Motor learning in man: A review of functional and clinical studies

Ulrike Halsband [a,*], Regine K. Lange [b]

[a] Department of Psychology and Neuropsychology, University of Freiburg, Engelbergerstr 41, D-79085 Freiberg, Germany
[b] Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Germany

Abstract

This chapter reviews results of clinical and functional imaging studies which investigated the time-course of cortical and subcortical activation during the acquisition of motor a skill.

During the early phases of learning by trial and error, activation in prefrontal areas, especially in the dorsolateral prefrontal cortex, is has been reported. The role of these areas is presumably related to explicit working memory and the establishment of a novel association between visual cues and motor commands. Furthermore, motor associated areas of the right hemisphere and distributed cerebellar areas reveal strong activation during the early motor learning. Activation in superior–posterior parietal cortex presumably arises from visuospatial processes, while sensory feedback is coded in the anterior–inferior parietal cortex and the neocerebellar structures.

With practice, motor associated areas of the left-hemisphere reveal increased activity. This shift to the left hemisphere has been observed regardless of the hand used during training, indicating a left-hemispheric dominance in the storage of visuomotor skills. Concerning frontal areas, learned actions of sequential character are represented in the caudal part of the supplementary motor area (SMA proper), whereas the lateral premotor cortex appears to be responsible for the coding of the association between visuo-spatial information and motor commands.

Functional imaging studies which investigated the activation patterns of motor learning under implicit conditions identified for the first, a motor circuit which includes lateral premotor cortex and SMA proper of the left hemisphere and primary motor cortex, for the second, a cognitive loop which consists of basal ganglia structures of the right hemisphere. Finally, activity patterns of intermanual transfer are discussed. After right-handed training, activity in motor associated areas maintains during performance of the mirror version, but is increased during the performance of the original-oriented version with the left hand. In contrary, increased activity during the mirror reversed action, but not during the original-oriented performance of the untrained right hand is observed after left-handed training.

These results indicate the transfer of acquired right-handed information which reflects the mirror symmetry of the body, whereas spatial information is mainly transferred after left-handed training. Taken together, a combined approach of clinical lesion studies and functional imaging is a promising tool for identifying the cerebral regions involved in the process of motor learning and provides insight into the mechanisms underlying the generalisation of actions.
© 2006 Elsevier Ltd. All rights reserved.

Keywords: Motor learning; Functional imaging; Sensorimotor transformation; Laterality; Intermanual transfer; Mirror neurons

1. Introduction

Motor learning can be conceived as the establishment of an internal model which represents the exact matching between perceived sensory and motor information (Wolpert et al., 1995). During the early phase of motor learning, movements are unskilled, highly-feedback dependent and require strong demands on attention (Atkeson, 1989). With practice, accuracy and velocity of actions increase, whereas feedback processing becomes less important (Preilowski, 1977).

Concerning the functional neuroanatomy, skill acquisition is paralleled by changes on regional level and on the level of neural circuitry. In the last few years, the development of functional imaging techniques as well as data from EEG studies provided insight into the neuronal mechanisms

underlying the changes of behaviour during motor skill acquisition. Importantly, functional imaging data provide a better understanding of clinical observations.

Several reasons can be made responsible for discrepant results, e.g. variations of the tasks investigated, methodological differences and the phase of motor learning.

Results of a single study represent only parts of a puzzle of the neuronal changes underlying motor learning. In this article, a combined view of functional imaging data will be presented.

In general, two forms of motor learning can be distinguished, namely explicit and implicit learning. Explicit learning involves conscious recollection of previous experiences. Implicit learning is defined as an unintentional, nonconscious form of learning characterised by behavioural improvement.

1.1. Stages of motor learning

Motor skill progresses from explicit control in the early stages of learning to a more implicit or automatic control when well learned. Finding suggests that motor learning consists of three distinct phases (Halsband, 2006):

(1) *Initial stage*: Slow performance under close sensory guidance, irregular shape of movements, variable time of performance.
(2) *Intermediate stage*: Gradual learning of the sensory-motor map, increase in speed.
(3) *Advanced stage*: Rapid, automised, skillful performance, isochronous movements, whole field sensory control.

During the initial phase of learning by trial and error, subjects have to find out the correct movement. The critical requirement of this phase is the novel establishment of perceived sensory cues with the correct motor commands. For this purpose, subjects have to attend to sensory cues. They have to decide which movement to initialise next and – if feedback is given – they have to encode the perceived response in memory. Thus, the establishment of a novel arbitrary sensorimotor association – as it is required during learning by trial and error – is closely related to attention (Petersen et al., 1994), decision and selection of movements, sensory feedback processing and working memory.

Once subjects find out the correct movements the map of sensorimotor translation is provided. Sensory stimuli have to be retained in working memory to be translated to the motor output (Deiber et al., 1997), performance of actions are still slow and unskilled and feedback and attentional processing play a critical role (Atkeson, 1989; Shadmehr and Mussa-Ivaldi, 1994). With practice, sensorimotor maps become stronger and are stored in long-term memory. Visual cues are transformed accurately and fast to the precise motor response. Hence, action can be performed with less intensive sensory feedback processing and at higher speed. After long-term practice, movements become automatic and can be performed at high speed and accuracy, even if subjects do not attend to the action.

Most recently Säfström and Edin (in press) examined how an entirely new sensorimotor transformation is established. The authors looked at a transformation that is different in kind from the normal visual motor map. The visual information was replaced with visual information with auditory information, where the frequency of a tone was log linearly related to the size of the object. In other words, it was investigated how a so-called "audiomotor map" is established using a reach-to-grasp task. Results indicate that learning of an auditory motor map also consisted of three distinct phases:

(i) subjects used the maximum grip aperture to grasp any reasonable sized objects; there were no overt signs of learning ($\sim$10–15 trials);
(ii) there was a period of fast learning where the slope of the relationship between maximum grip aperture and object size became steeper;
(iii) subjects reached a plateau level of performance, the slope was constant. The results are in agreement with the findings by Sailer et al. (2005) who reported similar learning stages for a task in which subjects had to coordinate bi manual motor actions.

Looking at the neural mechanisms underlying motor learning, two main questions arise: first, one may ask about the contribution of each brain region in the process of motor learning. Secondly, it is interesting to interpret cerebral activation patterns which are associated with early and advanced stages of learning in terms of neural circuits.

In the following, the role of cortical and subcortical regions is discussed first with respect to the critical demands during early and late motor stages. Thereafter, the phases of motor learning are attributed to distinct neural circuits during explicit and implicit learning. Finally, related forms of motor learning, bimanual tasks and intermanual approaches are described.

2. Involvement of cerebral areas in motor learning

2.1. Tertiary motor areas

2.1.1. Prefrontal cortex

Activation of prefrontal areas is commonly reported during the initial stages of explicit motor learning. This is well in accord with the reported involvement of the prefrontal cortex in decision and selection of movements and attentional processing (Deiber et al., 1997; Jueptner et al., 1997). Notably, the dorsolateral frontal cortex (DLPFC) apparently plays a specific role in learning by trial and error and there is indication that this is due to the sensorimotor association and working memory. The critical role of the right prefrontal cortex in the initial phase of motor learning is likely to be due to the learning of the association between visual and motor commands according to

arbitrary rules. Using positron emission tomography (PET) Toni and Passingham (1999) studied the neural network involved in the acquisition of an arbitrary visuomotor conditional task. Subjects were requested to associate different visual patterns with different finger movements. Results indicate activation patterns in the ventral, prefrontal and extrastriate cortex; in addition activation in the basal ganglia and hippocampus was reported.

The role of the prefrontal cortex in explicit working memory has been demonstrated in several studies. For example, Shadmehr and Holcomb (1997) reported prefrontal cortex activation within the first hour after learning had finished. They suggest that the prefrontal cortex is the temporary storage of arbitrary sensorimotor associations for use in the near term.

Furthermore, the observation of initial pronounced prefrontal activity in the left and prolonged activation in the right hemisphere was conceived of as a left-hemispheric specialisation in the encoding and a right-hemispheric dominance in the retrieval (Eliassen et al., 2000; Kawashima et al., 2000; Sakai et al., 1998; Shadmehr and Holcomb, 1997).

2.1.2. Cingulate cortex

Activation in the cingulate cortex is frequently observed together with prefrontal activation. However, the role of the cingulate cortex in motor learning is not the same as for prefrontal cortex or the supplementary motor area (SMA). Whereas the cingulate cortex has not been identified to be specifically involved in sensorimotor associations (Halsband and Freund, 1993), the processing of sensory feedback has been shown to be coded in the anterior cingulate cortex (Jueptner et al., 1997; Kawashima et al., 2000). Halsband and Freund (1993) were able to establish on neuropsychological grounds a clear functional difference in visuomotor association learning in patients with cingulate or SMA lesions. Patients had to learn to associate six coloured stimuli with six different arm movements which were previously rehearsed. A control task involved an association between the same set of sensory stimuli and six spatial locations. It was found that patients with cingulate lesion were not impaired on either of these conditional learning tasks; in contrast, patients with SMA lesions were severely impaired when they had to recall a movement on the basis of a sensory cue, but not for an association involving spatial location. Kinematic analysis of bimanual in-phase and anti-phase movements in patients with cingulate lesions showed an impairment in the establishment of (1) unimanual independence and (2) accurate temporal adjustments between the two hands (Stephan et al., 1999b).

Recent evidence suggests that the rostral cingulate zone is involved in response selection on the basis of the expected outcome of an action. For instance, Mars et al. (2005) found a learning-dependent shift in the timing of activation in the rostral cingulate zone of the anterior cingulate cortex from external error feedback to internal error detection.

2.1.3. Pre-supplementary motor area

The pre-supplementary motor area (pre-SMA) area has been demonstrated to be involved in the early, but not in the later stages of explicit motor learning (Hikosaka et al., 1995; Sakai et al., 1998). The observation of prolonged activation in the pre-SMA in comparison to the DPLFC led to the assumption that this area codes for the retrieval (Sakai et al., 1998). Interestingly, a right hemispheric activation – as it is observed in the DPLFC – could not been determined in the pre-SMA.

In monkeys pre-SMA neurons were found to be more active during the delay and pre-movement as compared to the movement, instruction, and reward periods. Interestingly, the activity in the pre-SMA was more related to externally triggered movements during the pre-movement period, but exhibited a preferential relationship to internally determined movements in the movement period (Halsband et al., 1994). Furthermore, it was found, that the pre-SMA contains a significantly higher proportion of neuron with cue responses, preparatory activity and time-logged activity to movement trigger signals than the SMA proper when the animal has to select a single movement according to a visual cue (Matsuzaka et al., 1992).

2.2. Secondary motor areas and sensory associated areas

2.2.1. SMA proper

Activation in this part of the SMA increases with practice. Contrary to an involvement of the pre-SMA during explicit learning, the SMA proper revealed practice-related increases also with implicit learning (Grafton et al., 1994, 2001; Hazeltine et al., 1997). It is worth to note that activation in the SMA proper exists in the left hemisphere not only when using the contralateral right hand, but also in tasks trained by the left hand or with both hands (Hazeltine et al., 1997; Grafton et al., 2002).

Furthermore, activation in the SMA proper has been observed particularly in studies which investigated actions with sequential character (Hikosaka et al., 1995, 1996; Jenkins et al., 1994; Van Mier et al., 1999), indicating that the SMA proper stores sequential movements which require the precise timing (Van Mier et al., 1999).

The finding from functional imaging studies that the left SMA seems to play a dominant role in the performance of sequential movement is in agreement with clinical observations. Strong disturbances in the reproduction of rhythms from memory have been documented in patients with damage in the supplementary motor area (Halsband et al., 1993). These disturbances were most severe during alternating rhythm tapping using the right and left hand in an alternating manner and in patients with left-sided lesions. Findings argue for a critical role of the SMA in the generation of sequences of memory that fit into a precise timing plan. Results are in agreement with the findings that patients with SMA of medial premotor damage were most severely impaired when executing different movements

simultaneously with the right and left hand (Halsband et al., 2001).

2.2.2. Premotor cortex

Activation in the lateral premotor cortex (PMC) during the early stages of skill learning has been observed bilaterally (Deiber et al., 1997; Inoue et al., 1997) and has been reported to be prominent in the right side (Deiber et al., 1997; Jenkins et al., 1994; Inoue et al., 1997). For instance, Jenkins et al. (1994) reported stronger activation in the PMC during the initial stages of learning as compared to the advanced stages. The task they investigated required subjects to learn sequences of key-presses by auditory feedback. These authors attributed feedback processing to the activation during early learning. During learning, subjects had to make use of auditory feedback; with automatisation of the task they could run the sequence off without feedback. However, increased activity in early stages in PMC has been shown in several studies where subjects had to learn the task without external feedback, such as drawing tasks (Seitz et al., 1997; Van Mier et al., 1999). There is indication that activation of the right PMC also reflects spatial processing which may be important during early motor learning. Inoue et al. (1997) as well as Ghilardi et al. (2000) demonstrated pronounced activation in the right PMC during optic rotation. Moreover, activation in the PMC of the right side which was especially seen during conditional motor learning using *spatial* rules led to the assumption that the new conversion between perceived sensory visual input and appropriate motor output is responsible for activity in the right PMC (Deiber et al., 1997). Contrary to the right-sided activation in the PMC during the early stages of motor learning, it appears to be the PMC of the left hemisphere which is involved in the later stages of motor learning.

Accordingly to the role in spatial processing of the PMC during early motor learning, it is likely that PMC reflects the internal representation of mapping between spatial cues and motor commands. Learning-related increases of activity in the left PMC was observed in tasks which require the interaction with peripersonal space, such as tracking of circuits (Frustiger et al., 2000), visually guided reaching tasks (Shadmehr and Holcomb, 1997), rotary pursuit (Grafton et al., 1994) as well as drawing and writing tasks (Seitz et al., 1997; Van Mier et al., 1999). In contrary, the training of a complex finger-to-thumb opposition task (Seitz et al., 1990) was not paralleled by an increase of activity in the lateral premotor cortex. Thus, the storage of motor skill in the PMC does not reflect the representation of mere motor commands, but the association between sensory cues and motor commands. Learning-related increases were found on the left side regardless of the hand used during training (Van Mier et al., 1999). Thus, it appears to be evident that the left frontal cortex is dominant in the storage of acquired skill.

Patients suffering from premotor lesions are not able to associate sensory stimuli with previously learned movements (Halsband and Freund, 1990). However, the same patients were able to pass a task which involved an association between the same set of sensory stimuli and six spatial locations. Results indicate that the premotor cortex plays a critical role in sensory conditional motor learning. This impairment was observed whether the right or the left hand was used. Findings suggest that the premotor areas are bilaterally organised parts of the frontal agranular motor field, and are relevant for the sensory cueing of movement and for motor learning.

Using fMRI Van Eimeren et al. (2006) systematically examined the neural mechanisms involved in the external and internal guidance of action. Results indicate that in the anterior part of rostral dorsal premotor cortex, the supplementary motor area, the rostral cingulate, and the right dorsolateral prefrontal cortex the increase in activity was independent of spatially defined restrictions. In contrast, an additional increase in activity was reported in the posterior part of rostral dorsal premotor cortex, superior parietal lobe and parieto-occipital sulcus bilaterally and in the right anterior intraparietal sulcus when the visuospatial cue imposed specific constrains on the response selection.

There is increasing evidence that the ventral premotor cortex contains so called "mirror neurons" that discharge both when the subject performs specific actions and when he observes another individual performing the same or similar actions. Findings suggest that a mirror neuron system exist in monkeys (Ferrari et al., 2005; Gallese et al., 1996; Rizzolatti et al., 1996a) and in humans (Binkofski and Buccino, 2004; Buccino et al., 2004; Fagida et al., 1995, 2005; Rizzolatti et al., 2002; Tai et al., 2004). The mirror system seems to be (1) biologically tuned: activations were not evident for the observation of action performed by a robot (Tai et al., 2004); (2) polymodal: audiovisual neurons were found that discharge when the animal observes an action or when it hears a related sound (Kohler et al., 2002). Interestingly, the same neural structures also appeared to be active when the same actions, sensations, and emotions are to be detected in others (Gallese, 2003).

2.2.3. Inferior frontal cortex

The inferior frontal cortex – classically known as Broca's area – has also been shown to be involved in skill acquisition. Activation found in the right inferior hemisphere has been attributed to the coding of counting and integration of numbers. Activation in the right inferior frontal cortex in the early phase of learning was found in a finger sequence learning task which required subjects to count the finger movements (Seitz et al., 1997). However, there are also reports of increased activation in the inferior frontal cortex in the advanced stages of learning. Honda et al. (2000) reported learning-related increased activity in the right inferior frontal cortex during sequence learning according to stimuli cued by numbers. Bilateral activity in the BA 44 was paralleled with acquisition of maze and square tracing (Van Mier et al., 1999).

2.3. Parietal cortex

Results of functional imaging agree with an increase of parietal activation in the right hemisphere in the early stages of motor learning, while higher activity in the advanced stages was found predominantly in posterior parietal areas of the left hemisphere (Jenkins et al., 1994; Deiber et al., 1997). However, anterior–inferior parietal cortex and superior–posterior cortex code for distinct functions.

2.3.1. Inferior parietal cortex

The role of the right inferior parietal cortex during initial motor learning can be attributed to the integration of sensory information and feedback processing. To investigate the areas which are specifically involved in the monitoring and feedback processing, activity during re-tracing of a line was compared with activation associated with line generation at free choice (Jueptner and Weiller, 1998). Significantly greater activation in the inferior parietal cortex of the right side (BA 39 and 40) was found during monitoring as compared to the second condition. Accordingly, Kawashima et al. (2000) investigated learning of a line-drawing task and reported activation in the right inferior parietal cortex when subjects received visual feedback about their performance. Moreover, inferior parietal activity was also found when subjects were informed verbally about task performance. Thus, according to the finding that the inferior parietal cortex integrates sensory information from multiple modalities, the inferior parietal cortex is involved in the processing of feedback both by visual and auditory (verbal) cues.

2.3.2. Superior-posterior parietal cortex

A critical role of the right superior-posterior parietal cortex in motor learning is presumably the coding of a novel translation between spatial and motor information. Activation of the right posterior parietal cortex in a serial reaction time task was pronounced when stimuli were coded by spatial position as compared to the use colour-coded stimuli (Hazeltine et al., 1997). Furthermore, the right posterior parietal cortex yielded activation when subjects had to adapt to manipulated visual information. For example, right posterior parietal cortex (BA7) is activated during pointing under visual rotated feedback. Similarly, Ghilardi et al. (2000) showed activation in BA 40 and BA 7 when subjects performed a previously learned reaching task according to a frame which was rotated to 90° as compared to the initially trained task. As indicated by increased activation in parietal cortex during implicit learning (Ghilardi et al., 2000; Hazeltine et al., 1997) spatial processing in the parietal cortex is independent on the awareness of learning.

In the advanced stages of motor learning, the posterior parietal cortex is crucially involved in the storage of acquired skill. Using positron emission tomography (PET), Shadmehr and Holcomb (1997) investigated the learning-related changes when subjects had to adapt to an external manipulated force-field. After learning had finished, initially (in the first minutes), activation in the prefrontal cortex was found. After a delay of five hours, however, activation shifted to the posterior parietal cortex (BA 7). In another PET study, Sakai et al. (1998) showed learning-related transition from prefrontal areas (the DLPFC to the pre-SMA) to precuneus and – finally – to the intraparietal sulcus. Most recently, Cavina-Pratesi et al. (2006) reported that a more complex stimulus-response mapping is associated with activation in the left superior parietal cortex.

Whereas the right hemisphere of the parietal cortex is predominantly involved during *initial* learning, the left or both parietal sites are activated in the late phase of motor learning (Frustiger et al., 2000; Honda et al., 2000; Sakai et al., 1998; Shadmehr and Holcomb, 1997).

The storage of an acquired skill in the PMC has to be interpreted with the connectivity to the parietal cortex (for review see: Rizzolatti et al., 1998; Wise et al., 1997). However, whereas the PMC represents both explicit and implicit acquired skills, the posterior parietal cortex appears to store sensorimotor information that can be consciously addressed. Increases of parietal activation in the advanced stages of skill acquisition have been observed only during explicit acquired skill and there are several reports that implicit learning of the same task was not associated with parietal activation (Eliassen et al., 2001; Hazeltine et al., 1997; Honda et al., 2000).

Clinical findings correlate with functional imaging data. The syndrome of apraxia, the inability of patients to perform previously learned actions (which can not be explained by neurological syndromes such as paresis), is predominantly found after lesions in the left parietal cortex. Interestingly, patients with parietal apraxia show most pronounced impairments in learning actions which are referred to their own body (e.g., Halsband et al., 2001). Thus, one may argue that the left parietal cortex stores information by use of a body-related reference frame – an assumption which fits well with the proposed representation of motor commands (Sakai et al., 1998; Soechting and Flanders, 1989).

Summed up, parietal areas of the right hemisphere code for spatial attention and the translation from visuo-spatial to body-related information in the early stages of motor learning. Acquired skill is represented in the posterior parietal cortex of the left hemisphere and is related to a body-reference frame.

2.4. Cerebellum

Strong activation in distributed cerebellar areas have been consistently reported in the initial stages of motor learning (Flament et al., 1996; Jenkins et al., 1994; Seitz et al., 1990, 1997; Van Mier et al., 1999). Studies investigating the role of the cerebellar areas in motor control demonstrated a critical role of the cerebellum for feedback

processing. Jueptner and Weiller (1998) compared cerebellar activation associated with the generation of lines by free choice and the re-tracing of lines. Massive activation in the line-re-tracing task – which required the detection and correction of errors – was found bilaterally in neocerebellar structures (including hemispheres, vermis and nuclei). Hence, the cerebellum controls the *actually* performed movement. Thus feedback processing by use of proprioceptive and visual information as well as error detection and correction are the critical motor control coded by cerebellar structures. High activation in the early stages of learning reflects the high dependence of feedback processing. Feedback processing in the cerebellum involves also the visuomotor transformation. Flament et al. (1996) measured cerebellar activation while subjects had to superimpose a cursor with a joystick to targets, whereby the relationship between cursor and target was reversed as in the standard task. Increased number of successful trials was paralleled with a general decrease of activation. Since this task required a new visuomotor transformation, cerebellar activation was attributed to the detection and correction of errors which are due to the visuomotor transformation. This interpretation is in line with the assumed role of the cerebellum in visuomotor transformation resulting from clinical observations (Sanes et al., 1990; Thach et al., 1992; Weiner et al., 1983).

Initial activation has been reported in widespread areas, vermal and lateral zones, anteriorly and posteriorly (Flament et al., 1996). However, most activity occurs in the posterior lobes of the cerebellar hemispheres (Deiber et al., 1997; Jenkins et al., 1994; Flament et al., 1996; Van Mier et al., 1999). Moreover, although activity is consistently reported to occur bilaterally, a preponderant involvement of the cerebellar hemispheres of the left side in early motor learning has been reported (Ghilardi et al., 1999). This assumption gains support from research in patients with cerebellar lesion: patients with damages in the left cerebellum had even more problems learning a motor task than patients with right cerebellar lesions (Molinari et al., 1997). Hence, one may attribute a critical role during initial motor learning to the left posterior cerebellar hemisphere.

As errors are minimized with practice, a feedback controller role becomes less important, reflecting a decrease of activation. However, there are some reports of remaining activation in the cerebellum, indicating a role in the storage of acquired skill. These reports agree with subcortical activation in the right cerebellum, namely in the right nucleus dentate. Doyon et al. (1996) showed increased activation in the right dentate nucleus but this structure did not reveal a learning-related decrease of activation in the study of Flament et al. (1996). When subjects perform a learned task as fast as they can (Van Mier et al., 1999), activation increases just in the right dentate nucleus and right posterior hemispheres. This observation confirms the assumption that these structures are involved in the storage and also indicate the cerebellum's role in the control of speed.

2.5. Primary motor areas

2.5.1. Primary motor cortex

Learning-related increases of activation during explicit motor training have been shown in the contralateral primary motor cortex (Seitz et al., 1990; Van Mier et al., 1999). It is likely that velocity-dependent effects dominate learning-related changes per se. When speed was held constant, activity in primary motor cortex did not change (Jenkins et al., 1994) or even decreased (Toni et al., 1999). These studies showed activity in primary motor cortex activation in the time-course of a few minutes after skill acquisition. In contrary, training of subjects in a finger sequence task over a week revealed an extension of activated areas in the primary motor cortex, presumably reflecting the spreading of neurons (Karni et al., 1995). Whereas activation in the primary motor cortex associated with explicit motor learning is related mainly to effects of velocity, increased activation during implicit acquisition presumably reflects learning-related activation per se (Hazeltine et al., 1997).

2.5.2. Basal ganglia

During the early phases of skill acquisition, activity has been reported in the anterior caudate nucleus. This activation has been attributed to reflect a reinforcement of sensorimotor associations made in the prefrontal cortex which is closely interconnected with the basal ganglia (Jueptner et al., 1997; Toni and Passingham, 1999). During the late phase of motor learning, the basal ganglia are likely to be involved in the storage of learned sequences. Seitz et al. (1990) reported learning-related activation in the basal ganglia associated with a finger-to-thumb-opposition task and interpreted this activity as final establishment of the motor programme.

A critical role of the basal ganglia in motor learning is the mediation during implicit learning. A series of imaging studies have shown striatal activation when healthy subjects are engaged in implicit sequence learning (Doyon et al., 1996; Grafton et al., 1994; Hazeltine et al., 1997; Krebs et al., 1998; Rauch et al., 1995, 1997). Patients with basal ganglia disorders, e.g. Huntington's or Parkinson's disease exhibit impaired performance on the serial reaction time task (SRT-task) which is a typical paradigm to determine the mediating neuroanatomy of implicit learning (Knopman and Nissen, 1991; Willingham and Koroshetz, 1993). Visual stimuli are presented at one of four positions on a computer screen and subjects had to press corresponding response-buttons as fast and accurate as possible after each stimulus appears. Unknown to the subjects, stimuli sometimes follow a specific repeating sequence. Learning can be accessed by the reaction time advantage from responding to stimuli in a repeating sequence compared to randomly positioned stimuli. The distinct activity pattern associated with implicit learning depends on the mechanisms of the task, i.e. whether the motor or cognitive-perceptual demands are prominent in the task. One

can distinguish two corticosubcortical loops which might be referred to as cognitive or motor loop rsp, as described in the following paragraph.

3. Neural circuits

3.1. Implicit learning

Cognitive-perceptual demands (rather than motor demands) are prominent in SRT variations which require learning of a long sequence learning (12 items) with one or two fingers of one hand. Using such a paradigm, learning-related changes were found in the right ventral striatum (Doyon et al., 1996; Rauch et al., 1997), in the right thalamus (Rauch et al., 1997), and in subcortical structures (Doyon et al., 1998). Most interestingly, a right-sided preponderance was observed irrespective if subjects used their right hand or both hands (Doyon et al., 1996; Rauch et al., 1997). Hence, implicit sequence learning seems to be mediated by cortico-striatal pathways, preferentially within the right hemisphere (Rauch et al., 1995).

3.2. Explicit learning

Activity patterns observed during early and late phases of explicit motor learning also suggest the involvement of distinct neural circuits. The initial requirement of the establishment of the association between arbitrary sensory stimuli and a particular motor response is coded in a loop between dorsolateral prefrontal cortex and anterior caudate nucleus. In parallel, explicit working memory engages connections between prefrontal cortex and pre-SMA. Moreover, the high demand of feedback processing is coded in a network including cingulate cortex, right anterior inferior parietal cortex, and neocerebellar structures. The critical circuit coding for a new mapping between external space and body-related motor program is the pathway from the right posterior parietal cortex to the right lateral premotor cortex.

For the storage of learned actions, connections between posterior parietal cortex and left lateral premotor cortex are likely to represent visuomotor maps. A loop including SMA proper, primary motor cortex, and basal ganglia is attributed to represent motor sequences.

4. Associated forms of motor learning

4.1. Bimanual tasks

Observations in patients, data from functional imaging, as well as recordings with EEG are in general agreement that cingulate structures and adjacent supplementary motor are the critical areas which control the coordination between the right and left hands. Patients with lesions in cingulate structures have difficulties in the temporal organisation of bimanual tasks, particularly with heterogeneous movements (Halsband, 1999; Stephan et al., 1999b). Ste-

phan et al. (1999b) reported a prominent activation of the ventral medial wall motor areas in normal volunteers and a bimanual coordination disorder in patients with lesions in the cingulate gyrus and/or SMA. Findings argue for a crucial role of the ventral medial wall motor areas in bimanual coordination.

Activation of the medial wall was previously studied by use of EEG with a similar task. Lang et al. (1990) measured negative potentials associated with the tapping of motor sequences in synchrony and tapping different rhythms simultaneously. Additional activation of the mesial central cortex was found during bimanually tapping different rhythms (as compared to synchrony tapping), suggesting that the SMA mainly controls movements in difficult sequences. Findings should be interpreted in the context of the role of SMA in the temporal organisation of movements. Using functional MRI, activation in the SMA was found to be significantly greater during parallel movements of the index finger as compared to bimanual mirror movements (Sadato et al., 1997).

4.2. Intermanual transfer

Functional imaging as well as neurophysiological research has offered insight into the mechanisms underlying intermanual transfer. It is well known that motor learning with the one hand effects performance of corresponding tasks with the opposite hand. Previous studies showed that the effect of opposite hand training depends on the hand used during initial training and on whether the original or the mirror reversed oriented action has to be performed with the untrained hand. Right-handed motor training improves both the original-oriented and the mirror-oriented task by the opposite hand. However, the benefit has been described to be more pronounced for the mirror-oriented task as compared to the original oriented task (Vaid and Stiles-Davis, 1989). In contrast, the transfer of acquired left-handed skill to the right hand facilitates the normal-oriented action as compared to a mirror reversed task (Grafton et al., 2002; Vaid and Stiles-Davis, 1989).

Using functional MRI, right-to-left hand transfer and transfer of the highly trained action of writing have been investigated. Patterns during performance of writing with the right hand in correct and mirror version with the untrained hand are depicted in Fig. 1. Activity in motor associated areas maintains during left-handed mirror writing as compared to activation observed during right-handed correct writing. In contrast, activity in pre-SMA, PMC of both sites as well as in posterior parietal areas of the left hemisphere increased during left-handed correct writing.

Similar activation during left-handed mirror writing and right-handed correct writing suggests that the internal representation of learned writing is recalled in its unchanged form during the control of the mirror task performed with the opposite hand, whereas additional computation is required to permit writing in the correct orientation with the left hand.
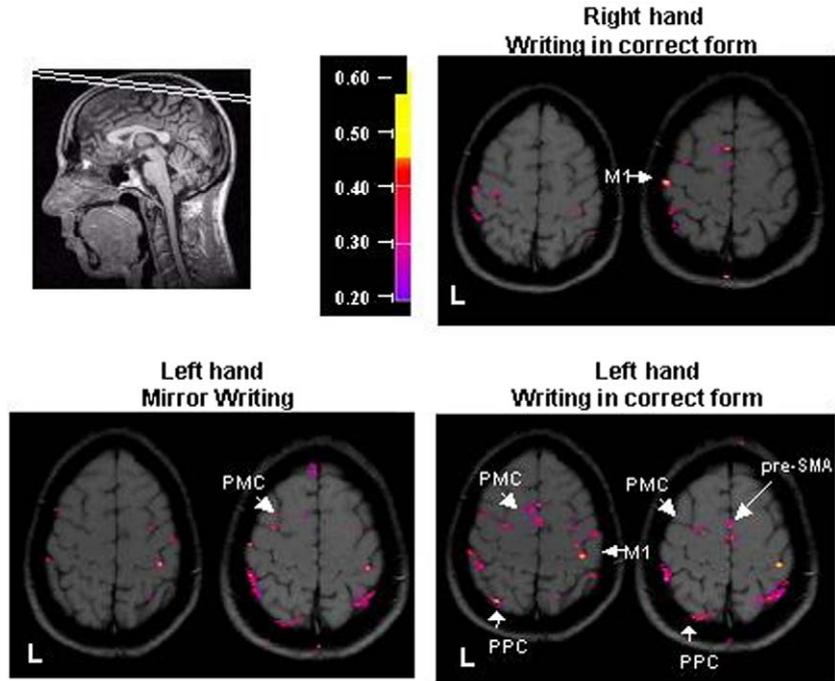
Fig. 1. Activation pattern in a single subject across the two slices associated with the transfer of writing. The images are sagittal sections located and depicted from the same slice for tasks within each hand. Task-rest comparisons were calculated and normalised to image baseline correlation coefficients r for the pixel intensity time courses and a box car reference function were computed so that a parametric map was produced. Pixels were colour-coded and superimposed onto the corresponding anatomical image. Only pixels reaching a threshold of $p < 0.05$ were taken into account. M1: Primary motor cortex, PPC: Posterior parietal cortex. L: Left hemisphere.
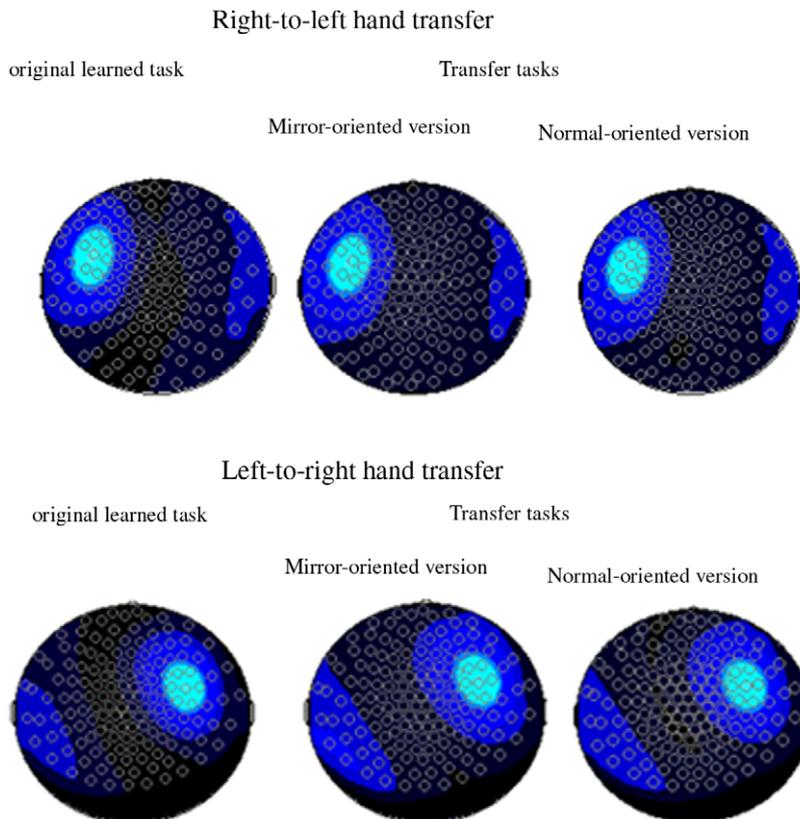

Fig. 2. Interelectrode coherence of the beta-band (18–22 Hz). Levels of coherence are scaled by colour. A: Right-to-left hand transfer: right: by colour. A: Right-to-left hand transfer: right: repetition of the right-handed learned visuomotor task (right) (left) (mid). B: Left-to-right hand transfer (see above).

This assumption is closely related to the interpretation that the action of right-handed writing is stored and transferred to the opposite by use of a so-called body-related reference frame (Soechting and Flanders, 1989) which considers the mirror symmetry of the muscles and joints. This learned body-related information is appropriate for both right-handed writing and left-handed mirror writing, resulting in similar activation patterns. To control the action of correct left-handed writing, acquired body-related information has to be transformed (Rodriguez et al., 1989; Rodriguez, 1990). These transformation processes seem to occur in the left hemisphere. The observation that both transfer tasks revealed prominent activity in the left-hemisphere adds to the hypothesis that the left hemisphere is dominant in motor control (Halsband, 1992, 1999) and is also in accord with the assumed control of the left hand via ipsilateral corticospinal pathways (Criscimagna-Hemminger et al., 2003).

Lange (2004) investigated the neural processes of recall and modification. Electroencephalogram (EEG) recording was employed during the performance of a figure drawing task previously trained with the right hand. The figure was reproduced with the right hand (Learned-task) and with the left hand in original (Normal-task) and mirror orientations (Mirror-task). Results indicate that prior to movement onset, beta-power and alpha- and beta-coherence decreased during the Normal-task as compared to the Learned-task. Negative amplitudes over fronto-central sites during the Normal-task exceeded amplitudes manifested during the Learned-task. In comparison to the Learned-task, coherences between fronto-parietal sites increased during the Mirror-task. Findings suggest that intrinsic coordinates are processed during the pre-movement period. During the Normal-task, modification of intrinsic coordinates was revealed by cerebral activation. Decreased coherences appeared to reflect suppressed inter-regional information flow associated with utilization of intrinsic coordinates. During the Mirror-task, modification of extrinsic coordinates induced activation of cortical networks.

Recent MEG-data offer further insight into the mechanisms underlying intermanual transfer. Fig. 2 demonstrates the coherence (a measurement of network activation) during repetition and transfer of a complex visuomotor task (performing of complex figures with the index finger on a touch-pad). During the repetition of the learned action with the right hand, coherence in frontal areas between left and right hemisphere is low – an observation that fits with an internal representation in the contralateral left hemisphere. Importantly, when executing the task in original or mirror versions with the untrained left hand, interhemispheric coherence did not change as compared to the right-handed learned task. This observation strongly suggests that the learned information of the left-hemisphere controls the left hand via ipsilateral pathways.

Investigating the learning of button sequence, learning-related activation was found in the ipsilateral left hemi-

sphere (Grafton et al., 2002). After switching to the right hand, activation in secondary motor areas maintained during the performance of the normal-oriented task, additional activation in left-sided motor areas was observed during the execution of the mirror reversed task. These patterns indicate that left-handed skill is recalled during transfer when the task is consistent with the left-handed task with reference to extrapersonal space.

Most recently Lange et al. (2006) recorded movement-related potentials, EEG power, and EEG coherence during the repetition of a drawing task previously trained by the non-dominant left hand (Learned-task) and its execution in original as well as mirror orientation by the right hand (Normal- and Mirror-task). Analyzing only the EEG data which differed between Normal- and Mirror-tasks, EEG correlates of coordinate processing during intermanual transfer were identified without the effects due to the use of the right versus the left hand. Beta coherence increased in the Mirror-task in the period ranging from 1 to 2 s after movement onset, whereas the Normal-task did not differ from the Learned-task in any of these predefined EEG parameters. These increases were especially prominent between the hemispheres, even though they were also observed symmetrically in the parieto-frontal electrode pairs of both hemispheres. The behavioural data revealed that after left-hand training the performance in the Learned-task and in both transfer tasks improved after left-hand training. The results of the study indicate that coordinate transformation during the left-to-right hand transfer occurs in the phase of movement execution and that the extrinsic coordinates are predominantly affected.

During the repetition of a left-handed trained task, coherence increased between contralateral right frontal and left parietal sites. This is in accord with an important role of the left hemisphere in the storage of left-handed skill. Coherence between these areas maintains during the performance of the original-oriented task, but increased when subjects were required to perform the mirror reversed task. This finding can be conceived as a correlate to activation patterns reported by Grafton et al. (1992, 1994, 2002). Left-handed skill is represented in extrinsic coordinates which are conserved in relearning the task in the original version. To perform the action in the mirror reversed orientation. These extrinsic representations have to be modified – a process which results in increased network activation.

References

Atkeson, C.G., 1989. Learning arm kinematics and dynamics. Annu. Rev. Neurosci. 3, 171–176.
Binkofski, F., Buccino, G., 2004. Motor functiions of the Broca's region. Brain Lang. 89, 362–369.
Buccino, G., Binkofski, F., Riggio, L., 2004. The mirror neuron system and action recognition. Brain Lang. 89, 370–376.
Cavina-Pratesi, C., Valyear, K.F., Culham, J.C., Köhler, S., Obhi, S.S., Marzi, C.A., Goodale, M.A., 2006. Dissociating arbitrary stimulus-response mapping from movement planning during preparatory

period: evidence from event-related functional magnetic resonance imaging. J. Neurosci. 26, 2704–2713.

Criscimagna-Hemminger, S.E., Donchin, O., Gazzaniga, M.S., Shadmehr, R., 2003. Learned dynamics of reaching movements generalize from dominant to nondominant arm. J. Neurophysiol. 89, 168–176.

Deiber, M.P., Wise, S.P., Honda, M., Catalan, M.J., Grafman, J., Hallett, M., 1997. Frontal and parietal networks for conditional motor learning: a positron emission tomography study. J. Neurophysiol. 78 (Aug), 977–991.

Doyon, J., Owen, A.M., Petrides, M., Sziklas, V., Evans, A.C., 1996. Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography. Eur. J. Neurosci. 8, 637–648.

Doyon, J., Laforce Jr., R., Bouchard, G., Gaudreau, D., Roy, J., Poirier, M., Bedard, P.J., Bedard, F., Bouchard, J.P., 1998. Role of the striatum, cerebellum and frontal lobes in the in the automatization of a repeated visuomotor sequence of movements. Neuropsychologia 36, 625–641.

Eliassen, J.C., Baynes, K., Gazzaniga, M.S., 2000. Anterior and posterior callosal contributions to simultaneous bimanual movements of the hands and fingers. Brain 12, 2501–2511.

Eliassen, J.C., Souza, T., Sanes, J.N., 2001. Human brain activation accompanying explicitly directed movement sequence learning. Exp. Brain Res. 141, 269–280.

Fagida, L., Fogasse, L., Pavesi, G., Rizzolatti, G., 1995. Motor facilitation during action observation: a magnetic stimulation study. J. Neuropshysiol. 71, 2608–2611.

Fagida, L., Craighero, L., Olivier, E., 2005. Human motor cortex excitability during the perception of others' action. Curr. Opin. Neurobiol. 15, 312–318.

Ferrari, P.F., Rozzi, S., Fogassi, L., 2005. Mirror neurons responding to observation of actions made with tools monkey ventral premotor cortex. J. Cogn. Neurosci. 17, 212–226.

Flament, D., Ellermann, J.M., Kim, S.G., Uyurbil, K., Ebner, T.J., 1996. Functional magnetic resonance imaging of cerebellar activation during the learning of a visuomotor task. Hum. Brain Mapp. 4, 210–226.

Frustiger, S.A., Strother, S.C., Anderson, J.R., Sidtis, J.J., Arnold, K.B., Rottenberg, D.A., 2000. Multivariate predictive relationship between kinematic and functional activation patterns in a PET study of visuomotor learning. Neuroimage 10, 515–528.

Gallese, V., 2003. The roots of empathy: the shared manifold hypothesis and the neural basis of intersubjectivity. Psychopathology 36, 171–180.

Gallese, V., Fagida, L., Fogassi, L., Rizzolatti, G., 1996. Action recognition in the premotor cortex. Brain 119, 593–609.

Ghilardi, M.F., Alberoni, M., Marelli, S., Rossi, M., Franceschi, M., Ghez, C., Fazio, F., 1999. Impaired movement control in Alzheimer's disease. Neurosci. Lett. 260, 45–48.

Ghilardi, M.F., Ghez, C., Dhawan, V.M., Moeller, J., Mentis, M., Nakamura, T., Antonini, A., Eidelberg, D., 2000. Patterns of regional brain activation associated with different forms of motor learning. Brain Res. 871, 127–145.

Grafton, S.T., Maziotta, J.C., Presty, S., Friston, K.J., Frackowiak, R.S.J., Phelps, M.E., 1992. Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET. J. Neurosci. 12, 2542–2548.

Grafton, S.T., Woods, R.P., Tyszka, J.M., 1994. Functional imaging of procedural motor learning relating cerebral blood flow with individual subject performance. Hum. Brain Mapp. 1, 221–234.

Grafton, S.T., Salidis, J., Willingham, D.B., 2001. Motor learning of compatible and incompatible visuomotor maps. J. Cogn. Neurosci. 13, 217–231.

Grafton, S.T., Hazeltine, E., Ivry, I.B., 2002. Motor sequence learning with the nondominant hand. Exp. Brain Res. 146, 369–378.

Halsband, U., 1992. Left hemisphere preponderance in trajectorial learning. Neuroreport 3, 397–400.

Halsband, U., 2006. Motorisches Lernen. In: Gauggel, S., Herrmann, M. (Eds.), Handbuch der Neuro- und Biopsychologie. Hogrefe, Göttingen.

Halsband, U., Freund, H-J., 1990. Premotor cortex and conditional motor learning in man. Brain 113, 207–222.

Halsband, U., Freund, H.-J., 1993. Motor learning. Curr. Opin. Neurobiol. 3, 940–949.

Halsband, U., Ito, N., Tanji, J., Freund, H.-J., 1993. The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. Brain 11, 243–266.

Halsband, U., Matsuzaka, Y., Tanji, J., 1994. Neuronal activity in the primate supplementary, pre-supplementary and premotor cortex during externally and internally instructed sequential movements. Neurosci. Res. 20, 149–155.

Halsband, U., 1999. Neuropsychologische und neurophysiologische Studien zum motorischen Lernen. Papst Science Publishers, Lengerich.

Halsband, U., Schmitt, J., Weyers, M., Binkofski, F., Gruetzner, G., Freund, H.-J., 2001. Recognition and imitation of pantomimed motor acts after unilateral parietal and premotor lesions: a perspektive on apraxia. Neuropsychologia 39, 200–216.

Hazeltine, E., Grafton, S.T., Ivry, R., 1997. Attention and stimulus characteristics determine the locus of motor-sequence learning: a PET study. Brain 120, 123–140.

Hikosaka, O., Rand, M.K., Miyachi, S., Miyashita, K., 1995. Learning of sequential movements in the monkey – process of learning and retention of memory. J. Neurophysiol. 74, 1652–1661.

Hikosaka, O., Sakai, K., Miyauchi, S., Takino, R., Sasaki, Y., Pütz, B., 1996. Activation of human presupplementary motor area in learning of sequential procedures: a functional MRI study. J. Neurophysiol. 76, 617–621.

Honda, K., Sawada, H., Kihara, T., Urushitani, M., Nakamizo, T., Akaike, A., Shimohama, S., 2000. Phosphatidylinositol 3-kinase mediates neuroprotection by estrogen in cultured cortical neurons. J. Neurosci. Res. 60, 312–327.

Inoue, K., Kawashima, R., Satoh, K., Kinomura, I., Goto, R., Sigiura, M., Ito, M., Fukuda, H., 1997. Activity in the parietal area during visuomotor learning with optical rotation. Neuroreport 8, 3979–3983.

Jenkins, L.H., Brooks, D.J., Nixon, P.D., Frackowiak, R.S.J., Passingham, R.E., 1994. Motor sequence learning: a study with positron emission tomography. J. Neurosci. 14, 3775–3779.

Jueptner, M., Weiller, C., 1998. A review of differences between basal ganglia and cerebral control of movements as revealed by functional imaging studies. Brain 121, 1437–1449.

Jueptner, M., Ottinger, S., Fellows, S.J., Adamschewski, J., Flerich, L., Muller, S.P., Diener, H.C., Thilmann, A.E., Weiller, C., 1997. The relevance of sensory input for the cerebellar control of movements. Neuroimage 5, 41–48.

Karni, A., Meyer, G., Jezzard, P., Adams, M.M., Turner, R., Ungerleider, L.G., 1995. Functional MRI evidence for adult motor plasticity during motor skill learning. Nature 377, 155–158.

Kawashima, R., Tajima, N., Yoshida, H., Okita, K., Sasaki, T., Schormann, T., Ogawa, A., Fukuda, H., Zilles, K., 2000. The effect of verbal feedback on motor learning: a PET study. Neuroimage 12, 690–706.

Knopman, D., Nissen, M.J., 1991. Procedural learning is impaired in Huntington's disease. Neuropsychologia 29, 245–254.

Kohler, E., Keysere, C., Umilta, M.A., Fogassi, L., Gallese, V., Rizzolatti, G., 2002. Hearing sounds, understanding actions: action representation in mirror neurons. Science 7 (5582), 846–848.

Krebs, H.I., Brashers-Krug, T., Rauch, S., Savage, C.R., Hogan, N., Rubin, R.H., Fischman, A.J., Alpert, N.M., 1998. Robot-aided functional imaging: application to a motor learning study. Hum. Brain Mapp. 6, 59–72.

Lang, W., Obrig, H., Lindinger, G., Deecke, L., 1990. Supplementary motor area activation while tapping bimanually different rhythms in musicians. Exp. Brain Res. 79, 504–514.

Lange, R.K., 2004. EEG-correlates of coordinate processing during intermanual transfer, unpublished thesis.

Lange, R.K., Braun, C., Godde, B., 2006. Coordinate processing during the left-to-right hand transfer by EEG. Exp. Brain Res. 168, 547–556.

Mars, R.B., Coles, M.G., Grol, M.J., Holroyd, C.B., Niewenhui, S., Hulstein, W., Toni, I., 2005. Neural dynamics of error processing in medial frontal cortex. Neuroimage 28, 1007–1013.

Matsuzaka, Y., Aizawa, H., Tanji, J., 1992. A motor area rostral to the supplentary motor area (presupplementary motor area) in the monkey: neural activity during a learned motor task. J. Neurophysiol. 68, 653–662.

Molinari, M., Leggio, M.G., Solidy, A., Clorra, R., Misciagna, S., Silveri, M.C., Pertrosoni, L., 1997. Cerebellum and procedural learning: evidence from focal cerebellar lesions. Brain 120, 1753–1762.

Petersen, S.E., Corbetta, M., Miezin, F.M., Shulman, G.L., 1994. PET study of parietal involvement in spatial attention: comparison of different task types. Can. J. Exp. Psychol. 48, 319–338.

Preilowski, B., 1977. Phases of motor skills acquisition: a neuropsychological approach. Hum. Mov. Stud. 3, 169–181.

Rauch, S.L., Savage, C.R., Brown, H.D., Curran, T., Alpert, N.M., Kendrick, A., Fischman, A.J., Kosslyn, S.M., 1995. A PET investigation of implicit and explicit sequence learning. Hum. Brain Mapp. 3, 271–286.

Rauch, S.L., Whalen, P.J., Savage, C.R., Curran, T., Kendrick, A., Brown, H.D., Bush, G., Breiter, H.C., Rosen, B.R., 1997. Striatal recruitment during an implicit sequence learning task as measured by functional magnetic resonance imaging. Hum. Brain Mapp. 5, 124–132.

Rizzolatti, G., Fagida, L., Gallese, V., Fogassi, L., 1996a. Premotor cortex and the recognition of motor actions. Brain Res. Cogn. Brain Res. 3, 131–141.

Rizzolatti, G., Luppino, G., Matelli, M., 1998. The organization of the cortical motor system: new concepts. Electroencephalogr. Clin. Neurophysiol. 106, 283–296.

Rizzolatti, G., Fogassi, L., Gallese, V., 2002. Motor and cognitive functions of the ventral premotor cortex. Curr. Opin. Neurobiol. 12, 149–154.

Rodriguez, R., Aguilar, M., Gonzalez, G., 1989. Left non-dominant hand mirror writing. Brain Lang. 37, 122–144.

Rodriguez, R., 1990. Hand motor patterns after the correction of left-nondominant hand mirror writing. Neuropsychologia 29, 1191–1203.

Sadato, N., Yonekura, Y., Waki, A., Yamada, H., Ishi, Y., 1997. Role of the supplementary motor area and right premotor cortex in the coordination of bimanual finger movements. J. Neurosci. 17, 9667–9674.

Säfström, D., Edin, B., B., in press. Aquiring and adapting a novel audiomotor map in human grasping. Exp Brain Res.

Sailer, U., Flanagan, J.R., Johansson, R.S., 2005. Eye-hand coordination during learning of a novelvisuomotor task. J. Neurosci. 25 (39), 8833–8842.

Sakai, K., Hikosaka, G., Miyauchi, S., Takino, R., Sasaki, Y., Putz, B., 1998. Transition of brain activations from frontal to parietal areas in visuomotor sequencing learning. J. Neurosci. 18, 1740–1827.

Sanes, J.N., Dimitrov, B., Hallett, M., 1990. Motor learning in patients with cerebellar dysfunctions. Brain 113, 103–120.

Seitz, R.J., Roland, P.E., Bohm, C., Greitz, T., Stone-Elander, S., 1990. Motor learning in man: a positron emission tomography study. Neuroreport 1, 57–66.

Seitz, R.J., Canvan, A.G.M., Yaguez, L., Herzog, H., Tellmann, L., Knorr, U., Huang, Y., Homberg, V., 1997. Representation of graphomotor trajectories in the human parietal cortex: evidence for controlled and automatic performance. Eur. J. Neurosci. 9, 378–389.

Shadmehr, R., Mussa-Ivaldi, F.A., 1994. Adaptive representations of dynamics during learning of a motor task. J. Neurosci. 4, 3208–3225.

Shadmehr, R., Holcomb, H.H., 1997. Neural correlates of motor memory consolidation. Science 277, 821–825.

Soechting, J.F., Flanders, M., 1989. Errors in pointing are due to approximations in sensorimotor transformations. J. Neurophysiol. 62, 595–608.

Stephan, K.M., Binkofski, F., Halsband, U., Dohle, C., Wunderlich, G., Schnitzler, A., Tass, P., Posse, S., Herzog, H., Zilles, K., Seitz, R.J., Freund, H.-J., 1999b. The role of ventral medial wall motor areas in bimanual co-ordination. A combined lesion and activation study. Brain 122, 351–368.

Tai, Y.F., Scherfler, C., Brooks, D.J., Sawamoto, N., Castiello, U., 2004. The human premotor cortex is "mirror" only for biological actions. Curr. Biol. 14, 117–120.

Thach, W.T., Goodkin, H.P., Keating, J.G., 1992. The cerebellum and adaptive coordination of movement. Annu. Rev. Neurosci. 15, 403–442.

Toni, I., Passingham, R.E., 1999. Prefrontal-basal ganglia pathways are involved in learning of arbitrary visuomotor associations: a PET study. Exp. Brain Res. 127, 19–32.

Toni, I., Schltuer, N.D., Josephs, O., Friston, K., Passingham, R.E., 1999. Signal-, set-, and movement-related activity in the human brain: an event-related fMRI study. Cereb. Cortex 9, 35–49.

Vaid, J., Stiles-Davis, J., 1989. Mirror writing: an advantage for the left-handed? Brain Lang. 37, 616–627.

Van Eimeren, T., Wolbers, T., Munchau, A., Buchel, C., Roman Siebner, H., 2006. Implementation of visuospatial cues in response selection. Neuroimage 29, 286–294.

Van Mier, H., Tempel, L.W., Perlmutter, J.S., Raichle, M.E., Petersen, S.E., 1999. Changes in brain activity during motor learning measured with PET: effects of hand of performance and practice. J. Neurophysiol. 80, 2177–2199.

Weiner, M.J., Hallett, M., Funkenstein, H.H., 1983. Adaptation to lateral displacement of vision in patients with lesions of the central nervous system. Neurology 33, 766–772.

Willingham, D.B., Koroshetz, W.J., 1993. Evidence for dissociable motor skills in Huntington's disease patients. Psychobiology 21, 173–182.

Wise, S.P., Boussaoud, D., Johnson, P.B., Caminiti, R., 1997. Premotor and parietal cortex: corticocortical connectivity and combinatorial computations. Annu. Rev. Neurosci. 74 (4), 469–482.

Wolpert, D.M., Ghahramani, Z., Jordan, M.I., 1995. An internal model for sensorimotor integration. Science 269, 1880–1882.