 1993. Individual patterns of functional reorganization in the human cerebral cortex after capsular infarction. Ann Neurol.; 33: 181-9.
25. Werhahn K.J., Conforto A.B., Kadom N. et al. 2003. Contribution of the ipsilateral motor cortex to recovery after chronic stroke. Ann Neurol.; 54: 464-72.

CZY MOŻNA PRZEWIDZIEĆ WYNIKI REHABILITACJI POUDAROWEJ PRZY POMOCY FUNKCJONALNEGO REZONANSU JĄDROWEGO (fMRI)?

P. Hluštík, M. Mayer, M. Köcher, P. Kaňovský, J. Opavský

Streszczenie

W ciągu ostatnich 10 lat znalazła zastosowanie nowa metoda nieinwazyjnego badania z użyciem Magnetycznego Rezonansu Jądrowego (fMRI) pozwalająca na mapowanie neuroanatomii funkcjonalnej kory ruchowej u pacjentów z niedowładem połowiczym po udarze mózgu zarówno w badaniach przekrojowych poprzecznych jak i podłużnych. Przekroje podłużne tak u chorych z pomyślnym jak i niepomyślnym przebiegiem pozwoliły na zidentyfikowanie licznych obszarów mózgu których zmienność aktywacji w czasie korelowała z poprawą kliniczną. Były to po stronie uszkodzenia: kora przedruchowa, wtórna kora somatosensoryczna i móżdżek. Obserwowano także wczesną nadaktywność obszarów kojarzeniowych malejącą w miarę upływu czasu. Jednakże wczesna aktywacja połączeń ruchowych nie pokrywała się w sposób istotny z poprawą lub brakiem poprawy klinicznej. Dlatego musimy stwierdzić, że dostępne dane pochodzące z badania fMRI nie stanowią wyraźnych markerów poprawy i nie pozwalają na przewidywanie przebiegu zdrowienia u chorych z niedowładem połowiczym poddanych rehabilitacji po udarze niedokrwiennym mózgu.

Słowa kluczowe: *funkcjonalny rezonans magnetyczny, udar mózgu, rehabilitacja, kora ruchowa*