NEUROREHABILITATION AFTER STROKE

Rüdiger J. Seitz,[1] Leeanne M. Carey[2]

1. Centre of Neurology and Neuropsychiatry, LVR-Klinikum Düsseldorf, and Department of Neurology, University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany
2. Neurorehabilitation and Recovery, Stroke Division, Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre - Austin Campus, Heidelberg Victoria, Australia; Department of Occupational Therapy, LaTrobe University, Bundoora, Australia

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ABSTRACT

Recovery from ischaemic stroke is determined in the acute phase by the lesion impact of ischaemia and subsequently, by functional and structural network changes in the spared brain tissue. Neurorehabilitation supports the restitution of function using repetitive, learning-based and, more recently, technology-based training strategies.

Keywords: Stroke, ischaemia, recovery potential, brain lesion, fibre tracts, structural connectivity, functional connectivity, rehabilitation, learning strategies, robot training, virtual reality.

PROGNOSIS OF ISCHAEMIC STROKE

Ischaemic stroke is an acute disease and one of the leading causes of persistent disability in Western countries.[1] It results from an interruption of cerebral blood supply, with subsequent ischaemic brain damage bearing a dubious prognosis. Recovery of the deficits of motion, sensation, cognition, or emotion resulting from stroke, depends on cerebrovascular factors and mechanisms of tissue-remodelling, ranging from hours to many months.[2,3] Thrombolysis has opened new avenues to substantially reverse the neurological deficits in the acute phase after stroke.[4-6] However, even large brain infarcts may lead to only minor and transient deficits that resolve completely within a couple of hours when they spare brain areas critical for motion, somatosensation and vision. This is illustrated in a patient who presented with transient ischaemic attack consisting of a two-hour period of abnormal sensation of her left hand and arm, and in whom magnetic resonance imaging (MRI) showed a large territorial infarct of cardioembolic origin (Figure 1). Thus, minor clinical symptoms may be caused by substantial brain lesions. However, this example also shows that the recovery from stroke commences early after the ischaemic event. The most important mechanism for early recovery is related to rapid arterial recanalisation and reperfusion of brain tissue. In the acute phase of stroke it is difficult to predict the degree of ultimate recovery, since even small infarcts may be caused by severe and life threatening diseases of the heart.[7] Moreover, a low socioeconomic status impairs the rate of functional recovery.[8] Finally, while longitudinal observations have shown that the neurological state by day 4 predicts the long-term neurological outcome,[9,10] there is good evidence that minor neurological deficits remain that become apparent only upon proper testing.[11,12]

Recent developments in neurorehabilitation have aimed at tailoring rehabilitation methods depending on the deficit pattern of the patients. Neurorehabilitation approaches vary and may include very early mobilisation,[13] anti-gravity support for walking,[14] basic arm training, arm ability training,[15] constraint movement therapy,[16] somatosensory discrimination training,[17] and language therapy.[18] Learning-based approaches

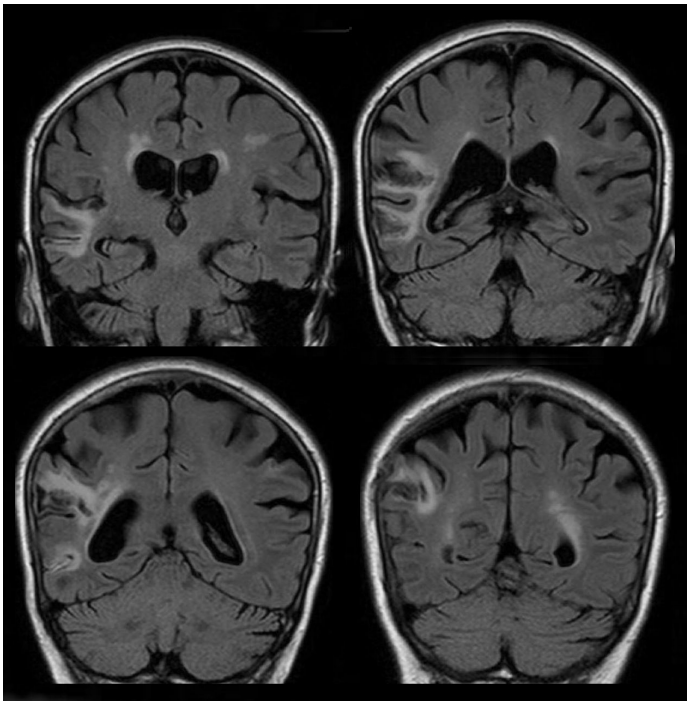

Figure 1. Transient sensory disturbance of the left hand that disappeared entirely within 2 hours, due to a large cardioembolic ischaemic brain infarct in the right cerebral hemisphere in a 72-year-old woman.

This coronal FLAIR-MRI was taken 6 weeks after the incident, showing involvement of the superior temporal gyrus and large parts of the inferior parietal lobule. The somatosensory cortex was spared. Note also the slight bilateral white matter changes typical of vascular encephalopathy probably due to inconsistent antihypertensive treatment.

are advocated, consistent with learning-dependent plasticity, and with the speciality of neurorehabilitation and its focus on the restoration and maximisation of functions.[19] It needs to be realised, however, that activities of daily living usually recover within 26 weeks after the stroke insult and are often accompanied by compensatory hand use.[20,21] This adaptation of the brain is functionally relevant but essentially not equivalent to cerebral plasticity affording restitution of function. Accordingly, the recovery potential of a stroke patient includes compensatory adaptation as well as functional restitution in the optimal and true sense of cerebral plasticity. The impact of the lesion on brain networks and knowledge of viable brain networks with capacity for plasticity is critical to target restorative stroke rehabilitation to the individual.[22]

RECOVERY POTENTIAL AFTER STROKE

The recovery potential is determined largely by the location and the volume of ischaemia and the cerebral infarct as determined on MRI.[3,23-28] Large brain lesions or small subcortical white matter lesions may affect multiple brain systems, resulting in complex neurological syndromes such as apraxia, spatial neglect or Gerstmann syndrome.[29-31] In particular, measures of fibre tract damage or cortical activations have been found to explain the recovery of motor,[23,32-35] language, somatosensory, and visual functions.[36-39] For example, the extent to which an individual patient will achieve good recovery of the upper limb function depends, in part, on the integrity of the corticospinal tract (CST) as determined by transcranial magnetic stimulation (TMS), on MRI, or with diffusion tensor imaging (DTI).[35,40,41] On clinical grounds, the degree of residual proximal arm movements determines the degree of recovery of hand function.[42] However, using clinical, neurophysiological and neuroimaging measures of CST integrity, a stepwise algorithm has been developed to predict upper limb function at the subacute phase.[40]

Beyond structural changes there are also functional changes in the brain following stroke. Regardless of subcortical or cortical location of infarction, these changes affect the perilesional tissue and the interhemispheric balance of activity.[43-45] Using paired-pulse TMS it was found that, within the first 7 days after a brain infarction, there is an enhanced cortical excitability in the cortex adjacent to the brain lesion but also in the contralateral hemisphere.[46-48] Notably, the enhanced perilesional excitability was transmitted to the intact motor cortex in the contralesional hemisphere. In keeping with these observations, functional MRI (fMRI), performed approximately 2 days after stroke, revealed an area in the ipsilesional postcentral gyrus and posterior cingulate gyrus that correlated with motor recovery approximately 3 months after stroke.[49] Furthermore, restoration of hand function, 3 months after stroke, was associated with highly lateralised activation of the affected sensorimotor cortex in fMRI, which developed over time.[50,51] In patients with a stable deficit in the chronic stage after stroke, a reduced strength of the precision grip of the affected hand was associated with an enhanced activation of the contralateral motor cortex in a demanding task involving the affected hand, while more severely

affected patients had greater motor cortex activation in the affected hemisphere.[52]

Apart from local activations, there is a pathological interhemispheric interaction between the ipsi and contralesional motor cortex as well as between the ipsilesional supplementary motor area (SMA) and contralesional motor cortex in patients with a single infarct lesion. This was shown by network type of analysis of functional imaging data.[53,54] In unilateral movements of the affected hand there was an inhibitory influence from the contralesional to the ipsilesional motor cortex, which correlated with the degree of motor impairment.[54] The importance of interhemispheric interactions and functional brain networks is further highlighted by evidence that disruption of interhemispheric connectivity predicts attention and motor performance deficits after stroke.[55]

Motor network connectivity strength was shown to correlate with motor outcome after stroke.[56] In chronic stroke patients, DTI-derived measures of transcallosal motor fibres, as well as the components of the ipsilesional corticospinal tract, could be used to explain the therapeutic response to rehabilitation: the more the diffusivity profiles resembled those observed in healthy subjects, the greater a patient's potential for functional recovery.[57] While these findings need to be substantiated by further investigations, they accord with the evidence from functional imaging, suggesting that the concerted action of both cerebral hemispheres is required for recovery. It is worthy of note that upper limb function is governed by a largely lateralised sensorimotor system, which allows identifications of the contribution of ipsilesional and contralesional changes in the motor and sensory system as well as network related changes in the brain contributing to recovery.

APPROACHES OF NEUROREHABILITATION

There are numerous reports about rehabilitative approaches to improve the neurological deficit following stroke.[58-60] By these measures, cortical and cortico-subcortical reorganisation (cerebral plasticity) is aimed at being enforced. The behavioural effects and neural mechanisms underlying evidence-based movement rehabilitation have been reviewed.[40] To date, most studies have been conducted in the chronic phase of recovery. Interventions that have been shown to improve motor function in the upper limbs and to influence brain activation in functional brain imaging and reorganisation, include constraint-induced movement therapy and task-specific interventions.[58,61,62] Notably, the intensity of the training rather than the type of targeted training appears to determine long-term improvement of motor function of the upper limbs.[63,64] Treadmill training was found to improve walking velocity, which correlated with brain activity in the posterior cerebellum in fMRI related to movement of the paretic limb.[65] Successful hand shaping and grasping of objects did not occur unless there was sufficient volitional control of finger and thumb extensions.[66] An important and largely neglected aspect of hemiparesis is the presence of spasticity that typically builds up progressively after stroke-counteracting voluntary movement. If botulinum toxin was combined with repetitive bilateral arm cycling training in chronic stroke patients, spasticity could be reduced. This was reflected clinically by a profound reduction of spasticity and a change of the cerebral activation pattern as evident from fMRI.[67]

The concept of 'learned non-use' was implemented in the so-called 'constraint-induced' therapy. It has been shown to be successful particularly when applied in the chronic state to moderately affected patients.[68,69] This beneficial effect of constraint-induced movement therapy is likely to be composed of focussing the patient's attention to the affected side. Imposing repetitive training results in improved motor function and enhanced functional brain activation in the partially damaged sensorimotor cortex.[32,69] Similar effects were achieved with bihemispheric direct cortical stimulation (DCS), which activated the affected motor cortex and inhibited the contralesional motor cortex.[70]

Mental training can also result in better functionality of the upper extremity and in greater gains of activities of daily living than standard physiotherapy.[71,72] FMRI revealed that motor imagery activated a widespread network of cerebral areas in motor, premotor and parietal cortex in both cerebral hemispheres.[56,72] In controlled trials, early after stroke, mirror therapy was found to improve the neurological status immediately after the intervention and at long-term follow-up.[73,74] Also, there is a transfer effect of the highly skilled hand to the affected hand in stroke patients.[75]

Based on the knowledge of postlesional pathophysiology it has been hypothesised that

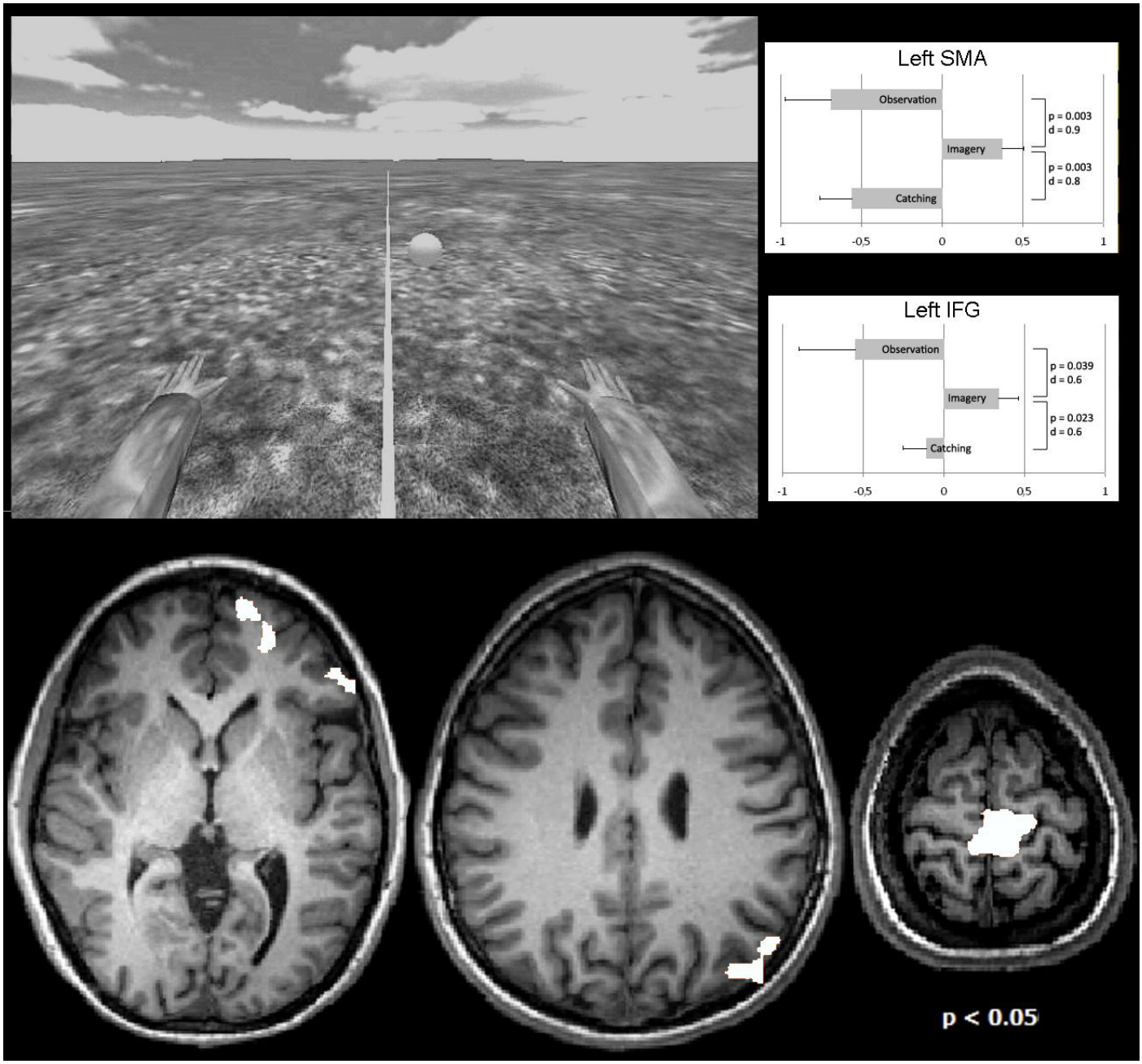

Figure 2. The Rehabilitation Gaming System.
Upper left panel: Virtual reality environment showing the two arms of the avatar and a sphere flying towards the viewer.
Lower panel (from left to right): Activation areas related to movement imagery in healthy volunteers located in the left anterior prefrontal cortex, the left inferior frontal gyrus (IFG), the left inferior parietal lobule, and the supplementary motor area (SMA).
Upper right panel: Strong activations during imagery in the left SMA and left IFG, no activation during simple observation, no change during actual catching in the left IFG.

the stimulation of the human brain can augment the effect of rehabilitation. The idea is to affect the threshold of cortical excitability which is abnormal after stroke. In fact, anodal stimulation of the affected motor cortex was found to augment motor skill acquisition.[76] Conversely, application of 1 Hz repetitive TMS of 10 minutes duration to the contralesional motor cortex, which down-regulates the contralesional motor cortex, improved the kinematics of finger and grasp movements in the affected hand.[77] This resulted in overactivity in the contralesional motor and

premotor cortical areas as found with fMRI. The combination of electrical stimulation of finger extensor muscles and tracking training over 2-3 weeks did not result in a greater improvement of dexterity of the affected hand, as assessed with the Jebson-Taylor Hand Function Test, than each intervention alone.[78] Subjects with an intact motor cortex showed a greater improvement than those who had direct involvement of the motor cortex. Similarly, in chronic stroke-induced aphasia, repetitive TMS over the left inferior frontal gyrus resulted in an increase of reaction time or error rate in a semantic task, suggesting restoration of a perilesional tissue in the left hemisphere.[79,80]

Also, to enhance the effect of rehabilitation, individually-tailored and adaptive robot-based rehabilitation techniques have been developed to provide a means for extended long-term training sessions.[81] The goal of these approaches is to maximise the effect of repetitive training while simultaneously limiting the demand of personal support per session and, thus, the economic expenditure.[82] For example, the Rehabilitation Gaming System (RGS) has been designed as a flexible, virtual reality-based device for rehabilitation of neurological patients. Recently, training of visuomotor processing with RGS was shown to effectively improve arm functions in acute and chronic stroke patients.[83,84] It was postulated that the RGS-based training protocol creates conditions that aid recovery by virtue of the human mirror neuron system. To test this hypothesis behind RGS, an fMRI study was performed which allowed identification of the brain areas engaged during performance of RGS.[85] The activation of a number of brain areas in the imagination condition including the left SMA, the left inferior frontal gyrus (IFG), the left posterior insula, the left postcentral gyrus, the left inferior parietal lobule (IPL), and the right cerebellum was observed (Figure 2). In fact, these areas constitute a widespread circuit of sensorimotor areas including key cortical areas of the human mirror neuron system.[86-88] This is consistent with earlier observations showing that the IFG and IPL are candidate areas for sensory control of action, movement imagery and imitation.[86-88]

Goal-driven attention and working memory are important in learning-based rehabilitation.[60] Rehabilitation may be viewed as 'an active process focused on facilitation of adaptive learning'.[60] Attention modulates neural plasticity and is involved in new learning.[89] Motivation and emotion help drive and prioritise attention.[90] Furthermore, attention and working memory share similar regions of activation in the brain.[91] The process of learning or relearning requires access to these functions and the brain networks that support them. It is therefore important to understand not only the focal brain lesion but also residual brain networks that can support recovery and learning. Interruption to these networks will impact on the process of recovery and ability to benefit from rehabilitation.

CONCLUSION

In summary, neurorehabilitation is a clinical subspecialty focused on the 'restoration and maximisation of functions' that have been lost due to brain injury.[92] The potential for recovery and ability to benefit from rehabilitation is impacted by interruption to brain networks as well as remote changes in the brain. Various rehabilitative approaches have been developed and tested. A learning-based approach is advocated to facilitate neural plastic changes and outcomes of restoration. Given individual variability in recovery and the interaction between brain networks involved in recovery, it is critical to identify not only the impact of the focal lesion but also viable brain networks that may be accessed during the recovery process.

REFERENCES

1. Bejot Y, Benatru I, Rouaud O, Fromont A, Besancenot, JP, Moreau T et al. Epidemiology of stroke in Europe: Geographic and environmental differences. J Neurol Sci. 2007;262:85-8.

2. Seitz RJ, Donnan GA. Role of neuroimaging in promoting long-term recovery from ischemic stroke. J Magnet Resonance Imaging. 2010;32:756–72.

3. Carey LM, Seitz RJ, Parsons M, Levi C, Farquharson S, Tournier JD, Palmer S, Connelly A. Beyond the Lesion – Neuroimaging foundations for poststroke recovery. Future Neurol. 2013;8:507-27.

4. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet. 2004;363:768-74.

5. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317-29.

6. Donnan GA, Baron JC, Ma M, Davis SM. Penumbral selection of patients for trials of acute stroke therapy. Lancet Neurol. 2009;8:261–9.

7. Alstadhaug KB, Sjulstad A. Isolated hand paresis: A case series. Cerebrovasc Dis. 2013;17:65-73.

8. Grube MM, Koennecke HC, Walter G, Thümmler J, Meisel A, Wellwood I, Heuschmann PU. Association between socioeconomic status and functional impairment 3 months after ischemic stroke. The Berlin Stroke Register. Stroke. 2012;43:3325-30.

9. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. Stroke. 2003;34:2181-6.

10. Sprigg N, Gray LJ, Bath PM, et al. Early recovery and functional outcome are related with causal stroke subtype: data from the tinzaparin in acute ischemic stroke trial. J Stroke Cerebrovasc Dis. 2007;16:180-4.

11. Dong W, Yan B, Johnson BP, Millist L, Davis S, Fielding J, White OB. Ischaemic stroke: the ocular motor system as a sensitive marker for motor and cognitive recovery. J Neurol Neurosurg Psychiatry. 2013;84:337-41.

12. Kitago T, Liang J, Huang VS, Hayes S, Simon P, Tenteromano L, Lazar RM, Marshall RS, Mazzoni P, Lennihan L, Krakauer JW. Improvement after constraint-induced movement therapy: recovery of normal motor control or task-specific compensation. Neurorehabilation Neural Repair. 2013;27:99-109.

13. Cumming TB, Thrift AG, Collier JM, et al. Very early mobilization after stroke fast-tracks return to walking: further results from Phase II of AVERT randomized controlled trail. Stroke. 2011;42:153-8.

14. Hesse S. Treadmill training with partial body weight support after stroke: a review. NeuroRehabilitation. 2008;23:55-65.

15. Platz T, van Kaick S, Mehrholz J, Leidner O, Eickhoff C, Pohl M. Best conventional therapy versus modular impairment-oriented training for arm paresis after stroke: a single-blind, multicenter randomized controlled trial. Neurorehabil Neural Repair. 2009;23:706-16.

16. Wolf S, Winstein C, Miller J, et al. Effect of constraint induced movement therapy on upper extremity function among patients 3-9 months following stroke: The EXCITE randomized clinical trial. JAMA. 2006;296:2095-104.

17. Carey LM, Macdonnell R, Matyas T. SENSe: Study of the Effectiveness of Neurorehabilitation on Sensation. A randomized controlled trial. Neurorehabil Neural Repair. 2011;25:304-13.

18. Connor LT. "Language." Carey LM (eds.), Stroke rehabilitation: insights from neuroscience and imaging (2012), New York: Oxford University Press, pp. 222-30.

19. Carey LM. Stroke rehabilitation: insights from neuroscience and imaging (2012), New York: Oxford University Press.

20. Schepers P, Ketelaar M, Visser-Meily AJ, de Groot V, Twisk JW, Lindeman E. Functional recovery differs between ischaemic and haemorrhagic stroke patients. J Rehabil Med. 2008;40:487-9.

21. Welmer AK, Holmqvist LW, Sommerfeld DK. Limited fine hand use after stroke and its association with other disabilities. J Rehabil Med. 2008;40:603-8.

22. van Vliet P, Carey LM, Nilsson M. Targeting stroke treatment to the individual. Int J Stroke. 2012;7:480-1.

23. Binkofski F, Seitz RJ, Arnold S, Claßen J, Benecke R, Freund HJ. Thalamic metabolism and integrity of the pyramidal tract determine motor recovery in stroke. Ann Neurol. 1996;39:460-70.

24. Kim JS. Predominant involvement of a particular group of fingers due to small, cortical infarction. Neurology. 2011;56:1677-82.

25. Binkofski F, Seitz RJ. Modulation of the BOLD-response in early recovery from sensorimotor stroke. Neurology. 2004;63:1223-9.

26. Schäfer R, Popp K, Jörgens S, Lindenberg R, Franz M, Seitz RJ. Alexithymia-like disorder in right anterior cingulate infarction. Neurocase. 2007;13:201-8.

27. Barton JJ. Structure and function in acquired prosopagnosia: lessons from a series of 10 patients with brain damage. J Neuropsychol. 2008;2:197-225.

28. Hömke L, Amunts K, Bönig L, et al. Analysis of lesions in patients with unilateral tactile agnosia using cytoarchitectonic probabilistic maps. Hum Brain Mapp. 2009;30:1444-56.

29. Karnath HO, Fruhmann Berger M, Kuker W, Rorden C. The anatomy of spatial neglect based on voxelwise statistical analysis: a study of 140 patients. Cereb Cortex. 2004;14:1164-72.

30. Pazzaglia M, Smania N, Corato E, Aglioti SM. Neural underpinnings of gesture discrimination in patients with limb apraxia. J Neurosci. 2008;28:3030-41.

31. Rusconi E, Pinel P, Eger E, et al. A disconnection account of Gerstmann syndrome: functional neuroanatomy evidence. 2009;66:654-62.

32. Hamzei F, Dettmers C, Rijntjes M, Weiller C. The effect of cortico-spinal tract damage on primary sensorimotor cortex activation after rehabilitation therapy. Exp Brain Res. 2008;190:329-36.

33. Kim YH, Kim DS, Hong JH, et al. Corticospinal tract location in internal capsule of human brain: diffusion tensor tractography and functional MRI study. Neuroreport. 2008;28:817-20.

34. Schiemanck SK, Kwakkel G, Post MW, Kappelle LJ, Prevo AJ. Impact of internal capsule lesions on outcome of motor hand function at one year post-stroke. J Rehabil Med. 2008;40:96-101.

35. Schaechter JD, Fricker ZP, Perdue KL, et al. Microstructural status of ipsilesional and contralesional corticospinal tract correlates with motor skill in chronic stroke patients. Hum Brain Mapp. 2009;30:3461-74.

36. Vitali P, Abutalebi J, Tettamanti M, et al. Training-induced brain remapping in chronic aphasia: a pilot study. Neurorehabil Neural Repair. 2007;21:152-60.

37. Connell LA, Lincoln NB, Radford KA. Somatosensory impairment after stroke: frequency of different deficits and their recovery. Clin Rehabil. 2008;22:758-67.

38. Poggel DA, Mueller I, Kasten E, Sabel BA. Multifactorial predictors and outcome variables of vision restoration training in patients with post-geniculate visual field loss. Restor Neurol Neurosci. 2008;26:321-39.

39. Brodtmann A, Puce A, Darby D, Donnan G. Serial functional imaging poststroke reveals visual cortex reorganization. Neurorehabil Neural Repair. 2009;23:150-9.

40. Stinear C, Hubbard I. "Movement." Carey LM (eds.), Stroke rehabilitation: insights from neuroscience and imaging (2012), New York: Oxford University Press, pp. 141-56.

41. Lindenberg R, Renga V, Zhu LL, Betzler F, Alsop D, Schlaug G. Structural integrity of corticospinal motor fibres predict motor impairment in chronic stroke. Neurology. 2010;74:280-7.

42. Houwink A, Nijland RH, Geurts AC, Kwakkel G. Functional recovery of the paretic upper limb after stroke: who regains hand capacity? Arch Phys Med Rehabil. 2013;94:839-44.

43. Liepert J, Storch P, Fritsch A, Weiller C. Motor cortex disinhibition in acute stroke. Clin Neurophysiol. 2000;111:671-6.

44. Bütefisch CM, Netz J, Wessling M, Seitz RJ, Hömberg V. Remote changes in cortical excitability after stroke. Brain. 2003;126:470-81.

45. Hummel FC, Steven B, Hoppe J, Heise K, Thomalla G, Cohen LG, Gerloff C. Deficient intracortical inhibition (SICI) during movement preparation after chronic stroke. Neurology. 2009;19:1766-72.

46. Cincenelli P, Pascualetti P, Zaccagnini M, Traversa R, Oliveri M, Rossini PM. Interhemispheric asymmetries of motor cortex excitability in the postacute stroke stage: a paired-pulse transcranial magnetic stimulation study. Stroke. 2003;34:2653-8.

47. Bütefisch CM, Wessling M, Netz J, Seitz RJ, Hömberg V. Relationship between interhemispheric inhibition and motor cortex excitability in subacute stroke

patients. Neurorehabil Neural Repair. 2008;22:4-21.

48. Manganotti P, Acler M, Zanette GP, Smania N, Fiaschi A. Motor cortical disinhibition during early and late recovery after stroke. Neurorehabil Neural Repair. 2008;22:396-403.

49. Marshall RS, Zarahn E, Alon L, Minzer B, Lazar RM, Krakauer JW. Early imaging correlates of subsequent motor recovery after stroke. Ann Neurol. 2009;65:596-602.

50. Askam T, Indredavik B, Vangberg T, Haberg A. Motor network changes associated with successful motor skill relearning after acute ischemic stroke: a longitudinal functional magnetic resonance imaging study. Neurorehabil Neural Repair. 2009;23:295-304.

51. Rehme AK, Eickhoff SB, Rottschy C, Fink GR, Grefkes C. Activation likelihood estimation meta-analysis of motor-related neural activity after stroke. Neuroimage. 2012;59:2771-82.

52. Lotze M, Beutling W, Loibl M, Domin M, Platz T, Schminke U, Byblow WD. Contralesional motor cortex activation depends on ipsilesional corticospinal tract integrity in well-recovered subcortical stroke patients. Neurorehabil Neural Repair. 2012;26:594-603.

53. Seitz RJ, Knorr U, Azari NP, Herzog H, Freund HJ. Visual network activation in recovery from sensorimotor stroke. Restor Neurol Neurosci. 1999;14:25-33.

54. Grefkes C, Nowak DA, Eickhoff SB, et al. Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. Ann Neurol. 2008;63:236-46.

55. Cramer S, Nudo R, "Brain Mapping of Attention and Neglect After Stroke," Carter A, Shulman G, Corbetta M (eds.), Brain Repair After Stroke (2010), Cambridge: Cambridge University Press, pp. 133-44.

56. Sharma N, Baron JC, Rowe JB. Motor imagery after stroke: relating outcome to motor network connectivity. Ann Neurol. 2009;66:604-16.

57. Lindenberg R, Zhu LL, Rüber T, Schlaug G. Predicting functional motor potential in chronic stroke patients using diffusion tensor imaging. Hum Brain Mapp. 2012;33:1040-51.

58. Carey LM, Seitz RJ. Functional neuroimaging in stroke recovery and neurorehabilitation: conceptual issues and perspectives. Int J Stroke. 2007;2:245-64.

59. Cramer SC. Repairing the human brain after stroke: II. Restorative therapies. Ann Neurol. 2008;63:549-60.

60. Carey LM, Polatajko HJ, Baum CM. "Stroke rehabilitation: a learning perspective." Carey LM (eds.), Stroke rehabilitation: insights from neuroscience and imaging. (2012) New York: Oxford University Press, pp. 11-23.

61. Hodics T, Cohen LG, Cramer SC. Functional imaging of intervention effects in stroke motor rehabilitation. Arch Phys Med Rehabil. 2006;87(12 Suppl 2):S36-42.

62. Richards LG, Stewart KC, Woodbury ML, Senesac C, Cauraugh JH. Movement-dependent stroke recovery: a systematic review and meta-analysis of TMS and fMRI evidence. Neuropsychologia. 2008;46:3-11.

63. Kwakkel G, Wagenaar RC, Twisk JW, Lankhorst GJ, Koetsier JC. Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial. Lancet. 1999;354:191-6.

64. Boake C, Noser EA, Baraniuk S, et al. Constraint-induced movement therapy during early stroke rehabilitation. Neurorehabil Neural Repair. 2008;21:14-24.

65. Luft AR, Macko RF, Forrester LW, et al. Treadmill exercise activates subcortical neural networks and improves walking after stroke: a randomized controlled trial. Stroke. 2008;39:3341-50.

66. Lang CE, Dejong SL, Beebe JA. Recovery of thumb and finger extension and its relation to grasp performance after stroke. J Neurophysiol. 2009;102:451-9.

67. Diserens K, Ruegg D, Kleiser R, Hyde S, Perret N, Vuadens P, Fornari E, Vingerhoets N, Seitz RJ. Effect of repetitive arm cycling following Botulinum toxin for post-stroke spasticity: evidence from fMRI. Neurorehabil Neural Repair. 2010;24:753-62.

68. Liepert J, Miltner W, Bauder H, et al. Motor cortex plasticity during constraint-induced movement therapy in stroke patients. Neurosci Lett. 1998;250:5-8.

69. Sawaki L, Butler AJ, Leng X, et al. Constraint-induced movement therapy results in increased motor map area in subjects 3 to 9 months after stroke. Neurorehabil Neural Repair. 2008;22:505-13.

70. Lindenberg R, Renga V, Zhu LL, Nair D, Schlaug G. Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. Neurology. 2010;75:2176-84.

71. Müller K, Bütefisch CM, Seitz RJ, Hömberg V. Mental practice improves hand function after hemiparetic stroke. Restor Neurol Neurosci. 2007;25:501-11.

72. Page SJ, Szaflarski JP, Eliassen JC, Pan H, Cramer SC. Cortical plasticity following motor skill learning during mental practice in stroke. Neurorehabil Neural Repair. 2009;23:382-8.

73. Yavuzer G, Selles R, Sezer N, et al. Mirror therapy improves hand function in subacute stroke: a ramdomized controlled trail. Arch Phys Med Rehabil. 2008;89:393-8.

74. Dohle C, Püllen J, Nakaten A, Küst J, Rietz C, Karbe H. Mirror therapy promotes recovery from severe hemiparesis: a randomized controlled trial. Neurorehabil Neural Repair. 2009;23:209-17.

75. Iosa M, Morone G, Ragaglini MR, Fusco A, Paolucci S. Motor strategies and bilateral transfer in sensori motor learning of patients with subacute stroke and healthy subjects. A randomized controlled trial. Eur J Phys Rehabil Med. 2013;49:291-9.

76. Reis J, Schambra HM, Cohen LG, et al. Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc Natl Acad Sci USA. 2009;106:1590-5.

77. Nowak DA, Grefkes C, Dafotakis M, et al. Effects of low-frequency repetitive transcranial magnetic stimulation of the contralesional primary motor cortex on movement kinematics and neural activity in subcortical stroke. Arch Neurol. 2008;65:741-7.

78. Bhatt E, Nagpal A, Greer KH, et al. Effect of finger tracking combined with electrical stimulation on brain reorganization and hand function in subjects with stroke. Exp Brain Res. 2007;182:435-47.

79. Winhuisen L, Thiel A, Schumacher B, et al. The right inferior frontal gyrus and poststroke aphasia: a follow-up investigation. Stroke. 2007;38:1286-92.

80. Marangolo P, Rizzi C, Peran P, Piras F, Sabatini U. Parallel recovery in a bilingual aphasic: a neurolinguistic and fMRI study. Neuropsychology. 2009;23:405-9.

81. Seitz RJ. How imaging will guide rehabilitation. Curr Opin Neurol. 2010;23:79-86.

82. Langhorne P, Bernhardt J, Kwakkel G. Stroke Rehabilitation. Lancet. 2011;377:1693-1702.

83. Cameirão MS, Bermúdez i Badia S, Duarte Oller E, Verschure PFMJ. Virtual reality based rehabilitation speeds up functional recovery of the upper extremities after stroke: a randomized controlled pilot study in the acute phase of stroke using the Rehabilitation Gaming System. Restor Neurol Neurosci. 2011;29:287-98.

84. Cameirão MS, Bermúdez i Badia S, Duarte E, Frisoli A, Verschure PFMJ. The combined impact of virtual reality neurorehabilitation and its interfaces on upper extremity functional recovery in patients with chronic stroke. Stroke. 2012;43:2720-8.

85. Prochnow D, Bermúdez i Badia S, Schmidt J, Duff A, Brunheim S, Kleiser R, Seitz RJ, Verschure PFMJ. A functional magnetic resonance imaging study of visuomotor processing in a virtual reality based paradigm: Rehabilitation Gaming

System. Eur J Neurosci. 2013;37:1441-7.

86. Gallese V, Fadiga V, Fogassi L, Rizzolatti G. Action recognition in the premotor cortex. Brain. 1996;119:593-609.

87. Iacoboni M, Mazziotta JC. Mirror neuron system: basic findings and clinical applications. Ann Neurol. 2007;62:213-8.

88. Sale P, Franceschini M. Action observation and mirror neuron network: a tool for motor stroke rehabilitation. Eur J Phys Rehabil Med. 2012;48:313-8.

89. Jagadeesh B. "Attentional modulation of cortical plasticity." Selzer M, Clarke S, Cohen L, Duncan P, Gage F (eds.), Textbook of Neural Repair and Rehabilitation (2006), Cambridge: Cambridge University Press, pp. 194-206.

90. Raymond J. "Interactions of attention, emotion and motivation." Srinivasan N (eds.), Progress in Brain Research: Attention (2009), Amsterdam: Elsevier, pp. 293-308.

91. Niendam TA, Laird AR, Ray KL, Dean VM, Glahn DC, Carter CS. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. Cogn Affect Behav Neurosci. 2012;12:241-68.

92. Selzer M, Clarke S, Cohen L, Duncan P, Gage F. "Neural repair and rehabilitation: an introduction." Selzer M, Clarke S, Cohen L, Duncan P, Gage F (eds.), Textbook of Neural Repair and Rehabilitation: Vol II Medical Neurorehabiltation (2006), Cambridge: Cambridge University Press, pp. xxvii-xxxv.