Published in final edited form as:

Brain Res. 2010 March 8; 1318C: 64–76. doi:10.1016/j.brainres.2009.12.073.

Changes in Regional Activity Are Accompanied with Changes in Inter-Regional Connectivity during Four Weeks Motor Learning

Liangsuo Ma^{1,2}, Binqun Wang³, Shalini Narayana³, Eliot Hazeltine⁴, Xiyong Chen², Donald A. Robin³, Peter T. Fox³, and Jinhu Xiong²

¹Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center, Houston, TX 77030

²Department of Radiology, University of Iowa, Iowa City, IA 52242

³Research Imaging Center, University of Texas Health Science Center, San Antonio, TX 78284

⁴Department of Psychology, University of Iowa, Iowa City, IA 52242

Abstract

Structural equation modeling (SEM) and fMRI were used to test whether changes in the regional activity are accompanied by changes in the inter-regional connectivity as motor practice progresses. Ten healthy subjects were trained to perform finger movement task daily for 4 weeks. Three sessions of fMRI images were acquired within four weeks. The changes in inter-regional connectivity were evaluated by measuring the effective connectivity between the primary motor area (M1), supplementary motor area (SMA), dorsal premotor cortex (PMd), basal ganglia (BG), cerebellum (CB), and posterior ventrolateral prefrontal cortex (pVLPFC). The regional activities in M1 and SMA increased from pre-training to Week 2 and decreased from Week 2 to Week 4. The inter-regional connectivity generally increased in strength (with SEM path coefficients becoming more positive or negative) as practice progressed. The increases in the strength of the inter-regional connectivity may reflect long-term reorganization of the skilled motor network. We suggest that the performance gain was achieved by dynamically tuning the inter-regional connectivity in the motor network.

Keywords

effective connectivity; inter-regional connectivity; motor skill learning; motor plasticity; structural equation modeling

1. Introduction

Neural plasticity refers to changes in the response characteristics of a neuron (or an ensemble of neurons) based on experience or any change in inputs to nervous system. It has been extensively investigated at the molecular (Fontan-Lozano et al., 2008), cellular (Balaban, 2008), system (Huxlin, 2008), functional (Holland et al., 2007), and anatomical (Draganski

© 2009 Elsevier B.V. All rights reserved.

Correspondence: Liangsuo Ma, Ph.D. Department of Psychiatry and Behavioral Sciences University of Texas Health Science Center Mental Science Institute Building #279, 1300 Moursund St Houston, TX 77030 Phone: 713-500-2638 Fax: 713-500-2624 liangsuo.ma@uth.tmc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

and May, 2008) levels of the nervous system. Studies in cellular and molecular mechanisms of motor learning have suggested that synaptic plasticity, a process believed to be involved in long-term potentiation, long-term depression, and alterations in intracortical inhibition, is a potential candidate for producing changes in motor cortex during learning (Ito, 2001; Martin and Morris, 2001; Sanes and Donoghue, 2000). Previous studies in humans, both in intact (Hlustik et al., 2004; Jueptner et al., 1997a; Jueptner et al., 1997b; Karni et al., 1995; Lehericy et al., 2005; Penhune and Doyon, 2002; Toni and Passingham, 1999) and patient populations (Catalan et al., 1999; Hallett, 2001; Winstein et al., 1999), have focused on identifying the neural substrates mediating the incremental acquisition of skilled motor behaviors. Neuroimaging experiments have reported practice-related neural activation changes in the cortical area, subcortical area, and cerebellum (Doyon and Benali, 2005; Doyon, 2008; Willingham, 1998).

Neuroimaging studies of the human brain are commonly based on investigating regional activation or inter-regional connectivity. The former approach focuses on local changes of activation in targeted brain regions. During motor learning, the region-specific activation changes presumably reflect alterations in neural responsiveness based on practice. Thus, when a region shows greater activation later compared to early in practice, it can be inferred that changes in some localized process underlies learning and that regional activation changes reflect the plasticity of that area (Poldrack, 2006). The second approach emphasizes changes in inter-regional connectivity. It is assumed that the complex processing required for motor learning is the consequence of dynamic network interactions that finally reduced the processing demands for a particular operation (Duncan et al., 1997; Tononi et al., 1994). The distinguishing feature of different mental operations is the interactivity pattern of neural ensembles rather than whether a particular ensemble is active (Sakurai, 1996). To quantify the inter-regional connectivity, the concept of effective connectivity was introduced (Friston, 1994b). Effective connectivity refers to the influence one neural system exerts over another by quantifying the effect that one region's activity has on that of another region. Effective connectivity conceptually distinguishes from functional connectivity (Friston, 1994b), which is defined as the correlations between spatially remote neurophysiological events.

Motor plasticity has been extensively studied by evaluating changes in regional activity. Motor learning-related changes in regional activity have been reported by different groups in a number of cortical areas, subcortical areas, and cerebellum (Doyon et al., 1996; Friston et al., 1992; Hlustik et al., 2004; Karni et al., 1995; Lehericy et al., 2005; Xiong et al., 2009). Some of these studies have investigated changes in regional activity within several weeks when subjects were trained to perform sequential finger movement tasks (Hlustik et al., 2004; Karni et al., 1995; Lehericy et al., 2005; Xiong et al., 2009). Although the motor system has been extensively investigated by using effective connectivity approach (Chouinard et al., 2006; Eickhoff et al., 2008; Grafton et al., 1994; Grefkes et al., 2008; Grol et al., 2007; Honey et al., 2003; Kasess et al., 2008; Laird et al., 2008; Nezafat et al., 2001; Palmer et al., 2009; Rogers et al., 2004; Rowe et al., 2002; Solodkin et al., 2004; Toni et al., 2002; Zhuang et al., 2005), only a small number of studies have focused on motor plasticity. Using positron emission tomography (PET) and SEM, Grafton and colleagues (1994) examined the effect of a short term movement practice (5 minutes) on the effective connectivity between cortical and subcortical motor areas. In another PET study, Nezafat and colleagues (2001) investigated changes in the cerebellum after subjects learned an arm movement task. They found that, during long-term recall, the same input to the cerebellar cortex produced less synaptic activity cortex output to the deep cerebellar nuclei. Using fMRI and SEM, Rowe and colleagues (2002) investigated the effect of a short training (pre-training occurred on the same day as scanning) on the neural basis of attention to action. It was found that Parkinson's Diseases resulted in a functional disconnection of the SMA and premotor cortex from other frontal regions. Using fMRI and SEM, Toni and colleagues (2002) found that altered cortico-striatal functional couplings were associated with

learning to visual instructions. In another fMRI study, Honey and colleagues (2003) used SEM to determine that a dopaminergic drug could enhance the effective connectivity of human caudate nucleus. These studies represent a diverse approach to understanding the neurobiology of motor learning. They focused on the effects of short-term training (Grafton et al., 1994; Rowe et al., 2002), post-training (Nezafat et al., 2001), visual instructions (Toni et al., 2002), or a dopaminergic drug (Honey et al., 2003) on the motor system. None of these effective connectivity studies investigated the effect of long-term training (e.g. several weeks).

With different emphases, regional activity and effective connectivity approaches are both useful in understanding motor plasticity. In this paper, we combined these two approaches to identify long-term training induced changes. Three sessions of functional MRI (fMRI) images were acquired within four weeks when subjects were trained to perform an explicit finger sequencing task (Karni et al., 1995; Xiong et al., 2009). Structural equation modeling (SEM) was used as a system modeling tool to measure effective connectivity. We considered different SEM models, each of which encloses the primary motor area (M1), supplementary motor area (SMA), dorsal premotor cortex (PMd), basal ganglia (BG), cerebellum (CB), and posterior ventrolateral prefrontal cortex (pVLPFC). All the SEM models are same except the connections among the selected regions. All the SEM models were tested by the three sets of fMRI data. The models that fitted all data were compared across the three testing periods.

2. Results

Learning curve for the trained sequence is shown in Figure 2. In the first practice session, the mean error rate was 1.5% during performance of the finger sequence, but the error rate quickly dropped to zero after several days. There were no errors during scanning session. From pre-training to Week 2, the mean movement rate increased from 38 to 66 sequences per minute. From Week 2 to the end of practice (Week 4), the mean movement rate further increased from 66 to 72 sequences per minute. A two (subject group factors: Group A and Group B) by three (scanning time points: pre-training, Week 2, Week 4) ANOVA analysis based on the movement rate revealed significant difference between the scanning time points ($F_{(2,24)} = 25.84$, $p < 0.00001$). The difference between the two subject groups ($F_{(1,24)} = 0.39$, $p = 0.54$), and the interaction between the subject group and the scanning time point ($F_{(2,24)} = 0.02$, $p = 0.98$) were not significant. Tukey post hoc analyses indicate that the mean movement rates at Week 2 ($p < 0.01$) and Week 4 ($p < 0.01$) were significantly greater than pre-training. No significant difference was found between Week 2 and Week 4. These results suggest that the subjects' skill was mainly improved during the first two weeks. The video analysis suggests that the improvement in movement rate is mainly due to a decrease in inter-movement delays with a minor contribution coming from increased finger velocity.

For each scanning time point, an fMRI activation map was generated using a traditional differentiated data analysis strategy by contrasting the task performance with the control state (i.e., the resting state). At the subject level, significant activations were found in M1, SMA, PMd, PFC, BG, CB, and thalamus. Most of the activations are bilateral. However the activations in cortical and sub-cortical areas are highly dominant in right hemisphere and the activations in the cerebellum are highly dominant in left hemisphere. Figure 2 shows the activation maps for the three test periods that were averaged across subjects. The region of PFC did not show up in the average map, probably due to relatively weak signal and inter-subject variability in this region. The percent signal changes in the six VOIs were depicted in Figure 4. A one-way ANOVA indicated that significant changes in percent signal change only happened in M1 ($F_{(2,29)} = 3.92$, $p = 0.027$) and SMA ($F_{(2,29)} = 4.79$, $p = 0.017$). No significant changes were found in the other four VOIs. Tukey post-hoc analyses revealed that the percent signal changes in M1 and SMA in Week 2 were significantly higher than those in pre-training

and Week 4. No significant difference was found between pre-training and Week 4 in both M1 and SMA.

All the SEM models were tested using data from the three test periods. A P-value $P = 0.05$ was selected as threshold for model rejection. Based on this criterion, the base model was rejected, as at least one P-value among the three sessions in these two models was lower than the threshold. Among all models we considered, only one model (Figure 5) simultaneously fitted all three test periods (pre-training, $\chi^2=0.25$, $df=1$, $P>0.05$, RMSEA=0.00; Week 2, $\chi^2=1.36$, $df=1$, $P>0.05$, RMSEA=0.01; Week 4, $\chi^2=3.25$, $df=1$, $P>0.05$, RMSEA=0.04). Figure 5 also depicts the path coefficients (positive or negative strengths) of the fitted model across the three test periods. The details of the three sets of path coefficients are given in Table 2. An omnibus test using a stacked model approach in LISREL showed that the model at pre-training was significantly different from the model at Week 2 ($\Delta\chi^2(21)=365.9$, $P<0.001$). In addition, there were significant differences between the model at Week 2 and the model at Week 4 ($\Delta\chi^2(21)=472.4$, $P<0.001$) and between the model at pre-training and Week 4 ($\Delta\chi^2(21)=645.9$, $P<0.001$). Changes in each path coefficient are depicted in Table 2 (using stacked model approach). These results revealed that significant changes occurred in most of the path coefficients of the effective connectivity as motor training progressed. The changes in the path coefficients can be classified into four classes: (I) consistent increasing: SMA→pVLPFC, SMA→PMd, SMA→BG, PMd→M1, PMd→CB, BG→M1, BG→SMA and CB→pVLPFC (II) consistent decreasing: M1→BG, pVLPFC→M1, pVLPFC→SMA, pVLPFC→CB SMA→M1, BG→pVLPFC, and CB→M1 (III) first increasing then decreasing: BG→CB (IV) first decreasing then increasing: M1→CB, PMd→pVLPFC, and CB→BG.

3. Discussion

The objective of the present study was to identify changes in the motor system during four weeks of motor practice to elucidate the mechanisms of neural plasticity associated with motor learning. Our results confirmed clear changes in motor system across three different test periods (pre-training, Weeks 2, and Week 4). These changes were reflected in behavior, regional activation, and inter-regional connectivity levels.

Motor Behavior

The statistical analyses on the behavior data indicate that the mean movement rates at Week 2 and Week 4 were significantly greater than pre-training. No significant difference was found between Week 2 and Week 4. These results suggest that the subjects' skill was mainly improved during the first two weeks, predicting significant alterations in the motor system from pre-training to Week 2. However, behavioral equivalence between Week 2 and Week 4 does not imply neural equivalence. It is known that patients can achieve the same behavioral performance as normal controls by recruiting additional neural systems (Mentis et al., 2003; Tomasi et al., 2007). In Week 4, the subjects achieved similar performance as Week 2 using different neural processes as revealed by regional activity and effective connectivity measurements.

Regional Activity

The results on percent signal change implies that the regional activities in M1 and SMA increased on Week 2 and returned to the pre-training level on Week 4. This outcome is consistent with our previous reported results using activation volume on the same subjects (Xiong et al., 2009). Long term motor learning associated changes in regional activity in M1 have been investigated by a number of groups. Karni et al. (1995), who had subjects practice at least 4 weeks, reported that regional activity in M1 increased after 3 weeks of practice. Another study (Hlustik et al., 2004), in which subjects practiced finger sequential movement

for 3 weeks, reported that the regional activity in M1 only increased in the first two weeks; after that, there was an obvious trend of decrease. Thus, our results on M1 activation follows trend observed by (Hlustik et al., 2004). We did not find significant changes in PMd, pVLPFC, CB, and BG although there was a trend of significance in BG. The lack of significant difference in these regions may be due to the relatively small subject number, fairly large age range, and relatively weak signal changes in these regions.

The experimental design is an important factor that could account for different observations in M1 activations across different research groups. An important difference between Karni et al.'s study and the studies by us and Hlustik et al. (2004) is that Karni et al. (1995) used two sampling points while we three and Hlustik et al. (2004) used four. More sampling points should be more capable of capturing the characteristic of dynamic changes in regional activity than less sampling points. This is particularly true if the dynamic changes are not monotonously increasing or decreasing. Apart from the difference in the number of sampling points, the difference in sampling interval (3 weeks for Karni's group, 1 weeks for Hlustik's group, and 2 weeks for our group) may also account for the different results observed by different groups. We observed significant decrease in M1 activation from Week 2 to Week 4, while Hlustik et al. (2004) only observed a trend of decrease from Week 2 to Week 3. This difference may be due to the longer follow-up in our study.

The changes in regional activity are likely due to systematic differences in task difficulty as practice proceeds. Indeed, motor learning is generally acknowledged to proceed in stages (Schmidt and Lee, 2005). When a learner is engaged in a novel task, the cognitive stage of learning is operative. This stage of motor learning is characterized by a high degree of cognitive effort and is the stage in which explicit training (e.g., feedback, instructions) has the greatest effect on learning. This stage of learning is characterized by the need for attention. We would argue that the large increases in regional activity in the first few weeks of learning are an index of the cognitive stage and reflect that behavior gains at the early stage of learning were achieved through recruitment of additional neurons and increment of neural firing.

Over time, the task begins to be well-rehearsed and the need for attention-based learning reduces. This is the hallmark of the associative stage of motor learning in which subjects begin to make subtle changes in how the task is performed because the basics of the task have been learned. During this stage, there is a decline in recruiting extra neurons and neural firing to perform the task (it is becoming functionally more efficient). As such, we found that the regional activity returned to baseline at Week 4 (declined from Week 2 to Week 4). This stage is followed by the autonomous stage, which becomes operative only after months or even years of practice and was probably not a factor in the current experiment. However, the autonomous stage is apparent in expert performers and is marked by the need for little cognitive effort.

Alternatively, the reduced regional activity in M1 and SMA from Week 2 to Week 4 may be due to the use of a rest period as the baseline control condition. Previously, using PET, we have found significant increases in regional cerebral blood flow (rCBF) in both task and resting states within 4 weeks' training (Xiong et al., 2009). Since the regional activations were determined by comparing images acquired during task performance period with those from the resting period, the significant decrease in activation may actually result from a greater increase in activity in the resting state, rather than a decrease in the task state.

To summarize, there is a progression where activation increases at the outset of learning and returns to baseline as the task is learned in terms of regional activation. However, such changes reflect only one aspect of learning. An alternative measure, inter-regional connectivity appears to provide a complementary means of probing long-term changes in brain organization induced by motor practice.

Inter-regional Connectivity

The central topic of the present study is to investigate if there are changes in the strength of connectivity as a function of learning. To answer this question, we constructed a base SEM model, and performed random model search based on it. Based on explicit goodness of fit criteria, only one model could fit the three test periods of data simultaneously. In the fitted model, we could not find anatomical support for a direct connection from PMd to CB in either human or primate studies. The effective connectivity from PMd to CB may quantify an indirect connection (e.g., through a relay). Although anatomical connectivity is generally used to construct SEM models, direct anatomical connectivity is not necessary in quantifying effective connectivity (Haslinger et al., 2002; Petersson et al., 2006).

As according to Hebb's rule (Fuster, 1994; Kandel et al., 1991), synaptic connectivity changes as a function of repetitive firing. This rule states that when one cell fires another repeatedly, the efficiency of exciting the second cell increases over time. Long term potentiation (or, broadly, long term depression) provides strong evidence to support Hebb because the postsynaptic cell's depolarization is coincident with the presynaptic neuron. Thus, Hebb predicted that simultaneous repeated activation of cells will lead to pronounced changes in synaptic strength. High amounts of motor practice have led to repetitive stimulation of the neurons in the motor network. Our data reveal that most path coefficients in the fitted model increased or decreased significantly as the motor training progressed. Thus our results are in accordance with Hebb's law.

Dramatic and inverse modes of changes happened to connections from CB to M1, and from BG to M1. The connection from CB to M1 was weakened across the training (from positive to negative). On the other hand, the connection from BG to M1 was gradually strengthened (from negative to positive). These results suggest that CB is more involved in the motor sequence learning in the earlier stage than the later stages (consolidation, and automatization). In contrast, BG is more and more involved across the learning stages. BG becomes more and more crucial with the progression of the training, and there is an inverse trend for the CB. This observation is consistent with Doyon's model (Doyon and Benali, 2005; Doyon, 2008; Doyon et al., 2009) which predicts that the CB is not essential with extended practice motor sequence, and the long-lasting retention of the motor skill involves representational changes in the striatum and associated motor cortical areas (Doyon and Benali, 2005; Doyon, 2008; Doyon et al., 2009).

Compared to the changes in regional activity (increasing to Week 2 and then returning to baseline), the changes in the path coefficients in the fitted model appear complex. Despite the complexity, it is possible to speculate on the meaning of some changes based on the functional role of the regions and mode of changes in the connectivity between them. Lateral prefrontal cortex has a function of controlling the focus of attention (Hampshire and Owen, 2006). Thus, the gradual reduction of strength from pVLPFC to M1 may be a sign of reduced necessity in paying attention. SMA (Passingham, 1987) and PMd (Weinrich and Wise, 1982) are both functional in movement planning. The connection from SMA to PMd was strengthened across the training, perhaps reflecting increased effectiveness of movement planning. Both SMA (Grafton et al., 1992) and BG (Stern et al., 1983) are critical in movement sequencing. Thus the gradually strengthened connection from BG to SMA may reflect an enhancement of movement sequence control. One of the functions of CB is error correction (Day et al., 1998). The gradually weakened connection from CB to M1 may thus reflect reduced requirement of error correction.

Some meaningful speculations can also be made by combining changes in a number of connections. For example, the gradually weakened connections originated from PFC (to M1, SMA, and CB) suggest the reduced engagement of this high level brain region. In addition, the

gradually strengthened connections (from BG to M1, from BG to SMA, from SMA to PMd, and from PMd to M1) suggest that well-rehearsed or automatic behavior was adaptively integrated at lower levels (e.g., basal ganglia, and PMd) without encumbering higher level brain region like PFC.

Consistent with existing motor learning system model, our connectivity data reveal clear plasticity in the cortico-basal ganglionic and cortico-cerebeller circuits within four weeks training. The changes in the connections suggest gradually reduced processes in attention and error correction and increased effectiveness in motor planning and sequence control occurred as training progressed. The findings in effective connectivity provide a novel approach for understanding the mechanisms of long term motor learning even during phases of practice when changes in behavior and regional activation are no longer apparent. Thus, this technique may provide a more sensitive index of motor skill learning.

Methodological Issues

Apart from training induced functional changes, motor learning could also induce changes in brain structures (Altenmuller, 2003; Draganski et al., 2006; Draganski and May, 2008). Although visuomotor training induced structural changes could happen in some brain regions (for example, occipital-temporal cortex) as early as 7 days (Driemeyer et al., 2008), no structural changes were observed in the motor regions even after 3 months of training (Draganski et al., 2004; Driemeyer et al., 2008). As the intensity of training used in the present study is relatively low (the subjects practiced the tasks for only 15 minutes each day), it is reasonable to hypothesize that training induced structural changes did not occur in the motor system yet in the present study (4 weeks in duration). Even if brain structure does change, the effect of structural changes on functional changes should be minimized in the present study because the location, shape, and size of the VOIs were all same across the three sessions of training.

In the neuroimaging literature, interregional connectivity is generally quantified by using functional connectivity or effective connectivity analysis techniques (Friston, 1994b). Functional connectivity is defined as the correlations between spatially remote neurophysiologic events (Friston, 1994b). Independent component analysis (ICA) (McKeown et al., 1998) and cross-correlation analysis (CCA) are two of the general tools for evaluating functional connectivity. The relative merits of ICA and CCA have been investigated (Ma et al., 2007; Quigley et al., 2002). In contrast to functional connectivity, effective connectivity refers to the influence one neural system exerts over another by quantifying the effect that one region's activity has on that of another region (Friston, 1994b). A multitude of techniques are currently available for quantifying effective connectivity. Among them, SEM (Buchel and Friston, 1997; McIntosh and Gonzalez-Lima, 1994), dynamical causal modeling (DCM) (Friston et al., 2003; Stephan et al., 2007), and Granger causality analysis (GCA) (Goebel et al., 2003; Roebroeck et al., 2005) are the methods that are extensively used. GCA is a data-driven approach which does not rely on a priori information to specify connections. Although GCA has been used as a method for effective connectivity analysis, whether it measures effective connectivity or functional connectivity is still in debate (David, 2009; Friston, 2009a; Friston, 2009b; Roebroeck et al., 2009a; Roebroeck et al., 2009b). In contrast to GCA, DCM and SEM are both hypothesis driven methods. Two of the most important features that DCM possesses are (Friston et al., 2003; Stephan et al., 2007): the connections in DCM are at the neuronal level rather than the measured signal level; and the modulation effects of experimental conditions can be explicitly evaluated. DCM generally requires a sensory driving input, which is not available in the present study. Compared to GCA and DCM, SEM has a relatively long history in its application to connectivity analysis in neuroimaging literature, and has been widely accepted as a system level modeling approach for effective connectivity

analysis. A recent study has shown that SEM is a reliable and competent method for measuring effective connectivity when the causal structure is well specified (Witt and Meyerand, 2009).

A SEM model is an approximation of a real neural system. The tradeoff between model complexity and interpretability is a concern for SEM modeling approach. A complicated model is better at approximating a real neural system, but it is worse at providing interpretable results (de Marco et al., 2009). For example, the real connection from CB to BG is through the thalamus, but we have to treat it as an intermediate node and did not include it in our models. Fortunately, this step does not affect us in evaluating the trend of changes in the effective connectivity among the end nodes (Grefkes et al., 2008; Petersson et al., 2006), the target of this study. The anatomical connections between some selected regions appear to be bidirectional, but these connections were chosen as unidirectional due to the consideration of model stability (Schlosser et al., 2006).

SEM models can be tested subject by subject (Buchel and Friston, 1997) or pool the data over all the subjects and then test one model by group (Grafton et al., 1994). The former approach allows the investigator to observe inter-subject variability in the path coefficients, but it is generally difficult to generalize the results to a group level (Buchel and Friston, 1997). In addition, this approach assumes that the subjects implement a sufficiently similar functional organization which generally can not be reached in practice. The latter approach allows one to evaluate the results in a group level. However, the confounding effect can be introduced because of the difficulty in distinguishing between variances introduced by different subjects (Buchel and Friston, 1997). Possessing advantages as well disadvantages, these two approaches are used in parallel (Boucard et al., 2007). In this study, our focus is general effects of motor skill learning on normal subjects, rather than on each individual subject, group level modeling is thus preferred.

The sample size is an important issue for a SEM study. Theoretically, the more sample points, the more accurate results SEM can provide. However, to our best knowledge, there is no theoretical criterion on how to determine the optimal number of sample points for SEM. A recent empirical study has shown that the results of SEM are reliable when the number of sample points is over 100 (Boucard et al., 2007). In the present study, our sample size is 2300 (230 temporal sample points for each subjects) which is much larger than 100. It is reasonable to believe that the number of sample points did not have negative effect on the SEM results in the present study.

One limitation of the present study is that subjects performed the training sequence as quick as possible in the training sessions, but followed a particular pace during scanning. This was to minimize the confounding effect due to different movement rates because a previous study have showed clear linear relation between neural activity within sensorimotor cortex and movement frequency (Jancke et al., 1998). Furthermore, we can not rule out the possible confound effect that some of the activity observed in the motor regions might be related to some sort of “inhibition of movement speed”. However, the video analysis indicates that the improvement in movement rate is chiefly due to a decrease in inter-movement delays. The contribution coming from increased finger velocity is only minor. This result reduced the possibility of inhibition activation. In addition, although we required the subjects to perform the tasks with a fixed rate in scanner, there was no guarantee that the subjects followed this instruction. Therefore it is possible that there existed confounding effect due to different movement rate. This is another limitation of this study.

Summary

We have investigated motor learning by examining the changes in behavior performance, regional activity in specific regions, and their effective connectivity. The increasing-then-

decreasing mode of change in regional activity may reflect that the brain returned to baseline status after the skill was well-learned. Alternatively, the significant decrease in activation at the end of training may result from simultaneous plasticity in task and resting states. In the fitted SEM model, the changes in the strength of the effective connectivity reflect long term reorganization of the skilled motor network. We argue that connectivity measures are a more sensitive index of long term learning and that they provide information when some behavioral measures and regional activities cannot properly capture changes in learning. We suggest that the performance gain was achieved by dynamically reorganizing the inter-regional connectivity in the motor network. Although we have speculated on some of the connections, the meanings of most connections are still unknown. More research is thus warranted to assess these connections.

4. Methods and Materials

Subjects

Thirteen healthy normal volunteers participated in our study, and ten of them (5 male and 5 female, ranging from 18 to 45 years old) completed the experiment. Self-report indicated that none of them was a professional typist or musician. All subjects were right-handed, with no known neurological and psychiatric disorders, by self-report. Informed consent was obtained from each subject before beginning the study. The study was approved by the Institutional Review Board of University of Iowa, Iowa city, Iowa and University of Texas Health Science Center, San Antonio, Texas.

Task Paradigm

We used a motor sequence learning task previously used by (Karni et al., 1995). The fingers of the subject's left hand were opposed to the thumb in specific sequences. The left (or non-dominant) hand was chosen to ensure that subjects were involved in learning the task and did not acquire skill too quickly (i.e., after one session) (Hund-Georgiadis and von Cramon, 1999). During the task, subjects performed one of two specific sequences (Sequence A and B) which were mirror images of one another without visual feedback. The order of finger movement in Sequence A is 5, 2, 4, 3, 5 (fingers are numbered as: index finger, 2; middle finger, 3; ring finger, 4; and little finger, 5). In Sequence B, the order of finger movement is 5, 3, 4, 2, 5. Each subject was randomly assigned to either Sequence A or B as the training sequence, and the other sequence was used as the control sequence. Five subjects (Group A) were randomly assigned Sequence A as the training sequence, and the other five subjects (Group B) were assigned Sequence B. All subjects practiced the training sequence for four weeks (including weekend). One practice session occurred each day for a total of 15 minutes. Subjects were instructed that during practice they were to perform the sequence as accurately and quickly as possible. Each practice session was recorded by a video camera. Video recordings were reviewed in slow motion by an observer, who scored the number of correct sequences completed (movement rate) and the number of errors (out-of-sequence movements) per session. In addition to the practice sessions, there were three sessions performed during fMRI scanning. The first scanning session was performed just prior to the onset of training (pre-training). After two weeks of practice, there was a second scanning session (Week 2). Finally, the last scanning session occurred immediately after 4 weeks of practice (Week 4). The control sequence was only performed during scanning.

There were six functional imaging scans in each of these sessions. Scan 1 and Scan 6 were resting state scans. Scan 2 to Scan 5 were task performance scans, lasting 8 min each. In each task performance scan, a block design was used: two 2-min finger tapping periods were interposed with 2-min rest periods. The task blocks consisted of either the training task or the control sequence, randomized across the session. To minimize the confound effects of different

movement rates (Jancke et al., 1998) (both inter-subject and inter-scan), subjects were required to perform the tasks with a speed of approximately two movements per second during scanning (cued by scanner acoustic noise). Their compliance was monitored by a research assistant through a scanner-built-in video device.

Data Acquisition

During scanning, the subjects lay supine with their heads supported by a foam-padded, hemicylindrical head holder. Each subject's head was immobilized within a tightly fitting thermally molded plastic facial mask extending from hairline to chin. The fMRI images were acquired on an Elscint Prestige 2-T whole-body MRI scanner (Elscint Prestige, Haifa, Israel). In each task performance scan, a total of 240 volumes of MRI images were acquired in a transverse plane using a T2*-weighted gradient-echo echo-planar-imaging (EPI) sequence (repetition time (TR) = 2 s, echo time (TE) = 45 ms, flip angle (α) = 90°, FOV = 411 mm×229 mm, 72 × 72 voxels image matrix, 3.28 × 3.28 mm² in-plane voxel resolution, 16 contiguous fMRI slices, slice thickness = 5 mm, interslice gap = 1 mm, receive bandwidth = 12.21Hz). At the end of the fMRI data collection, spin echo, T1-weighted anatomical images (TR = 33 ms, TE = 12 ms, flip angle (α) = 60°, 16 contiguous slices, slice thickness = 5 mm, interslice gap = 1 mm, matrix size = 256 × 256 voxels, 1 mm×1 mm voxel resolution) in the same slice positions were acquired to facilitate the precise determination of the structures corresponding to the functional activation foci. Off-line reconstruction algorithms were used to reconstruct the echo-planar images.

Preprocesses

The first 10 fMRI images of each run were discarded to allow MRI signal to reach a steady state. SPM2 (The Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, <http://www.fil.ion.ucl.ac.uk>) and in-house MATLAB (The MathWorks, Inc., Natick, MA) programs were used in data preprocessing. The fMRI images were spatially realigned to the first volume to correct the bias due to head movements. The fMRI images were co-registered with the T1 image and normalized to the standard T1 template volume. After spatial normalization, a linear drift correction (Tanabe et al., 2002) was applied to all functional images. To increase the signal-noise-ratio, the data were spatially smoothed by an isotropic Gaussian filter with a full-width at half-maximum (FWHM) of 4.8 mm. All the programs were run on a platform of MATLAB 7.0.

Data Processing

Statistical parametric images (SPIs) were created by using the method of cross correlation analysis (Friston, 1994a; Xiong et al., 1999; Xiong et al., 2009), in which hemodynamical responses were detected by evaluating the correlation between the time course of each voxel and a reference function (a boxcar function convolved with a hemodynamical response function of BOLD). A cluster of voxels in a SPI image was considered to be part of an active area if it simultaneously satisfies the following conditions: (I) the intensity of each element voxel was over a specified threshold (2.5) ($p < 0.02$, uncorrected); (II) the number of voxels was over 10.

SEM Network Models

The regions selected for constructing SEM models were based on the detected activation networks. M1, SMA, PMd, pVLPFC, BG, and CB were consistently active regions across subjects and the three test points. All these regions are known to be associated with motor skill learning (Bisley and Goldberg, 2003; Fuster, 1994; Grafton et al., 1998; Jueptner et al., 1997a; Jueptner et al., 1997b; Ungerleider et al., 2002; Willingham, 1998). In addition, most of these regions are components of some motor skill learning models (Doyon and Ungerleider,

2002; Doyon and Benali, 2005; Doyon, 2008; Hikosaka et al., 2002; Willingham, 1998). Thus these six regions were included into the SEM models.

The connections in SEM models are generally specified based on known anatomical connections found in primates (McIntosh and Gonzalez-Lima, 1994). One drawback of this approach is that it may lose some connections that are preferred by the model but have yet to be discovered or indirectly connected. To deal with this problem, we decided to borrow the idea of model searching (Peltier et al., 2007; Zhuang et al., 2005). The model search was based on a base model with three initial connections (the connections from SMA to M1, from SMA to PMd, and from PMd to M1). These connections have been previously shown to be essential for motor execution (Solodkin et al., 2004). Apart from the initial connections, a connection was added to the base model if (I) it improved model fit, and (II) there exists such an anatomical connection in primates. The base model used in this study is depicted in Figure 1. The references (anatomical connectivity studies in primates) supporting the connections in the base model are listed in Table 1. After the base model is available, the model search was conducted under three principles: (I), the search was based on the base model; (II), the number of connections was kept constant (i.e., the number of connections in the base model); (III), a random disconnection of one existent path and random connection of a nonexistent path (the disconnected and connected path are never repeated across models). Based on the three principles, a total of 209 models (including the base model) were constructed and tested. The model which fitted the three sessions of data simultaneously was considered as the best model. If more than one models fitted the three sessions of data simultaneously, the model with the best fit parameters (please see the section of Structural Equation Modeling for fit parameters) was considered as the best model.

Volumes of Interest

Given that our subjects performed the task with their left hands, and given the detected activation networks were dominant in right hemisphere (left hemisphere for CB), the volumes of interest (VOIs) for M1, PMd, pVLPFC, and BG were chosen in right hemisphere; the VOIs for CB was chosen in the left hemisphere. SMA was not limited in right or left because the detected activations in left and right SMA generally spanned together. The VOIs were selected subject by subject. The locations of the VOIs were mainly determined by functional activations, with the assistance of Anatomical Automatic Labeling (Tzourio-Mazoyer et al., 2002), and SPM Anatomy Toolbox (Eickhoff et al., 2005; Eickhoff et al., 2007; Toga et al., 2006). Each VOI is a box with the center defined as the center-of-mass of the activation. The size of each VOI was standardized and was $5 \times 5 \times 5$ voxels (1000 mm^3). The training-induced change in each VOI was assessed by evaluating cross session percent signal change (task vs. resting) within this VOI. A one-way ANOVA, with scanning time points as factors and with percent signal change across different subjects as repeated measurements, was then performed for each VOI.

Structural Equation Modeling

A complete SEM model can be decomposed into a measurement model and a structure model (Gonzalez-Lima and McIntosh, 1994). The measurement model is expressed as $x = LX + E$. Here x is a 6×1 vector of indicator variables of the selected regions (i.e., M1, SMA, and so on); X is a 6×1 vector of latent variables of the selected regions; L is a 6×6 diagonal matrix, each diagonal element of L denotes the degree to which a latent variable is expressed by a indicator variable; and E is a 6×1 vector of measurement error. The structured model can be expressed as $X = \beta X + \Psi$. Here β is a 6×6 matrix, and Ψ is a 6×1 vector of residual effects. The causal structure is defined by matrix β and the path coefficients were contained in it. The elements in matrix β that are fixed at zeros indicate no anatomical connections. The effective connectivity was analyzed by estimating the non-zero path coefficients. A path coefficient represents the

change in activity of a target area for a unit change in activity of a source area while the activities in other areas in the model are held constant (McIntosh and Gonzalez-Lima, 1994).

A measurement covariance matrix used for SEM analysis was generated based on the indicator variable, x , in each of the three sessions of fMRI data. To reduce the inter-scan variability of fMRI signal intensity, the time courses of each subject were normalized to unit variances (Buchel and Friston, 1997). The normalized time courses of individual subjects were concatenated into a group matrix and a group covariance matrix was then computed.

LISREL 8.53 (Scientific Software International, Inc) for Windows (Microsoft, Inc) was used to solve the SEM equations. The parameters were estimated by using an iterative maximum likelihood algorithm which minimizes the difference between the predicted covariance and the measurement covariance. Hierarchical model building strategy, in which a smaller part of the model was estimated first, more paths or regions were then added to the complete model after the parameters in this smaller part of model were fixed at those estimates (McIntosh and Gonzalez-Lima, 1994), was used when the number of parameters to be estimated exceeds the number of observed covariances. Path coefficients were standardized by specifying SS (standard solution) LISREL output option. The goodness of model fit was evaluated by using chi-square minimum fit function (χ^2), P-value, and root mean square error of approximation (RMSEA) (Schlosser et al., 2006).

Group differences between various models (including pair-wise comparison of a path coefficient between groups) were evaluated by using a stacked model approach (Buchel and Friston, 1997; Grafton et al., 1994; McIntosh and Gonzalez-Lima, 1994). This was done by comparing a free model, in which all the connections were allowed to vary between the groups, to a constrained model in which a given connection was forced to be equal for the groups (Buchel and Friston, 1997; Schlosser et al., 2003). The comparison was realized by evaluating the difference ($\Delta\chi^2$) (obtained by subtracting the χ^2 value of the free model from that of the constrained model) with a degree of freedom equal to the difference in the degrees of freedom of the constrained model and the free model (Buchel and Friston, 1997; Schlosser et al., 2003).

Acknowledgments

This work is financially supported by National Science Foundation (NSF) (BCS 05-09626) and National Institute of Health (NIH) (5 RO1 NS046082) grants.

Abbreviations

SEM	structural equation modeling
M1	primary motor area
SMA	supplementary motor area
PMd	dorsal premotor cortex
BG	basal ganglia
CB	cerebellum
pVLPFC	posterior ventrolateral prefrontal cortex
PFC	prefrontal cortex
VOI	volumes of interest
rCBF	regional cerebral blood flow

DCM	dynamical causal modeling
GCA	Granger causal analysis
ICA	independent component analysis
CCA	cross correlation analysis.

References

- Altenmuller E. Focal dystonia: advances in brain imaging and understanding of fine motor control in musicians. *Hand Clin* 2003;19:523–38. xi. [PubMed: 12945651]
- Balaban PM. Cellular mechanisms of behavioral plasticity in simple nervous systems. *Neurosci Behav Physiol* 2008;38:453–9. [PubMed: 18607755]
- Bisley JW, Goldberg ME. Neuronal activity in the lateral intraparietal area and spatial attention. *Science* 2003;299:81–6. [PubMed: 12511644]
- Boucard A, Marchand A, Nogues X. Reliability and validity of structural equation modeling applied to neuroimaging data: a simulation study. *J Neurosci Methods* 2007;166:278–92. [PubMed: 17825426]
- Buchel C, Friston KJ. Modulation of connectivity in visual pathways by attention: cortical interactions evaluated with structural equation modelling and fMRI. *Cereb Cortex* 1997;7:768–78. [PubMed: 9408041]
- Catalan MJ, Ishii K, Honda M, Samii A, Hallett M. A PET study of sequential finger movements of varying length in patients with Parkinson's disease. *Brain* 1999;122(Pt 3):483–95. [PubMed: 10094257]
- Chouinard PA, Leonard G, Paus T. Changes in effective connectivity of the primary motor cortex in stroke patients after rehabilitative therapy. *Exp Neurol* 2006;201:375–87. [PubMed: 16828743]
- David O. fMRI connectivity, meaning and empiricism Comments on: Roebroeck et al. The identification of interacting networks in the brain using fMRI: Model selection, causality and deconvolution. *Neuroimage*. 2009
- Day BL, Thompson PD, Harding AE, Marsden CD. Influence of vision on upper limb reaching movements in patients with cerebellar ataxia. *Brain* 1998;121(Pt 2):357–72. [PubMed: 9549511]
- de Marco G, Vrignaud P, Destrieux C, de Marco D, Testelin S, Devauchelle B, Berquin P. Principle of structural equation modeling for exploring functional interactivity within a putative network of interconnected brain areas. *Magn Reson Imaging* 2009;27:1–12. [PubMed: 18584986]
- Doyon J, Owen AM, Petrides M, Sziklas V, Evans AC. Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography. *Eur J Neurosci* 1996;8:637–48. [PubMed: 9081615]
- Doyon J.; Ungerleider, LG. Functional anatomy of motor skill learning. In: Squire, LR.; Schacter, DL., editors. *Neuropsychology of Memory*. Guilford Press; New York: 2002.
- Doyon J, Benali H. Reorganization and plasticity in the adult brain during learning of motor skills. *Curr Opin Neurobiol* 2005;15:161–7. [PubMed: 15831397]
- Doyon J. Motor sequence learning and movement disorders. *Curr Opin Neurol* 2008;21:478–83. [PubMed: 18607210]
- Doyon J, Bellec P, Amsel R, Penhune V, Monchi O, Carrier J, Lehericy S, Benali H. Contributions of the basal ganglia and functionally related brain structures to motor learning. *Behav Brain Res* 2009;199:61–75. [PubMed: 19061920]
- Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. Neuroplasticity: changes in grey matter induced by training. *Nature* 2004;427:311–2. [PubMed: 14737157]
- Draganski B, Gaser C, Kempermann G, Kuhn HG, Winkler J, Buchel C, May A. Temporal and spatial dynamics of brain structure changes during extensive learning. *J Neurosci* 2006;26:6314–7. [PubMed: 16763039]
- Draganski B, May A. Training-induced structural changes in the adult human brain. *Behav Brain Res* 2008;192:137–42. [PubMed: 18378330]

- Driemeyer J, Boyke J, Gaser C, Buchel C, May A. Changes in gray matter induced by learning--revisited. *PLoS ONE* 2008;3:e2669. [PubMed: 18648501]
- Duncan J, Humphreys G, Ward R. Competitive brain activity in visual attention. *Curr Opin Neurobiol* 1997;7:255–61. [PubMed: 9142748]
- Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage* 2005;25:1325–35. [PubMed: 15850749]
- Eickhoff SB, Paus T, Caspers S, Grosbras MH, Evans AC, Zilles K, Amunts K. Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. *Neuroimage* 2007;36:511–21. [PubMed: 17499520]
- Eickhoff SB, Dafotakis M, Grefkes C, Shah NJ, Zilles K, Piza-Katzer H. Central adaptation following heterotopic hand replantation probed by fMRI and effective connectivity analysis. *Exp Neurol* 2008;212:132–44. [PubMed: 18501895]
- Fontan-Lozano A, Lopez-Lluch G, Delgado-Garcia JM, Navas P, Carrion AM. Molecular bases of caloric restriction regulation of neuronal synaptic plasticity. *Mol Neurobiol* 2008;38:167–77. [PubMed: 18759009]
- Friston K. Causal modelling and brain connectivity in functional magnetic resonance imaging. *PLoS Biol* 2009a;7:e33. [PubMed: 19226186]
- Friston K. Dynamic causal modeling and Granger causality Comments on: The identification of interacting networks in the brain using fMRI: Model selection, causality and deconvolution. *Neuroimage*. 2009b
- Friston KJ, Frith CD, Passingham RE, Liddle PF, Frackowiak RS. Motor practice and neurophysiological adaptation in the cerebellum: a positron tomography study. *Proc Biol Sci* 1992;248:223–8. [PubMed: 1354360]
- Friston KJ. Statistical parametric maps in functional imaging: a general linear approach. *Human Brain Mapping* 1994a;2:189–210.
- Friston KJ. Functional and effective connectivity in neuroimaging: a synthesis. *Human Brain Mapping* 1994b;2:56–78.
- Friston KJ, Harrison L, Penny W. Dynamic causal modelling. *Neuroimage* 2003;19:1273–302. [PubMed: 12948688]
- Fuster, JM. Memory in the cerebral cortex: Approach to neural networks in the human and nonhuman primate. MIT Press; 1994.
- Goebel R, Roebroeck A, Kim DS, Formisano E. Investigating directed cortical interactions in time-resolved fMRI data using vector autoregressive modeling and Granger causality mapping. *Magn Reson Imaging* 2003;21:1251–61. [PubMed: 14725933]
- Gonzalez-Lima F, McIntosh AR. Neural network interactions related to auditory learning analyzed with structural equation modeling. *Human Brain Mapping* 1994;2:23–44.
- Grafton ST, Mazziotta JC, Woods RP, Phelps ME. Human functional anatomy of visually guided finger movements. *Brain* 1992;115(Pt 2):565–87. [PubMed: 1606482]
- Grafton ST, Sutton J, Couldwell W, Lew M, Waters C. Network analysis of motor system connectivity in parkinson's disease: modulation of thalamocortical interactions after pallidotomy. *Human Brain Mapping* 1994;2:45–55.
- Grafton ST, Hazeltine E, Ivry RB. Abstract and effector-specific representations of motor sequences identified with PET. *J Neurosci* 1998;18:9420–8. [PubMed: 9801380]
- Grefkes C, Eickhoff SB, Nowak DA, Dafotakis M, Fink GR. Dynamic intra- and interhemispheric interactions during unilateral and bilateral hand movements assessed with fMRI and DCM. *Neuroimage* 2008;41:1382–94. [PubMed: 18486490]
- Grol MJ, Majdandzic J, Stephan KE, Verhagen L, Dijkerman HC, Bekkering H, Verstraten FA, Toni I. Parieto-frontal connectivity during visually guided grasping. *J Neurosci* 2007;27:11877–87. [PubMed: 17978028]
- Hallett M. Plasticity of the human motor cortex and recovery from stroke. *Brain Res Brain Res Rev* 2001;36:169–74. [PubMed: 11690613]
- Hampshire A, Owen AM. Fractionating attentional control using event-related fMRI. *Cereb Cortex* 2006;16:1679–89. [PubMed: 16436686]

- Haslinger B, Erhard P, Weilke F, Ceballos-Baumann AO, Bartenstein P, Graf von Einsiedel H, Schwaiger M, Conrad B, Boecker H. The role of lateral premotor-cerebellar-parietal circuits in motor sequence control: a parametric fMRI study. *Brain Res Cogn Brain Res* 2002;13:159–68. [PubMed: 11958958]
- Hikosaka O, Nakamura K, Sakai K, Nakahara H. Central mechanisms of motor skill learning. *Curr Opin Neurobiol* 2002;12:217–22. [PubMed: 12015240]
- Hlustik P, Solodkin A, Noll DC, Small SL. Cortical plasticity during three-week motor skill learning. *J Clin Neurophysiol* 2004;21:180–91. [PubMed: 15375348]
- Holland SK, Vannest J, Mecoli M, Jacola LM, Tillema JM, Karunanayaka PR, Schmithorst VJ, Yuan W, Plante E, Byars AW. Functional MRI of language lateralization during development in children. *Int J Audiol* 2007;46:533–51. [PubMed: 17828669]
- Honey GD, Suckling J, Zelaya F, Long C, Routledge C, Jackson S, Ng V, Fletcher PC, Williams SC, Brown J, Bullmore ET. Dopaminergic drug effects on physiological connectivity in a human cortico-striato-thalamic system. *Brain* 2003;126:1767–81. [PubMed: 12805106]
- Hund-Georgiadis M, von Cramon DY. Motor-learning-related changes in piano players and non-musicians revealed by functional magnetic-resonance signals. *Exp Brain Res* 1999;125:417–25. [PubMed: 10323287]
- Huxlin KR. Perceptual plasticity in damaged adult visual systems. *Vision Res* 2008;48:2154–66. [PubMed: 18582488]
- Ito M. Cerebellar long-term depression: characterization, signal transduction, and functional roles. *Physiol Rev* 2001;81:1143–95. [PubMed: 11427694]
- Jancke L, Specht K, Mirzazade S, Loose R, Himmelbach M, Lutz K, Shah NJ. A parametric analysis of the 'rate effect' in the sensorimotor cortex: a functional magnetic resonance imaging analysis in human subjects. *Neurosci Lett* 1998;252:37–40. [PubMed: 9756353]
- Jueptner M, Frith CD, Brooks DJ, Frackowiak RS, Passingham RE. Anatomy of motor learning. II. Subcortical structures and learning by trial and error. *J Neurophysiol* 1997a;77:1325–37. [PubMed: 9084600]
- Jueptner M, Stephan KM, Frith CD, Brooks DJ, Frackowiak RS, Passingham RE. Anatomy of motor learning. I. Frontal cortex and attention to action. *J Neurophysiol* 1997b;77:1313–24. [PubMed: 9084599]
- Kandel, ER.; Schwartz, JH.; Jessel, TM. *Principles of Neural Science*. 3rd edn. Elsevier; New York: 1991.
- Karni A, Meyer G, Jezzard P, Adams MM, Turner R, Ungerleider LG. Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature* 1995;377:155–8. [PubMed: 7675082]
- Kasess CH, Windischberger C, Cunningham R, Lanzenberger R, Pezawas L, Moser E. The suppressive influence of SMA on M1 in motor imagery revealed by fMRI and dynamic causal modeling. *Neuroimage* 2008;40:828–37. [PubMed: 18234512]
- Laird AR, Robbins JM, Li K, Price LR, Cykowski MD, Narayana S, Laird RW, Franklin C, Fox PT. Modeling motor connectivity using TMS/PET and structural equation modeling. *Neuroimage* 2008;41:424–36. [PubMed: 18387823]
- Lehericy S, Benali H, Van de Moortele PF, Pelegriani-Issac M, Waechter T, Ugurbil K, Doyon J. Distinct basal ganglia territories are engaged in early and advanced motor sequence learning. *Proc Natl Acad Sci U S A* 2005;102:12566–71. [PubMed: 16107540]
- Ma L, Wang B, Chen X, Xiong J. Detecting functional connectivity in the resting brain: a comparison between ICA and CCA. *Magn Reson Imaging* 2007;25:47–56. [PubMed: 17222714]
- Martin SJ, Morris RG. Cortical plasticity: It's all the range! *Curr Biol* 2001;11:R57–9. [PubMed: 11231142]
- McIntosh AR, Gonzalez-Lima F. Structural equation modeling and its application to network analysis in functional brain imaging. *Human Brain Mapping* 1994;2:2–22.
- McKeown MJ, Makeig S, Brown GG, Jung TP, Kindermann SS, Bell AJ, Sejnowski TJ. Analysis of fMRI data by blind separation into independent spatial components. *Hum Brain Mapp* 1998;6:160–88. [PubMed: 9673671]

- Mentis MJ, Dhawan V, Nakamura T, Ghilardi MF, Feigin A, Edwards C, Ghez C, Eidelberg D. Enhancement of brain activation during trial-and-error sequence learning in early PD. *Neurology* 2003;60:612–9. [PubMed: 12601101]
- Nezafat R, Shadmehr R, Holcomb HH. Long-term adaptation to dynamics of reaching movements: a PET study. *Exp Brain Res* 2001;140:66–76. [PubMed: 11500799]
- Palmer SJ, Eigenraam L, Hoque T, McCaig RG, Troiano A, McKeown MJ. Levodopa-sensitive, dynamic changes in effective connectivity during simultaneous movements in Parkinson's disease. *Neuroscience* 2009;158:693–704. [PubMed: 18722512]
- Passingham RE. Two cortical systems for directing movement. *Ciba Found Symp* 1987;132:151–64. [PubMed: 3322713]
- Peltier S, Stilla R, Mariola E, LaConte S, Hu X, Sathian K. Activity and effective connectivity of parietal and occipital cortical regions during haptic shape perception. *Neuropsychologia* 2007;45:476–83. [PubMed: 16616940]
- Penhune VB, Doyon J. Dynamic cortical and subcortical networks in learning and delayed recall of timed motor sequences. *J Neurosci* 2002;22:1397–406. [PubMed: 11850466]
- Petersson KM, Gisselgard J, Gretzer M, Ingvar M. Interaction between a verbal working memory network and the medial temporal lobe. *Neuroimage* 2006;33:1207–17. [PubMed: 17011215]
- Poldrack RA. Can cognitive processes be inferred from neuroimaging data? *Trends Cogn Sci* 2006;10:59–63. [PubMed: 16406760]
- Quigley MA, Haughton VM, Carew J, Cordes D, Moritz CH, Meyerand ME. Comparison of independent component analysis and conventional hypothesis-driven analysis for clinical functional MR image processing. *AJNR Am J Neuroradiol* 2002;23:49–58. [PubMed: 11827875]
- Roebroeck A, Formisano E, Goebel R. Mapping directed influence over the brain using Granger causality and fMRI. *Neuroimage* 2005;25:230–42. [PubMed: 15734358]
- Roebroeck A, Formisano E, Goebel R. The identification of interacting networks in the brain using fMRI: Model selection, causality and deconvolution. *Neuroimage*. 2009a
- Roebroeck A, Formisano E, Goebel R. Reply to Friston and David After comments on: The identification of interacting networks in the brain using fMRI: Model selection, causality and deconvolution. *Neuroimage*. 2009b
- Rogers BP, Carew JD, Meyerand ME. Hemispheric asymmetry in supplementary motor area connectivity during unilateral finger movements. *Neuroimage* 2004;22:855–9. [PubMed: 15193615]
- Rowe J, Stephan KE, Friston K, Frackowiak R, Lees A, Passingham R. Attention to action in Parkinson's disease: impaired effective connectivity among frontal cortical regions. *Brain* 2002;125:276–89. [PubMed: 11844728]
- Sakurai Y. Population coding by cell assemblies--what it really is in the brain. *Neurosci Res* 1996;26:1–16. [PubMed: 8895888]
- Sanes JN, Donoghue JP. Plasticity and primary motor cortex. *Annu Rev Neurosci* 2000;23:393–415. [PubMed: 10845069]
- Schlosser R, Gesierich T, Kaufmann B, Vucurevic G, Hunsche S, Gawehn J, Stoeter P. Altered effective connectivity during working memory performance in schizophrenia: a study with fMRI and structural equation modeling. *Neuroimage* 2003;19:751–63. [PubMed: 12880804]
- Schlosser RG, Wagner G, Sauer H. Assessing the working memory network: studies with functional magnetic resonance imaging and structural equation modeling. *Neuroscience* 2006;139:91–103. [PubMed: 16324797]
- Schmidt RA, Lee T. *Motor Control and Learning: A Behavioral Emphasis*. 2005
- Solodkin A, Hlustik P, Chen EE, Small SL. Fine modulation in network activation during motor execution and motor imagery. *Cereb Cortex* 2004;14:1246–55. [PubMed: 15166100]
- Stephan KE, Harrison LM, Kiebel SJ, David O, Penny WD, Friston KJ. Dynamic causal models of neural system dynamics: current state and future extensions. *J Biosci* 2007;32:129–44. [PubMed: 17426386]
- Stern Y, Mayeux R, Rosen J, Ilson J. Perceptual motor dysfunction in Parkinson's disease: a deficit in sequential and predictive voluntary movement. *J Neurol Neurosurg Psychiatry* 1983;46:145–51. [PubMed: 6842218]

- Tanabe J, Miller D, Tregellas J, Freedman R, Meyer FG. Comparison of detrending methods for optimal fMRI preprocessing. *Neuroimage* 2002;15:902–7. [PubMed: 11906230]
- Toga AW, Thompson PM, Mori S, Amunts K, Zilles K. Towards multimodal atlases of the human brain. *Nat Rev Neurosci* 2006;7:952–66. [PubMed: 17115077]
- Tomasi D, Goldstein RZ, Telang F, Maloney T, Alia-Klein N, Caparelli EC, Volkow ND. Thalamo-cortical dysfunction in cocaine abusers: implications in attention and perception. *Psychiatry Res* 2007;155:189–201. [PubMed: 17582746]
- Toni I, Passingham RE. Prefrontal-basal ganglia pathways are involved in the learning of arbitrary visuomotor associations: a PET study. *Exp Brain Res* 1999;127:19–32. [PubMed: 10424411]
- Toni I, Rowe J, Stephan KE, Passingham RE. Changes of cortico-striatal effective connectivity during visuomotor learning. *Cereb Cortex* 2002;12:1040–7. [PubMed: 12217967]
- Tononi G, Sporns O, Edelman GM. A measure for brain complexity: relating functional segregation and integration in the nervous system. *Proc Natl Acad Sci U S A* 1994;91:5033–7. [PubMed: 8197179]
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2002;15:273–89. [PubMed: 11771995]
- Ungerleider LG, Doyon J, Karni A. Imaging brain plasticity during motor skill learning. *Neurobiol Learn Mem* 2002;78:553–64. [PubMed: 12559834]
- Weinrich M, Wise SP. The premotor cortex of the monkey. *J Neurosci* 1982;2:1329–45. [PubMed: 7119878]
- Willingham DB. A neuropsychological theory of motor skill learning. *Psychol Rev* 1998;105:558–84. [PubMed: 9697430]
- Winstein CJ, Merians AS, Sullivan KJ. Motor learning after unilateral brain damage. *Neuropsychologia* 1999;37:975–87. [PubMed: 10426521]
- Witt ST, Meyerand ME. The Effects of Computational Method, Data Modeling, and TR on Effective Connectivity Results. *Brain Imaging Behav* 2009;3:220–231. [PubMed: 19714255]
- Xiong J, Parsons LM, Gao JH, Fox PT. Interregional connectivity to primary motor cortex revealed using MRI resting state images. *Hum Brain Mapp* 1999;8:151–6. [PubMed: 10524607]
- Xiong J, Ma L, Wang B, Narayana S, Duff EP, Egan GF, Fox PT. Long-term motor training induced changes in regional cerebral blood flow in both task and resting states. *Neuroimage* 2009;45:75–82. [PubMed: 19100845]
- Zhuang J, LaConte S, Peltier S, Zhang K, Hu X. Connectivity exploration with structural equation modeling: an fMRI study of bimanual motor coordination. *Neuroimage* 2005;25:462–70. [PubMed: 15784425]

Figure 1.

The base SEM model. M1 = primary motor area, SMA = supplementary motor area, PMd = dorsal premotor cortex, PFC = posterior ventrolateral prefrontal cortex, BG = basal ganglia, and CB = cerebellum.

Figure 2.

Learning curve for the trained sequence. The curve depicts the statistical performance (mean and standard deviation of the movement rate, which was quantified as sequences per-minute) as a function of time.

Figure 3. Averaged (across subjects) fMRI activation maps (threshold: $Z=2.5$). Data were acquired on pre-training (top panel), Week 2 (middle panel), and Week 4 (bottom panel). Right side of the image corresponds to the left side of the brain.

Figure 4.

Changes in percent signal change in the six VOIs as training progressed. The percent signal changes in M1 and SMA first increased and then returned to the pre-training state. The error bars represent standard error of measurement. M1 = primary motor area, SMA = supplementary motor area, PMd = dorsal premotor cortex, PFC = posterior ventrolateral prefrontal cortex, BG = basal ganglia, and CB = cerebellum.

Figure 5.

The fitted model at (1) pre-training, (2) Week 2, and (3) Week 4. Different types of lines were used to provide rough information of path coefficients. M1 = primary motor area, SMA = supplementary motor area, PMd = dorsal premotor cortex, PFC = posterior ventrolateral prefrontal cortex, BG = basal ganglia, and CB = cerebellum.

Table 1

Anatomical connectivity found in primates and corresponding references. M1 = primary motor area, SMA = supplementary motor area, PMd = dorsal premotor cortex, PFC = prefrontal cortex, BG=basal ganglia, and CB=cerebellum.

Connection	Reference
M1→BG	Parent and Parent (2006)
M1→CB	Kelly and Strick (2003)
SMA→M1	Rouiller et al. (1994)
SMA→PMd	Rouiller et al. (1994)
SMA→PFC	Bates and Goldman-Rakic (1993)
SMA→BG	Inase et al. (1996)
PMd→M1	Muakkassa and Strick (1979)
PMd→PFC	Lu et al. (1994)
PFC→M1	Morecraft and Van Hoesen (1993)
PFC→SMA	Morecraft and Van Hoesen (1993)
PFC→PMd	Boussaoud et al. (2005)
PFC→CB	Schmahmann and Pandya (1997)
BG→M1	Hoover and Strick (1999)
BG→SMA	Tokuno et al. (1992)
BG→PMd	Kurata (1994)
BG→PFC	Middleton and Strick (2002)
CB→M1	Hoover and Strick (1999)
CB→PFC	Middleton and Strick (2001)
CB→BG	Hoshi et al. (2005)

Table 2

Path coefficients of the fitted model for pre-training, Week 2, and Week 4, $\Delta\chi^2$ (with 1 degree of freedom) and P values for group comparison using stacked model approach. Pr-T denotes pre-training, and Wk denotes Week. M1 = primary motor area, SMA = supplementary motor area, PMd = dorsal premotor cortex, PFC = posterior ventrolateral prefrontal cortex, BG=basal ganglia, and CB=cerebellum.

Pathway	Pr-P	Wk 2	Wk 4	Pr-T→Wk 2			Wk 2→Wk 4			Pr-T→Wk 4		
				$\Delta\chi^2$	P		$\Delta\chi^2$	P		$\Delta\chi^2$	P	
M1→BG	0.76	0.79	-0.09	2.0	0.16		63.4	0.00		39.1	0.00	
M1→CB	0.68	0.60	0.99	5.3	0.02		28.1	0.00		14.2	0.00	
pVLPFC→M1	0.19	0.01	-0.29	11.9	0.00		21.6	0.00		22.1	0.00	
pVLPFC→SMA	0.40	-0.11	-0.53	33.8	0.00		30.2	0.00		42.8	0.00	
pVLPFC→CB	0.23	-0.18	-0.36	27.2	0.00		13.0	0.00		27.2	0.00	
SMA→M1	0.92	0.81	0.74	7.3	0.00		5.0	0.03		8.3	0.00	
SMA→pVLPFC	0.05	0.13	0.24	5.3	0.02		7.9	0.00		8.7	0.00	
SMA→PMd	0.23	0.30	0.60	4.6	0.03		21.6	0.00		17.0	0.00	
SMA→BG	-0.36	0.17	0.18	35.1	0.00		0.72	0.40		24.9	0.00	
PMd→M1	0.07	0.23	0.56	10.6	0.00		23.8	0.00		22.6	0.00	
PMd→pVLPFC	0.38	0.24	0.69	9.3	0.00		32.4	0.00		14.3	0.00	
PMd→CB	-0.27	-0.07	0.00	13.3	0.00		5.0	0.03		12.4	0.00	
BG→M1	-0.59	-0.13	0.30	30.5	0.00		31.0	0.00		41.0	0.002	
BG→pVLPFC	0.11	-0.26	-0.34	24.5	0.00		5.8	0.02		20.7	0.00	
BG→SMA	-0.06	0.13	0.62	12.6	0.00		35.3	0.00		31.3	0.00	
BG→CB	0.08	0.54	0.10	30.5	0.00		31.7	0.00		0.9	0.34	
CB→M1	0.01	-0.40	-0.58	27.2	0.00		12.9	0.00		27.2	0.00	
CB→pVLPFC	-0.41	0.32	0.41	48.4	0.00		6.5	0.00		37.7	0.00	
CB→BG	0.48	-0.47	-0.10	63.0	0.00		26.6	0.00		29.6	0.00	