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The Potential for Utilizing the "Mirror Neurone System" to Enhance Recovery of the Severely Affected Upper Limb Early after Stroke: A Review and Hypothesis

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Recovery of upper limb movement control after stroke might be enhanced by repetitive goal-directed functional activities. Providing such activity is challenging in the presence of severe paresis. A possible new approach is based on the discovery of mirror neurons in the monkey cortical area F5, which are active both in observing and executing a movement. Indirect evidence for a comparable human "mirror neurone system" is provided by functional imaging. The primary motor cortex, the premotor cortex, other brain areas, and muscles appropriate for the action being observed are probably activated in healthy volunteers observing another's movement. These findings raise the hypothesis that observation of another's movement might train the movement execution system of stroke patients who have severe paresis to bring them to the point at which they could actively participate in rehabilitation consisting of goal-directed activities. The point of providing an observation therapy would be to facilitate the voluntary production of movement; therefore, the condition of interest would be observation with intent to imitate. However, there is as yet insufficient evidence to enable the testing of this hypothesis in stroke patients. Studies in normal subjects are needed to determine which brain sites are activated in response to observation with intent to imitate. Studies in stroke subjects are needed to determine how activation is affected after damage to different brain areas. The information from such studies should aid identification of those stroke patients who might be most likely to benefit from observation to imitate and therefore guide phase I clinical studies.

Key Words: *Stroke—Physical therapy—Mirror neurones—Rehabilitation.*

Advances in imaging the living brain have delivered knowledge about the neuroplastic processes that underlie clinical, observable, motor recovery after stroke. Neuroimaging has also revealed that physical therapy may induce brain plasticity after stroke in patients, not only in the subacute phase but also in the chronic phase of recovery (reviewed by Calautti and Baron[1]). Physical therapy can promote neuroplasticity as well as enhance motor recovery after stroke,[2,3] and "rehabilitation interventions can be designed around these experience-dependent neural systems."[4]

Two recent reports highlight how current neurorehabilitation research promises treatments that may bring greater benefits for brain-damaged patients than are able to be provided now. The Academy of Medical Sciences Report[5] and the report of the First International Workshop on Neuroimaging and Stroke Recovery[6]

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both emphasize the need for basic and clinical scientists to exploit advances of current research and to undertake research collaboratively. "A new science of neurorehabilitation therefore lies within our grasp."[5]

A possible new approach to promote recovery of movement control of the upper limb is based on the discovery of mirror neurones in cortical area F5 of the monkey, which are active both in observing and executing a movement.[7–11] On indirect evidence of functional imaging, a comparable mirror neurone system is proposed in man, that is, there is a functional correspondence between imagining and motor action, observing another person doing it and executing the motor action.[12] The aim of this review is therefore to explore whether the mirror neurone system could be harnessed by a physical therapy intervention consisting of patients observing another's upper limb movement with intent to imitate it.

The review is divided into 3 parts. Part 1 is a narrative review of the pointers toward potential effective therapy arising out of published clinical neurorehabilitation research and the potential of harnessing the mirror neurone system by observation to imitate therapy. Part 2 is a systematic review of the published human neuroimaging studies of the mirror neurone system to identify brain areas activated by observation and observation with intent to imitate. Part 3 provides a synthesis of the findings of parts 1 and 2 and also caries a hypothesis for further research.

PART 1. CLINICAL POINTERS AND THE "MIRROR NEURONE SYSTEM"

Clinical Science Clues for Effective Therapy

Motor recovery of voluntary movement control of the upper limb after stroke presents a major clinical challenge. Six months after stroke, only 38% of patients recovered some dexterity in the paretic arm and only 12% showed substantial functional recovery despite having received rehabilitation.[13] As there are approximately 80,000 new stroke survivors each year in the UK alone, the impact of poor motor recovery is clear. More effective therapy is urgently required.

Clinical reports that the amount of therapy might be inadequate are supported by the finding of an observational survey that patients within the first 14 days after stroke spent only 13% of the "working day" in therapeutic activities.[14] Narrative and systematic reviews of clinical studies suggest that more therapy might provide a better outcome after stroke.[15,16] However, 5 subsequent trials that provided different amounts of extra physical therapy (mostly that conventional in the UK and thus based largely on the Bobath approach[17]) did not find that increased intensity of therapy improved outcome.[18–22] It is nevertheless possible that the dose of extra therapy provided (maximum 30 min a day, 5 days a week for 6 weeks[22]) was still insufficient, in that the extra therapy provided by Kwakkel and colleagues,[23,24] 30 min per day 5 days a week for 20 weeks was found to improve outcome. Uncertainty remains, however, as dosage determinations have not featured in therapy research as a precursor to clinical trials. Another difference between the positive and equivocal trials was that the therapy provided by Kwakkel and colleagues[23,24] consisted of functional activity, that is, movements forming components of everyday living. In addition, a post hoc analysis of data from the trial conducted by Lincoln and colleagues[18] concludes that improvement might have resulted from additional therapy consisting of repetitive functional activity.[25] Taken together, the results of these studies suggest that repetitive functional activity might improve outcome, a proposal supported by observations that repetitive training of sit-to-stand enhances the ability of stroke patients to rise safely to standing.[26] This is consistent with experimental observations of changes in the shape and size of cortical activation areas and improvements in voluntary movement control following activities that are repetitive, functional, and challenging.[27] Human studies of such therapies have also found beneficial effects. For example, finger tracking training provided for a group of patients with chronic stroke (0.8 to 21 years after the ictus) resulted in improved hand function and a switch from ipsilateral to contralateral cortical activation as measured by fMRI,[28] a change that has been associated with better motor recovery.[29] The present evidence therefore indicates that therapeutic activities need to be associated with an adequate dose of goal-directed functional activities, which is known to further promote stroke recovery.[30]

If patients have sufficient voluntary activation of muscles to produce movement early after stroke, they can be expected to execute repetitive, functional activities (e.g., functional training). Indeed, patients at least 1 year after stroke who have some ability to produce voluntary extension of the wrist have been shown to improve following constraint-induced therapy, which “forces” increased activity with the paretic limb.[2,31–38] If, however, patients do not have sufficient voluntary activation of muscles, the challenge is how to provide such functionally related input. Clinical studies suggest that some function can be gained early after stroke following repetitive movement to stimulate muscle activity particularly around the shoulder complex,[39,40] but normal movement during functional activity requires activation of muscles in functionally related temporal sequences.[41] This may be facilitated by motor imagery[42]: a form of mental imagery in which even paralyzed patients could participate. It is reported to be beneficial in stroke rehabilitation,[43,44] although studies on healthy adults suggest that it will probably not replace actual physical practice in those stroke patients with sufficient residual movement control and power to attempt functional goals.[45,46]

Mental imagery is said to occur when “perceptual information is accessed from memory.”[47] In the case of motor imagery, this is when movement is imagined rather than executed. Studies with small samples of individuals after stroke have found that motor imagery training may improve performance on the trained task.[48,49] In intact normal individuals, motor imagery activates brain areas used in movement control, including the premotor cortex, primary motor cortex, and parietal lobe,[50–53] which may be the basis of “mental practice” to improve motor performance (reviewed by Kosslyn and colleagues[47] and Page[43]). In stroke patients (aged 51–82 years with left hemiplegia associated with a variety of lesion sites in the right hemisphere), EEG studies have shown that brain activity changes during motor imagery and that these changes are similar to those obtained in healthy adults.[54] But not all brain areas involved in the execution of movement are activated by motor imagery,[55,56] and early after stroke many patients experience fatigue,[57–59] reducing the level of attention.[57] This may impair the ability to concentrate sufficiently to participate in motor imagery. A key limitation is that compliance with mental imagery is difficult to assess, as no movement is observable and thus clinical assessment and correction of performance is difficult.

The Mirror Neurone System

One way of overcoming these limitations and developing motor imagery as a therapeutic strategy is suggested by simulation theory: a philosophical account of how intentions of others are inferred from their actions by the observer’s internal generation of similar activities and processes.[7,60] The theory proposed the existence of a central nervous functional correspondence between movement (action) imagery, movement observation, and movement execution. This proposal has been supported by studies in the monkey that an observation/execution matching system, the “mirror neurone system,” exists in monkeys for goal-directed activity involving manipulation of objects and mouth movements and that mirror neurones could be identified in brain area F5.[7–11]

In humans, there is evidence that when Broca’s area (Brodmann area 44, which is held to be the human equivalent of monkey area F5) is inhibited by transcranial magnetic stimulation (TMS), imitation and manual dexterity may then be adversely affected. For example, the number of errors for an imitation task executed with the dominant right hand was found to be significantly higher when activity in the pars opercularis was inhibited by TMS than when activity in the occipital cortex was similarly inhibited.[61] In another experimental study, TMS over area 44 in all subjects gave rise to immediate slowing and clumsiness of contralateral fine finger movements.[62] These experimental findings suggest that mirror neurones, found in monkeys, probably also exist in healthy adult humans. Indeed, Broca’s area has been found to be activated during preparation to imitate a movement,[63] by imagining hand actions and by observing hand actions (reviewed by Rizzolatti and colleagues[64]). In man, it might be possible therefore to use observation of another’s hand and arm movements as a therapy to produce activity in the “mirror neurone system” and thus facilitate activity in stroke patients. This could serve as a substrate for rebuilding sufficient activity in the movement execution system for the production of voluntary movement in paretic limbs after stroke. However, the success of an observation therapy would be dependent on a mirror neurone system being present in humans as well as monkeys and that this has correspondence with the movement execution system. Therapeutic benefit would also be expected to be dependent on certain brain areas being intact after stroke. Indeed, experimental findings[61–64] indicate that an intact Broca's area might be essential for benefit from observation therapy after stroke. Other areas of the movement execution system might also need to be intact, although white matter connectivity might be more important after stroke.[6]

In a meta-analysis of fMRI and PET studies, it was found that key parts of the human movement execution system were activated by execution, imagining action, and observing action.[12] These findings provide further evidence for a mirror neurone system in humans corresponding with the movement execution system, although activation of the primary motor cortex (M1) and the ventral premotor cortex (Brodmann area 44) was not found during observation and observation with intent to imitate (OTI). There is some support therefore for using observation of another's motor action as a therapy for stroke patients with severe paresis. The point of providing an observation therapy would be to facilitate the voluntary production of movement; in therapeutic use, therefore, the condition of interest would be observation with intent to imitate (OTI). Indeed, healthy volunteers have been found to produce a finger movement faster when observing and intending to imitate the same movement produced by another than in response to symbolic or spatial cues to move their fingers.[65,66] In addition, clinical reports suggest that copying the therapist after observation with intent to imitate has a greater beneficial effect on functional ability than following verbal instructions to complete a functional task. It is important to note that it is possible that the mirror neurone system provides the mechanism underlying these experimental and clinical reports.

Direct support from the meta-analysis for a potential therapy of OTI is limited for 4 main reasons:

1. The primary studies included in a previous meta-analysis[12] analyzed imaging data using a subtraction method, that is, the subtraction of functionally activated regions in one experimental condition from those activated during another condition. This provides data only on the *differences* between the experimental conditions examined. Thus, the full extent of the functional network attributed to a given experimental condition could not be determined. Essentially the meta-analysis provides information about differences between conditions rather than what all the conditions have in common. But the possibility remains that observation conditions do produce activity in the areas of motor and premotor cortex activated by both execution and imagining action.
2. It is not possible to separate data relating to differences between observation and OTI from the results of the meta-analysis as these were combined for the purposes of the study.[12] Of the 8 observation studies included in the meta-analysis, only 2 used the paradigm of observation with intent to imitate. Whether observation and OTI produce activation in the same parts of the brain consequently cannot be determined from this meta-analysis.
3. The aim of the meta-analysis[12] was to find whether a mirror neurone system exists in the human brain and whether there is functional correspondence with the movement execution system. No data were provided regarding the activity of upper limb muscles in relation to the task. However, it would be of clinical importance if observation of another's action, with or without the intention to imitate, increased activity in the motor neurones and muscles that would be employed in the observed action, that is, to prime them for actual, observable functional activity. There is some independent evidence that activity is increased in muscles by observation of another's action. For example, observation of arm wrestling has been found to increase EMG activity in arm muscles, whereas observation of stuttering was found to increase EMG activity in lip muscles.[67] Furthermore, in TMS studies, observation of another's motor action facilitates the cortex and thereby activates the muscles relevant for the action being observed.[62,68–70] Thus, observing another's movement might increase activity in the motor neurones supplying effector muscles and thus prime them for actual observable movement.
4. Although these findings suggest that observation of another's movement may be a potential therapy after stroke to facilitate activity in brain areas activated during movement execution,[12] none of the primary studies was undertaken in stroke patients, and consequently there is no direct evidence that the same networks will be activated in stroke patients. Moreover, the meta-analysis provided no direct information about the effects of different sites of brain damage on activation of the movement execution system and muscles relevant to the observed movement. This information will be of critical importance for the identification of stroke patients who might be most likely to benefit from this potential therapy.

In summary, there is substantial indirect evidence of a human mirror neurone system and for increased activity in relevant muscles when motor activity is observed. This leads to the hypothesis that performance of movement could be improved by the therapeutic use of OTI to train the movement execution system of stroke patients who have paralysis or severe paresis, to bring them to the point at which they could actively participate in a rehabilitation program consisting of repetitive functional activities. However, it is reasonable to assume that benefit from OTI after stroke might be limited by the areas of brain that have been damaged. What is immediately lacking is information about the full extent of activation in the movement execution system by OTI in groups of stroke patients with different brain lesions to inform clinical studies of the potential therapeutic use of OTI after stroke.

PART 2. AREAS OF THE MOVEMENT EXECUTION SYSTEM ACTIVATED BY OBSERVATION AND OBSERVATION WITH INTENT TO IMITATE

Purpose

The primary purpose of the published meta-analysis was to review the evidence for the existence of the mirror neurone system and not to determine the potential for using OTI for treating stroke patients. Moreover, further primary studies have been published since publication of the meta-analysis in 2001. We therefore conducted a systematic review of the published neuroimaging studies to determine whether there was sufficient information as yet to answer the following clinical questions:

1. In healthy volunteers, what is the full extent of the movement execution system activated by observation and observation with intent to imitate?
2. In healthy volunteers, are there differences in the areas of the movement execution system (including muscles that would be involved in execution of the observed movement) activated by mere observation of another's movement as opposed to observation of another's movement with the intention to imitate?
3. In stroke patients observing another's movement with the intention to imitate, what are the effects of different sites of brain damage on activation of the movement execution system including the muscle activity that would be involved in the execution of the observed movement?

Literature Search

We used the search terms *imitative behaviour (physiology)* and *mirror neurones* to search the electronic databases: MEDLINE, EMBASE, AMED, and CINAHL (1966 to June 2004). In addition, we searched our own "library" of published papers and the reference lists of included papers.

Inclusion Criteria for Identified Published Studies

All studies.

1. Adult human subjects (healthy volunteers and people who have suffered a stroke)
2. Data provided on upper limb activity

Studies examining areas of brain activity.

3. Neuroimaging of brain activity using fMRI, PET, or MEG (magneto-encephalography)
4. Compared the brain areas activated by observation and OTI of another's upper limb movement and/or provided data on the full extent of areas activated by observation or OTI (with or without the presence of an object)

Studies examining muscle activation.

5. Examined muscles activated by observation of another's upper limb movement with and without the intention to imitate using TMS

Identification of Relevant Trials and Extraction of Data

Two researchers independently assessed the abstracts of identified studies against the inclusion criteria to identify those papers that were likely to meet the inclusion criteria. These full papers were then read independently by 2 researchers who assessed whether they did or did not meet the inclusion criteria. Any disagreements were resolved through discussion and referral to the full paper to decide whether or not the paper was to be included in this systematic review. This process

Table 1. Outline of Relevant Experimental Conditions in Neuroimaging Studies Included in the Systematic Review

Study Reference	Imaging Modality	Subjects	Outline of Experimental Conditions Relevant to This Review
Aziz-Zadeh 2002[68]	TMS	16 healthy right-handed volunteers aged 26 (19–38)	1. Observed a movement of left and right hands on a computer screen. The index finger of each stimulus hand moved toward a red dot every 600 ms 2. Observed an object movement on a computer screen
Buccino 2001[75]	fMRI	12 healthy right-handed volunteers aged 25–38	1. Observed videotaped object-related upper limb actions performed by another 2. Observed videotaped non-object-related upper limb actions performed by another
Fadiga 1995[69]	TMS	12 healthy volunteers, (handedness)	1. Observed another tracing a complex geometric shape in the air 2. Observed another grasping objects of different sizes and shapes 3. Observed same objects as in object-grasping condition
Grafton 1996[72]	PET	7 healthy right-handed volunteers aged 22.6 (19–28)	1. Observed object being held by examiner 2. Observed object being grasped by examiner using precision grasp—“only the final enclosure of the examiner’s fingers with each object was viewed”
Grezes 1998[73]	PET	10 healthy right-handed volunteers aged 20–28	1. Observed a pantomime of a meaningful action (e.g., opening bottle, sewing button) 2. Observed with intent to imitate a pantomime of a meaningful action 3. Observed a pantomime of action meaningless to subjects (American Sign Language) 4. Observed with intent to imitate a pantomime of a meaningless action
Grezes 1999[74]	PET	9 healthy right-handed volunteers aged 23–36	1. Observed without purpose—learned meaningless movements 2. Observed to imitate—learned meaningless movements 3. Observed without purpose—unknown meaningless movements 4. Observed to imitate—unknown meaningless movements
Grezes 2003[76]	fMRI	12 healthy right-handed volunteers aged 19–39	1. Observed an object, a grasp and an object being grasped 2. Observed a stationary background 3. Executed grasp appropriate for object, pantomime of grasping object, and grasping object
Jarvelainen 2004[71]	MEG	9 healthy right-handed volunteers aged 28.1 ± 3.1	1. Observed experimenter using chopsticks to move small objects, with chopsticks making same movements but not moving objects, moving small objects using thumb/index finger 2. Rested fixating eyes on a point on the wall
Strafella 2000[70]	TMS	8 healthy right-handed volunteers aged 25 ± 5	1. Observed experimenter handwriting and moving arm 2. Resting condition

resulted in a set of papers from which data were then extracted independently by 2 researchers (these are referred to as *included papers*).

Results

The literature search identified 89 papers, and a further 12 were identified from our library. Of these 101 papers, 42 passed through the abstract screen for review of the full papers. Nine papers met all the study criteria and were included for data extraction. The neuroimaging modality was MEG in 1 study.[71] PET in 3 studies,[72–74] fMRI in 2 studies,[75,76] and TMS in the remaining 3 studies.[68–70] The subjects were healthy volunteers in all the studies and were described as right-handed in 8 of the 9 (one study did not state which hand was dominant). The experimental conditions used in included studies are outlined in Table 1.

Table 2. Areas Activated by Observation of Movement and Observation of Movement with Intention to Imitate as Found by Studies Included in This Review

Areas	Brodmann Area (Where Known or Relevant)	Observation	Observation to Imitate
Primary motor cortex (M1)		Left[71]	No data available
Premotor cortex	6, 44, 45	Left[72]; bilateral[75,76]	No data available
Supplementary motor area	6	Right[72]	No data available
Ventral precentral sulcus		Left[76]	No data available
Anterior intraparietal area		Bilateral[75]	No data available
Inferior parietal sulcus	40/42	Left[72]	No data available
Intraparietal sulcus		Bilateral[76]	
Parietal operculum	22/40	Left[72]; right[76]	No data available
Superior temporal sulcus	21/22	Left[72]; bilateral[76]	No data available
Posterior cerebellum: medial		Right[72]	No data available
Muscles appropriate for action being observed		Yes[68–70]	No data available

Extent of activation of movement execution system by observation and OTI. The studies included in the present systematic review provided no information about the extent of activation of the movement execution system by OTI (Table 2). For observation of another's movement, activation was found in the ventral precentral sulcus, primary motor cortex, premotor cortex, supplementary motor area, anterior intraparietal area, intraparietal sulcus, inferior parietal sulcus, parietal operculum, superior temporal sulcus, posterior cerebellum, and also the muscles that would be included in execution of the activity being observed (Table 2).

Differences between observation and observation with intent to imitate. The effects of observation and OTI on the activation of areas of the movement execution system are shown in Table 3. Differences were found between observation and OTI including activation of the parietal lobe and cerebellum in OTI but not in observation.

Effects of stroke lesions. No studies were identified by the present systematic review.

Interpretation

The findings of this systematic review extend those of Grezes and Decety,[12] as they provide evidence that M1, the premotor cortex, and muscles appropriate for the action being observed are probably activated in healthy volunteers observing another's motor activity (Table 2). However, it is clear from Table 2 that the full extent of the movement execution system activated by observation and OTI remains to be elucidated in healthy volunteers. It is conspicuous that little information is available on the extent of the movement execution network activated by OTI (Table 2), although some information about brain areas involved is provided by 2 studies conducted by Grezes and colleagues[73,74] (Table 3). These data, though, are limited, as the primary studies used the subtraction method to analyze imaging data. It is, however, reasonable to assume that as muscles appropriate for the action being observed are activated by observing another's movement, then they would also be activated by observation with intent to imitate (OTI). Consequently, in healthy volunteers, there is indirect evidence that sufficient areas of the movement execution system are activated by OTI to increase EMG activity in relevant motorneurones and muscles, but it remains unknown exactly which brain areas are activated.

In stroke subjects, the present systematic review found no evidence to guide the use of OTI as a potential therapeutic strategy. Further work is needed to explore the effects of OTI on activation of the movement execution system in groups of stroke patients with different brain lesions. In addition, the experimental conditions used by Grezes and colleagues[73,74] are not directly related to the upper limb motor activity that would be trained after stroke, as they included meaningless movements (Table 1). Clinical experience and experimental studies[18,23–25] indicate that therapy is probably best directed at improving ability to use the paretic upper limb to undertake everyday tasks such as brushing teeth or in tasks requiring some dexterity such as turning the pages of a book. Fur-

Table 3. Areas Differentially Activated by Observation of Movement and Observation of Movement with Intention to Imitate as Found by Studies Included in This Review

Areas	Brodmann Area (Where Known or Relevant)	Observation	Observation to Imitate
Bilateral areas (generally left more active)			
Precentral gyrus	4		Yes[74]
Superior parietal lobule	19		Yes[74]
Precuneus			Yes[74]
Cerebellum			Yes[74]
Left areas			
Inferior frontal gyrus	44–45	Yes[73]	
Fusiform gyrus	20	Yes[73]	
Cuneus	7		Yes[74]
Superior parietal lobule	7		Yes[73]
Inferior temporal gyrus	20/38	Yes[73]	
Right areas			
Dorsolateral prefrontal cortex following middle frontal sulcus			Yes[74]
Lingual gyrus	19/18	Yes[73]	
Anterior cingulate gyrus			Yes[74]
Superior parietal lobule crossing intraparietal sulcus and extending into the inferior parietal lobule (BA 40)	$7 \rightarrow 40$		Yes[73]
Inferior parietal			Yes[74]
Cerebellum			Yes[73]

ther work is required to investigate whether the findings summarized in Table 3 can be generalized to stroke subjects observing meaningful, object-related motor tasks with the intent to imitate them.

PART 3. SYNTHESIS AND HYPOTHESIS

In the presence of severe paralysis or paresis, precluding sufficient voluntary activation of muscle to produce functional activity, it is possible that OTI might produce activity in the movement execution system including the motorneurones and paretic muscles required to produce the observed action, and hence might improve the recovery of movement and functional ability after stroke.

The present review demonstrates there is as yet insufficient direct evidence to enable the testing of this hypothesis in stroke subjects. First, studies in normal subjects are needed to determine the activation of different brain sites in response to OTI. Second, studies are needed in stroke subjects to determine how activation is affected after damage to different brain areas. The information from such studies should provide important knowledge to inform the identification of those stroke patients who might be most likely to benefit from OTI and therefore guide essential phase I clinical studies.

REFERENCES

1. Calautti C, Baron J-C. Functional neuroimaging studies of motor recovery after stroke in adults. A review. *Stroke* 2003;34:1553-66.
2. Johansen-Berg H, Dawes H, Guy C, Smith S, Wade D, Matthews P. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain* 2002;125:2731-42.
3. Liepert J, Bauder H, Miltner W, Taub E, Weiller C. Treatment-induced cortical reorganization after stroke in humans. *Stroke* 2000;31:1210-6.
4. Dobkin BH. Functional rewiring of brain and spinal cord after injury: the three Rs of neural repair and neurological rehabilitation. *Curr Opin Neurol* 2000;13:655-9.
5. The Academy of Medical Sciences. *Restoring neurological function: putting the neurosciences to work in neurorehabilitation*. London: The Academy of Medical Sciences; 2004.
6. Baron J-C, Cohen LG, Cramer SC, et al. Neuroimaging in stroke recovery: a position paper from the First International Workshop on neuroimagining and stroke recovery. *Cerebrovasc Dis* 2004;18:260-7.
7. Gallese V, Goldman A. Mirror neurons and the simulation theory of mind-reading. *Trends Cognit Sci* 1998;2(12):493-500.
8. Ferrari P, Gallese V, Rizzolatti G, Fogassi L. Mirror neurons responding to the observation of ingestive and communicative mouth actions in the monkey ventral premotor cortex. *Eur J Neurosci* 2003;17:1703-14.
9. Gallese V, Fadiga L, Fogassi L, Rizzolatti G. Action recognition in the premotor cortex. *Brain* 1996;119:593-609.
10. Rizzolatti G, Fadiga L, Gallese V, Fogassi L. Premotor cortex and the recognition of motor actions. *Cognit Brain Res* 1996;3:131-41.

11. Raos V, Evangeliou M, Savaki H. Observation of action: grasping with the mind's hand. *NeuroImage* 2004;23:193-201.
12. Grezes J, Decety J. Functional anatomy of execution, mental simulation, observation and verb generation of actions: a meta-analysis. *Hum Brain Mapp* 2001;12:1-19.
13. Kwakkel G, Kollen B, van der Grond J, Prevo A. Probability of regaining dexterity in the flaccid upper limb. *Stroke* 2003;34:2181-6.
14. Bernhardt J, Dewey H, Thrift A, Donnan G. Inactive and alone physical activity within the first 14 days of acute stroke unit care. *Stroke* 2004;35:1005-9.
15. Langhorne P, Wagenaar RC, Partridge C. Physiotherapy after stroke: more is better? *Physiother Res Int* 1996;1:75-88.
16. Kwakkel G, Wagenaar RC, Koelman TW, Lankhorst GJ, Koetsier JC. Effects of intensity of rehabilitation after stroke. A research synthesis. *Stroke* 1997;28:1550-6.
17. Bobath B. *Adult hemiplegia. Evaluation and treatment*. Oxford (UK): Butterworth-Heinemann; 1990.
18. Lincoln NB, Parry RH, Bass CD. Randomized, controlled trial to evaluate increased intensity of physiotherapy treatment of arm function after stroke. *Stroke* 1999;30:573-9.
19. Partridge C, Mackenzie M, Edwards S, et al. Is dosage of physiotherapy a critical factor in deciding patterns of recovery from stroke: a pragmatic randomized controlled trial. *Physiother Res Int* 2000;5:230-40.
20. Slade A, Tennant A, Chamberlain M. A randomised controlled trial to determine the effect of intensity of therapy upon length of stay in a neurological rehabilitation setting. *J Rehabil Med* 2002;34:260-6.
21. Pollock A, Durward B, Rowe P, Paul J. The effect of independent practice of motor tasks by stroke patients: a pilot randomized controlled trial. *Clin Rehabil* 2002;16:473-80.
22. Rodgers H, Mackintosh J, Price CI, et al. Does an early increased-intensity interdisciplinary upper limb therapy programme following acute stroke improve outcome? *Clin Rehabil* 2003;17:579-89.
23. Kwakkel G, Kollen B, Wagenaar R. Long term effects of intensity of upper and lower limb training after stroke: a randomised trial. *J Neurol Neurosurg Psychiatry* 2002;72:473-9.
24. Kwakkel G, Wagenaar R, Twisk J, Lankhorst G, Koetsier J. Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial. *Lancet* 1999;354:191-6.
25. Parry RH, Lincoln NB, Vass CD. Effect of severity of arm impairment on response to additional physiotherapy early after stroke. *Clin Rehabil* 1999;13:187-98.
26. Barreca S, Sigouin C, Lambert C, Ansley B. Effects of extra training on the ability of stroke survivors to perform an independent sit-to-stand: a randomized controlled trial. *J Geriatr Phys Ther* 2004;27(2):59-64.
27. Turkstra L, Holand A, Bays G. The neuroscience of recovery and rehabilitation: what have we learned from animal research? *Arch Phys Med Rehabil* 2003;84:604-12.
28. Carey J, Kimberley T, Lewis S, et al. Analysis of fMRI and finger tracking training in subjects with chronic stroke. *Brain* 2002;125(4):773-88.
29. Ward N, Brown M, Thompson A, Frackowiak R. Neural correlates of outcome after stroke: a cross-sectional fMRI study. *Brain* 2003;126:1430-48.
30. Buonomano D, Mersenich M. Cortical plasticity: from synapses to maps. *Annu Rev Neurosci* 1998;21:149-86.
31. Kopp B, Kinkel A, Muklnickel W, Villringer K, Taub E, Flor H. Plasticity in the motor system related to therapy-induced improvement of movement after stroke. *Neuroreport* 1999;10:807-10.
32. Liepert J, Miltner WHR, Bauder H, et al. Motor cortex plasticity during constraint-induced movement therapy in stroke patients. *Neurosci Lett* 1998;250:5-8.
33. Miltner W, Bauder H, Sommer M, Dettmers C, Taub E. Effects of constraint-induced movement therapy on patients with chronic motor deficits after stroke. *Stroke* 1999;30:586-92.
34. Ostendorf C, Wolf S. Effect of forced use of the upper extremity of a hemiplegic patient on changes in function. *Phys Ther* 1981;61(7):1022-8.
35. Schaechter J, Kraft E, Hilliard T, et al. Motor recovery and cortical reorganization after constraint-induced movement therapy in stroke patients: a preliminary study. *Neurorehabil Neural Rep* 2002;16(4):326-38.
36. Tremblay F, Tremblay L. Constraint-induced movement therapy: evidence for its applicability in the context of a home rehabilitation intervention for sub-acute stroke. *Physiother Can* 2002;54:116-31.
37. van der Lee JH, Wagenaar RC, Lankhorst GJ, Vogelaar TW, Deville WL, Bouter LM. Forced used of the upper extremity in chronic stroke patients. Results from a single-blind randomized clinical trial. *Stroke* 1999;30:2369-75.
38. Wolf SL, Lecraw DE, Barton LA, Jann BB. Forced use of hemiplegic upper extremities to reverse the effect of learned nonuse among chronic stroke and head-injured patients. *Exp Neurol* 1989;104:125-32.
39. Feys HM, De Weerdt W, Selz BE, et al. Effect of a therapeutic intervention for the hemiplegic upper limb in the acute phase after stroke: a single-blind, randomised controlled multicenter trial. *Stroke* 1998;29(4):785-92.
40. Feys H, De Weerdt W, Verbeke G, et al. Early and repetitive stimulation of the arm can substantially improve the long-term outcome after stroke: a 5-year follow-up study of a randomized trial. *Stroke* 2004;35:924-9.
41. van Ingen Schenau G. From rotation to translation: constraints on multi-joint movements and the unique action of bi-articular muscles. *Hum Move Sci* 1989;8:301-37.
42. Decety J. Should motor imagery be used in physiotherapy? Recent advances in cognitive neurosciences. *Physiother Theory Pract* 1993;9:193-203.
43. Page SJ. Mental practice: a promising restorative technique in stroke rehabilitation. *Top Stroke Rehabil* 2001;8:54-63.
44. Stevens JA, Stoykov MEP. Using motor imagery in the rehabilitation of hemiparesis. *Arch Phys Med Rehabil* 2003;84:1090-2.
45. Hird J, Landers D, Thomas J, Horan J. Physical practice is superior to mental practice in enhancing cognitive and motor task performance. *J Sport Exerc Psychol* 1991;8:281-93.
46. Yue G, Cole KJ. Strength increases from the motor program: comparison of training with maximal voluntary and imagined muscle contractions. *J Neurophysiol* 1992;67:1114-23.
47. Kosslyn SM, Ganis G, Thompson L. Neural foundations of imagery. *Nature Rev Neurosci* 2001;2:635-42.
48. Crosbie J, McDonough S, Gilmore D, Wiggam M. The adjunctive role of mental practice in the rehabilitation of the upper limb after hemiplegic stroke: a pilot study. *Clin Rehabil* 2004;18:60-8.
49. Dijkerman H, Letswaart M, Johnston M, MacWalter R. Does motor imagery training improve hand function in chronic stroke patients? A pilot study. *Clin Rehabil* 2004;18:538-49.
50. Binkofski F, Amunts K, Stephan KM, et al. Broca's region subserves imagery of motion: a combined cytoarchitectonic and fMRI study. *Hum Brain Mapp* 2000;11:273-85.

51. Decety J, Perani D, Jeannerod M, et al. Mapping motor representations with positron emission tomography. *Nature* 1994;371:600-2.
52. Ruby P, Decety J. Effect of subjective perspective taking during simulation of action: a PET investigation of agency. *Nature Neurosci* 2001;4(5):546-50.
53. Rodriguez M, Muniz R, Gonzalez B, Sabate M. Hand movement distribution in the motor cortex: the influence of a concurrent task and motor imagery. *Neuroimage* 2004;22:1480-91.
54. Weiss T, Hansen E, Beyer L, et al. Activation processes during mental practice in stroke patients. *Int J Psychophysiol* 1994;17:91-100.
55. Lotze M, Montoya P, Erb M, et al. Activation of cortical and cerebellar motor areas during executed and imagined hand movements: an fMRI study. *J Cognit Neurosci* 1999;11:491-501.
56. Stephan KM, Fink GR, Passingham RE, et al. Functional anatomy of the mental representation of upper extremity movements in healthy subjects. *J Neurophysiol* 1995;73:373-86.
57. Brodal A. Self-observations and neuro-anatomical considerations after a stroke. *Brain* 1973;96:675-94.
58. Glader E-L, Stegmayr B, Asplund K. Poststroke fatigue. *Stroke* 2002;33:1327-33.
59. Staub F, Bogousslavsky J. Fatigue after stroke: a major but neglected issue. *Cerebrovasc Dis* 2001;12:75-81.
60. Blakemore SJ, Decety J. From the perception of action to the understanding of intention. *Nature Rev Neurosci* 2001;2:561-7.
61. Heiser M, Iacoboni M, Maeda F, Marcus J, Mazziotta J. The essential role of Broca's area in imitation. *Eur J Neurosci* 2003;17:1123-8.
62. Uozumi T, Tamagawa A, Hashimoto T, Tsuji S. Motor hand representation in cortical area 44. *Neurology* 2004;62:757-61.
63. Krams M, Rushworth MFS, Deiber M-P, Frackowiak RSJ, Passingham RE. The preparation, execution and suppression of copied movements in the human brain. *Exp Brain Res* 1998;120:386-98.
64. Rizzolatti G, Fogassi L, Gallese V. Motor and cognitive functions of the ventral premotor cortex. *Curr Opin Neurobiol* 2002;12:149-54.
65. Brass M, Bekkering H, Wohlschlager A, Prinz W. Compatibility between observed and executed finger movements: comparing symbolic, spatial and imitative cues. *Brain Cognit* 2000;44:124-43.
66. Tessari A, Rumiati RI, Haggard P. Imitation without awareness. *Neuroreport* 2002;13:2531-5.
67. Berger SM, Hadley SW. Some effects of a model's performance on an observer's electromyographic activity. *Am J Psychol* 1975;2:263-76.
68. Aziz-Zadeh L, Maeda F, Zaidel E, Mazziotta JC, Iacoboni M. Lateralization in motor facilitation during action observation: a TMS study. *Exp Brain Res* 2002;144:127-31.
69. Fadiga L, Fogassi L, Pavesi G, Rizzolatti G. Motor facilitation during action observation: a magnetic stimulation study. *J Neurophysiol* 1995;73:2608-11.
70. Strafella AP, Paus T. Modulation of cortical excitability during action observation: a transcranial magnetic stimulation study. *Exp Brain Res* 2000;11:2289-92.
71. Jarvelainen J, Schurmann M, Hari R. Activation of the human primary motor cortex during observation of tool use. *Neuroimage* 2004;23:187-92.
72. Grafton S, Arbib M, Fadiga L, Rizzolatti G. Localization of grasp representations in humans by positron emission tomography. 2. Observation compared with imagination. *Exp Brain Res* 1996;112:103-11.
73. Grezes J, Costes N, Decety J. Top-down effect of strategy on the perception of human biological motion: a PET investigation. *Cognit Neuropsychol* 1998;15:553-82.
74. Grezes J, Costes N, Decety J. The effects of learning and intention on the neural network involved in the perception of meaningless actions. *Brain* 1999;122:1875-87.
75. Buccino G, Binkofski F, Fink G, et al. Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. *Eur J Neurosci* 2001;13:400-4.
76. Grezes J, Armony J, Rowe J, Passingham RE. Activations related to "mirror" and "canonical" neurones in the human brain: an fMRI study. *Neuroimage* 2003;18:928-37.