Available online at www.sciencedirect.com
ScienceDirect
Experimental Neurology 204 (2007) 491–495
Experimental Neurology
www.elsevier.com/locate/yexnr

Commentary

Avoiding performance and task confounds: Multimodal investigation of brain reorganization after stroke rehabilitation

John W. Krakauer

The Neurological Institute, Columbia University College of Physicians and Surgeons, NY 10032, USA

Received 17 October 2006; accepted 30 December 2006
Available online 25 January 2007

Stroke is the leading cause of disability worldwide despite significant advances in prevention and acute treatment. Thus there is an urgent need to understand the neural mechanisms of both spontaneous and rehabilitation-induced recovery. In the past 15 years, functional brain imaging has been used extensively to investigate recovery-related changes at the whole brain level (Calautti and Baron, 2003; Cramer et al., 1997; Krakauer, 2004; Marshall et al., 2000; Ward et al., 2003a, b). However, it has become apparent that functional imaging, when used alone to investigate post-stroke brain reorganization, has reached a near impasse. The reasons for this are briefly delineated here as they pertain to motor recovery. First, the definition of motor recovery has been surprisingly under-emphasized even though it is obvious that the regions or patterns of activation identified will depend on the motor task in the scanner and on the out of scanner behavioral measures chosen as predictors in the image analysis. Second, measures of recovery are often crude and insensitive to the difference between compensatory improvements versus true recovery, or vicariation, of function. This is a real problem for functional imaging because compensatory adjustments will also often lead to activation changes even though they have nothing to do with true recovery. For example, use of more proximal limb muscles to aid distal control might lead to contralesional activation, as proximal muscles have more bilateral cortical representation, but of course this novel activation would not indicate reorganization after stroke. The situation becomes even worse when one considers that true recovery may in fact never occur, if strictly understood to mean a return to identical pre-morbid behavior due to identical neural computations, albeit performed at a new anatomical site. The implication is that tasks and measures have to be carefully chosen so that investigators know what they are attributing activation changes to. Third, functional imaging is a correlative technique and at best can prove necessity but not sufficiency of a brain area to behavior. Identification of a novel area of activation does not in itself tell the investigator what the area is doing computationally. An implicit but unjustified assumption, common in the literature, is that a novel area is only involved in recovery if it contributes to motor execution. Alternatively, to conclude that an area performs function x in study A because when function x was directly tested with task y in study B it activated the same area is to engage in negative inference (Poldrack, 2006) and is best avoided. Last but not the least, the increased access to MR scanners in hospitals, the user friendliness of imaging analysis software packages, and the sheer seductiveness of the images themselves have led to a susceptibility to lose sight of the confounds that plague functional imaging in general, and issues of restoration of function in particular. The most problematic of these is the performance confound, others include the challenge of controlling subject attention, effort, and perception of task difficulty.

The performance confound can be understood as follows: patients with stroke are impaired and therefore they will perform a given motor task differently from control subjects. This performance difference alone could lead to a difference in activation and confound the more interesting interpretation, which is that the different activation represents reorganization to maintain motor output. This confound is also a spoiler for longitudinal studies because as patients recover, by definition, their performance also improves. The only compelling recovery-related result would be if activation was observed to *increase* in an area as performance improves and this area *not* be seen to activate in control subjects. Unfortunately, such a result has not been reliably observed (although see Small et al., 2002); instead studies consistently report a diminution in extra activation as patients recover (Marshall et al., 2000; Ward et al., 2003a,b), which is what would be expected if activation is

E-mail address: jwk18@columbia.edu.

0014-4886/$ - see front matter © 2007 Published by Elsevier Inc.
doi:10.1016/j.expneurol.2006.12.026

performance related. Thus to date, despite a frenzy of functional imaging, we cannot say much beyond the fact that patients show different activation when they perform differently—not exactly surprising. Rehabilitative therapy changes performance, therefore the performance confound is just as problematic for functional imaging studies of rehabilitation.

So how to disambiguate activation changes due to recovery-related reorganization from those related to recovered performance? One approach is the one used in a study recently published in Experimental Neurology (Chouinard et al., 2006). The approach was pioneered by Tomas Paus (senior author of the current study) and colleagues and is called "perturb-and-measure" because it combines transcranial magnetic stimulation (TMS) and PET (Paus, 2005; Paus et al., 1997, 1998). The basic idea is that TMS leads to PET cerebral blood flow (CBF) changes both locally and remotely. The performance confound is removed because the PET activation changes relate to TMS and not to overt motor behavior since subjects are at rest in the scanner with their eyes closed. Here, Chouinard and colleagues investigated changes in connectivity between primary cortex and non-primary motor cortical and subcortical areas in patients with stroke before and after constraint-induced movement therapy (CIMT). The paper brings together several techniques and principles: TMS, PET functional imaging, cortical reorganization, effective connectivity, and CIMT. Some of these will be briefly reviewed here.

TMS uses a time-varying magnetic field to induce electrical current in cortical axons underlying the coil. TMS has been used in four principal ways in the study of motor recovery and reorganization after stroke (Talelli et al., 2006). The first is to assess the integrity of the corticospinal tract based on the ability to elicit a motor evoked potential (MEP) at various times after stroke (Catano et al., 1996; Cicinelli et al., 1997; Traversa et al., 1997, 1998). Second, TMS is used to calculate changes in the area of motor map and shifts in hot spot location, either due to spontaneous reorganization after stroke or after rehabilitation (Cicinelli et al., 1997; Liepert et al., 2000, 2004, 2001; Traversa et al., 1997). Third, TMS can be used to investigate changes in corticocortical circuits. The most common technique is the paired-pulse paradigm (Kujirai et al., 1993), which involves giving a subthreshold stimulus at an interval (1 ms to 200 ms) before the suprathreshold pulse. Depending on the size of the interval there will be either intracortical facilitation or inhibition leading to increases or decreases in MEP amplitude, respectively. The fourth, and most relevant to the paper under review, use for TMS is to perturb local and remote cortical regions with either a single suprathreshold pulse or a *repetitive* train of subthreshold pulses at a frequency from 1 to 10 Hz (rTMS). The main interest using rTMS is that it can produce effects that outlast the application of the stimulus for minutes or hours. One concern with TMS-induced muscle twitches is that they are non-physiological and so changes in TMS parameters might be epiphenomenal and not relate to voluntarily induced muscle contractions. The way this problem is usually dealt with is to not interpret changes in TMS parameters alone but to correlate them with changes in meaningful behavioral measures.

Paus et al. (1998) applied subthreshold 10 Hz rTMS over M1 and varied the number of TMS trains delivered during each PET scan. They found that cerebral blood flow (CBF), both at the site of rTMS application and at remote sites known to be trans-synaptically connected to M1, was inversely correlated with the number of stimulus trains. The authors concluded that rTMS activated local inhibitory mechanisms with a subsequent reduction in excitatory synaptic activity in M1 and its connected areas, reflected as a decrease in CBF. The study by Chouinard and colleagues used the same approach in patients with stroke before and after 2 weeks of CIMT.

Functional brain imaging has successfully demonstrated that the brain has a modular organization with functional specialization. More recently, functional imaging has gone after the more difficult problem of how these functionally specialized areas integrate to produce behavior (Friston, 2002). *Functional* connectivity can be defined as statistical dependencies or correlations among separated neurophysiological events or measurements. However, two areas can respond to the same stimulus through a common input or both be recruited independently during a given task (task confound). In either case there would be a correlation but this would not mean the areas are connected. *Effective* connectivity, in contrast, refers explicitly to the influence one neural system exerts over another. As with the performance confound, the use of TMS to investigate CBF changes rather than behavior, allowed Chouinard and Colleagues to avoid the task confound and infer effective and not just functional connectivity.

CIMT has received the lion's share of attention with respect to new rehabilitation techniques (for a review, see Mark and Taub, 2004). The excitement is principally because studies suggest that even patients with chronic hemiparesis (>6 months post stroke) have a favorable response, which goes against the entrenched idea that patients hit a recovery plateau after 6 months (Page et al., 2004). Several studies have now been published showing a significant benefit for CIMT in patients with chronic hemiparesis. Most significantly, the results of the first large randomized single-blind clinical trial of CIMT (The EXCITE trial) have just been published (Wolf et al., 2006). This study compared CIMT to usual and customary care in 222 patients who had a first stroke in the previous 3 to 9 months. The results were positive: patients who received CIMT showed greater gains in almost all objective outcome measures right after treatment and in three of these measures at 12-month follow-up.

CIMT has two components and is usually given over 2 weeks: (i) restraint of the less-affected extremity for 90% of waking hours; (ii) massed practice with the affected limb for 6 h/day using *shaping*. In patients with chronic hemiparesis, the restraint is conjectured to help patients overcome *learned non-use*, whereas in patients with acute stroke it can be seen as a way to prevent adoption of compensatory strategies with the unaffected limb. Shaping is a form of operant conditioning whereby performance is titrated upwards and consistently rewarded—essentially the reverse of the mechanism by which patients are posited to learn non-use. The concept of non-use is somewhat confusing but the proponents of the concept appear to

reason as follows: certain patients, despite significant residual motor abilities in the affected arm (what Taub and colleagues refer to as "commanded limb movement"), become discouraged and use it less and less. It should be noted that there are no data about the time course of this presumptive non-use process, perhaps because it would be a challenge to acquire. The purported physiological consequence of this reduction in "spontaneous limb movement" is a contraction of cortical motor maps. The claim is that CIMT re-expands these cortical maps, a claim that has some support from TMS studies that show map enlargement after CIMT (Liepert et al., 2000). Thus CIMT seems to focus on a subset of patients who have residual corticospinal output with superimposed secondary contraction of cortical maps because of non-use. CIMT remains controversial (van der Lee, 2001, 2003) and much still needs to be resolved. With regard to the neural correlates of CIMT, the critical question is this: is there a categorical difference between increasing spontaneous movements at a particular level of execution versus practice-related changes that result in true improvements in the quality of motor execution? To make this point clearer one can consider that a form of CIMT occurs when healthy subjects practice handwriting with their non-dominant hand. The improvement has been analyzed kinematically and it appears to occur at the level of individual strokes with true increase in skill, with stroke duration and velocity decreasing without degradation in accuracy (Lindemann and Wright, 1998). It can be envisaged that the neural correlates of increased spontaneous use of the left hand are different from the neural correlates of true skill improvement with the left hand. Thus, it is critical to understand the framework proposed by Taub and colleagues in order to properly design functional imaging experiments to support or refute it.

Chouinard and colleagues asked whether there were changes in primary motor cortex (M1) and its effective connectivity before and after CIMT. Seven patients with residual hemiparesis, each at least 12 months out from an ischemic stroke, underwent PET imaging before and after 2 weeks of CIMT. Before each PET session, the resting motor threshold (rMT), which was defined as the minimum stimulation intensity that reliably induced an observable hand muscle twitch 50% of the time, was established for both hands in each subject. During the PET scanning protocol, the probabilistic hand-region of contralesional and ipsilesional M1 was stimulated at 95% of the rMT, a level that did not lead to muscle contraction. As the rMT was based on observed movement and not on detection of muscle activity with EMG, muscle activity may well have still been present if the EMG gain had been sensitive enough. This is acceptable, however, because the main purpose was to avoid overt TMS-induced movement and its associated reafference, which could cause activation changes and confound interpretation of the PET results. There was a total of seven 60s O^{15} scans. During the 1st, 2nd, and 3rd scans, 5, 15, and 30 trains of 10-Hz stimulation (each train lasted 1 s) were delivered over M1 in one hemisphere, the 4th scan was a baseline scan without TMS, and then during the 5th, 6th and 7th scans, the opposite M1 was stimulated with the same parameters as the first three scans. A varying number of TMS trains were investigated because, as mentioned above, an inverse relationship has been found between number of TMS trains and the local CBF response in healthy subjects (Paus et al., 1998). Tests of coordination, speed and strength (simple tapping, sequential tapping, pinch strength, and grip strength) were assessed before and after CIMT in both the affected and unaffected arms. In addition, functional ability was assessed with the Actual Amount of Use Test (AAUT; Taub et al., 1998) and the Wolfe Motor Function test (WMFT; Wolf et al., 1989). Finally, the motor activity log (MAL; Taub et al., 1993) allowed patients to self-report both quality and amount of use of the affected arm at home. These various tests were reduced using principle components analysis (PCA) into three improvement (change in performance from before to after therapy) components, two of which were used for correlation with CBF changes. Interestingly, the first component was associated with the more objective non-self-report measures and the second component with the self-reported measures in the MAL. The difference between objective measures of impairment and more subjective measures of function is of critical importance to rehabilitation as they can dissociate in response to a therapy. From a behavioral standpoint, all patients improved on the WMFT, the AAUT, sequential tapping, and grip strength. They also showed improved MAL scores. Analysis of CBF was performed in 2 ways. First, the investigators asked whether the relationship between CBF and number of TMS trains differed for any brain areas before and after CIMT. Second, they examined the relationship between motor improvement and the *difference* in the CBF response to TMS, pre- and post CIMT, both locally in M1 and in areas connected to M1. The emphasis on the difference is critical here because the central question of this study was: does CIMT lead to a change in CBF responses of areas connected to M1 and is this change correlated with motor improvement?

The first finding with respect to ipsilesional M1 was that there was a negative interaction for session x number of TMS trains in ipsilesional M1 after CIMT. This means that local CBF in ipsilesional M1 was inversely related to the number of TMS trains. A second finding was that the ipsilesional cingulate motor area also showed an inverse relationship between CBF and number of TMS trains. Thus ipsilesional M1 and the cingulate motor area, after CIMT, reverted to the more normal inverse relationship between CBF and number of TMS trains seen in healthy subjects (Paus et al., 1998). A third finding was that there was an inverse relationship between the average CBF response to TMS over ipsilesional M1 and the non-self-report component of motor improvement. The authors interpreted this as evidence for post-CIMT strengthening of local inhibitory neurons, which have been shown to be important for fractionation or isolation of proximal and distal muscles (Keller, 1993). This is interesting because one aspect of motor improvement after stroke consists of breaking out of synergies and regaining the ability to isolate joints so that they move independently of each other (Brunnstrom, 1970; Twitchell, 1950). A fourth finding was that an inverse relationship was also found between the mean local CBF response in contralesional M1 and the non-self-report component of motor improvement. This suggests that contralesional M1 does indeed

play a role in motor improvement after stroke. This is consistent with bilateral M1 activation in normal subjects performing complex hand tasks (Verstynen et al., 2005) and with a recent study in healthy subjects that showed that M1 ipsilateral to the moving limb can rapidly compensate for TMS disruption of contralateral M1 (Strens et al., 2003).

A fifth finding was that there were changes in effective connectivity both when applying TMS over ipsilesional and contralesional M1. Recall that effective connectivity was measured through finding *changes* in the CBF response in areas connected to M1before and after CIMT. The contralesional ventrolateral thalamus showed a change in effective connectivity with ipsilesional M1. The contralesional globus pallidus and ipsilesional putamen showed a change in effective connectivity with contralesional M1. Finally, improvement on the self-report component of motor improvement did not covary with CBF differences anywhere in the brain. This last result is interesting and important because it serves both as a sort of negative control—the perturb-and-measure approach does not find correlations for every measurement, and because it provides a clue as to how CIMT works. Namely, it suggests that the main effect of CIMT is driven by its massed practice component, which works through motor areas on objective measures of impairment and not through brain areas related to subjective measures of increased use, which will most likely always go up if the other hand is restrained!

There are some weaknesses to the study, however. The number of subjects studied was small and no power analysis was provided. In other words, no estimates of effect size from previous studies were used to calculate the minimum number of subjects required to control the false negative rate. This is important because those areas that did show a change in connectivity with ipsi- and contralesional M1 do not seem to be the most obvious candidates. For example, a change in connectivity between the two M1 areas might have been expected but perhaps was not detected because of inadequate power.

In summary, the study by Chouinard and colleagues used a multimodal approach that combined PET and TMS to control for two types of confound that usually make interpretation of functional imaging studies of motor recovery after stroke very difficult. The performance confound was controlled for by making TMS induce activation changes in motor areas rather than overt motor behavior. Conclusions about effective connectivity changes could be drawn because the CBF changes before and after CIMT were related to TMS applied to M1 only and not to a performance of a motor task that could have activated separate motor areas independently. It can be concluded that CIMT, and probably any kind of intense practice, can lead to widespread reorganization in the brain that promotes recovery from focal damage to the corticospinal tract. The widespread nature to this reorganization suggests that many brain areas can work together in order to activate remaining corticospinal connections, which themselves might originate from a more restricted locus.

Acknowledgments

Thanks to Toni Pearson for critical reading of the manuscript. This work was supported by NS 048099.

References

Brunnstrom, S., 1970. Movement Therapy in Hemiplegia. Harper & Row, New York.

Calautti, C., Baron, J.C., 2003. Functional neuroimaging studies of motor recovery after stroke in adults. Stroke 34, 1553–1566.

Catano, A., Houa, M., Caroyer, J.M., Ducarne, H., Noel, P., 1996. Magnetic transcranial stimulation in acute stroke: early excitation threshold and functional prognosis. Electroencephalogr. Clin. Neurophysiol. 101, 233–239.

Chouinard, P.A., Leonard, G., Paus, T., 2006. Changes in effective connectivity of the primary motor cortex in stroke patients after rehabilitative therapy. Exp. Neurol. 201, 375–387.

Cicinelli, P., Traversa, R., Rossini, P.M., 1997. Post-stroke reorganization of brain motor output to the hand: a 2–4 month follow-up with focal magnetic transcranial stimulation. Electroencephalogr. Clin. Neurophysiol. 105, 438–450.

Cramer, S.C., Nelles, G., Benson, R.R., Kaplan, J.D., Parker, R.A., Kwong, K.K., Kennedy, D.N., Finklestein, S.P., Rosen, B.R., 1997. A functional MRI study of subjects recovered from hemiparetic stroke. Stroke 28, 2518–2527.

Friston, K., 2002. Beyond phrenology: what can neuroimaging tell us about distributed circuitry? Annu. Rev. Neurosci. 25, 221–250.

Keller, A., 1993. Intrinsic synaptic organization of the motor cortex. Cereb. Cortex 3, 430–441.

Krakauer, J.W., 2004. Functional imaging of motor recovery after stroke: remaining challenges. Curr. Neurol. Neurosci. Rep. 4, 42–46.

Kujirai, T., Caramia, M.D., Rothwell, J.C., Day, B.L., Thompson, P.D., Ferbert, A., Wroe, S., Asselman, P., Marsden, C.D., 1993. Corticocortical inhibition in human motor cortex. J. Physiol. 471, 501–519.

Liepert, J., Bauder, H., Wolfgang, H.R., Miltner, W.H., Taub, E., Weiller, C., 2000. Treatment-induced cortical reorganization after stroke in humans. Stroke 31, 1210–1216.

Liepert, J., Uhde, I., Graf, S., Leidner, O., Weiller, C., 2001. Motor cortex plasticity during forced-use therapy in stroke patients: a preliminary study. J. Neurol. 248, 315–321.

Liepert, J., Hamzei, F., Weiller, C., 2004. Lesion-induced and training-induced brain reorganization. Restor. Neurol. Neurosci. 22, 269–277.

Lindemann, P.G., Wright, C.E., 1998. Skill acquisition and plans for actions: learning to write with your other hand. In: Sternberg, S., Scarborough, D. (Eds.), Invitation to Cognitive Science. MIT Press, pp. 523–584.

Mark, V.W., Taub, E., 2004. Constraint-induced movement therapy for chronic stroke hemiparesis and other disabilities. Restor. Neurol. Neurosci. 22, 317–336.

Marshall, R.S., Perera, G.M., Lazar, R.M., Krakauer, J.W., Constantine, R.C., DeLaPaz, R.L., 2000. Evolution of cortical activation during recovery from corticospinal tract infarction. Stroke 31, 656–661.

Page, S.J., Gater, D.R., Bach, Y.R.P., 2004. Reconsidering the motor recovery plateau in stroke rehabilitation. Arch. Phys. Med. Rehabil. 85, 1377–1381.

Paus, T., 2005. Inferring causality in brain images: a perturbation approach. Philos. Trans. R. Soc. Lond., B Biol. Sci. 360, 1109–1114.

Paus, T., Jech, R., Thompson, C.J., Comeau, R., Peters, T., Evans, A.C., 1997. Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. J. Neurosci. 17, 3178–3184.

Paus, T., Jech, R., Thompson, C.J., Comeau, R., Peters, T., Evans, A.C., 1998. Dose-dependent reduction of cerebral blood flow during rapid-rate transcranial magnetic stimulation of the human sensorimotor cortex. J. Neurophysiol. 79, 1102–1107.

Poldrack, R.A., 2006. Can cognitive processes be inferred from neuroimaging data? Trends Cogn. Sci. 10, 59–63.

Small, S.L., Hlustik, P., Noll, D.C., Genovese, C., Solodkin, A., 2002. Cerebellar hemispheric activation ipsilateral to the paretic hand correlates with functional recovery after stroke. Brain 125, 1544–1557.

Strens, L.H., Fogelson, N., Shanahan, P., Rothwell, J.C., Brown, P., 2003. The ipsilateral human motor cortex can functionally compensate for acute contralateral motor cortex dysfunction. Curr. Biol. 13, 1201–1205.

Talelli, P., Greenwood, R.J., Rothwell, J.C., 2006. Arm function after stroke: neurophysiological correlates and recovery mechanisms assessed by transcranial magnetic stimulation. Clin. Neurophysiol. 117, 1641–1659.

Taub, E., Miller, N.E., Novack, T.A., Cook III, E.W., Fleming, W.C., Nepomuceno, C.S., Connell, J.S., Crago, J.E., 1993. Technique to improve chronic motor deficit after stroke. Arch. Phys. Med. Rehabil. 74, 347–354.

Taub, E., Crago, J.E., Uswatte, G., 1998. Constraint-induced movement therapy: a new approach to treatment in physical rehabilitation. Rehabil. Psychol. 43, 152–170.

Traversa, R., Cicinelli, P., Bassi, A., Rossini, P.M., Bernardi, G., 1997. Mapping of motor cortical reorganization after stroke. A brain stimulation study with focal magnetic pulses. Stroke 28, 110–117.

Traversa, R., Cicinelli, P., Pasqualetti, P., Filippi, M., Rossini, P.M., 1998. Follow-up of interhemispheric differences of motor evoked potentials from the 'affected' and 'unaffected' hemispheres in human stroke. Brain Res. 803, 1–8.

Twitchell, T.E., 1950. The restoration of motor function following hemiplegia in man. Brain 74, 443–480.

van der Lee, J.H., 2001. Constraint-induced therapy for stroke: more of the same or something completely different? Curr. Opin. Neurol. 14, 741–744.

van der Lee, J.H., 2003. Constraint-induced movement therapy: some thoughts about theories and evidence. J. Rehabil. 41–45.

Verstynen, T., Diedrichsen, J., Albert, N., Aparicio, P., Ivry, R.B., 2005. Ipsilateral motor cortex activity during unimanual hand movements relates to task complexity. J. Neurophysiol. 93, 1209–1222.

Ward, N.S., Brown, M.M., Thompson, A.J., Frackowiak, R.S., 2003a. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain 126, 2476–2496.

Ward, N.S., Brown, M.M., Thompson, A.J., Frackowiak, R.S., 2003b. Neural correlates of outcome after stroke: a cross-sectional fMRI study. Brain 126, 1430–1448.

Wolf, S.L., Lecraw, D.E., Barton, L.A., Jann, B.B., 1989. Forced use of hemiplegic upper extremities to reverse the effect of learned nonuse among chronic stroke and head-injured patients. Exp. Neurol. 104, 125–132.

Wolf, S.L., Winstein, C.J., Miller, J.P., Taub, E., Uswatte, G., Morris, D., Giuliani, C., Light, K.E., Nichols-Larsen, D., 2006. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA 296, 2095–2104.