HHS Public Access

Author manuscript

*PM R*. Author manuscript; available in PMC 2015 July 06.

Published in final edited form as:

*PM R*. 2011 June ; 3(6 0 1): S45–S51. doi:10.1016/j.pmrj.2011.05.007.

# Cognitive Impairment in Acquired Brain Injury: A Predictor of Rehabilitation Outcomes and an Opportunity for Novel Interventions

**Ellen Whyte, MD**[a], **Elizabeth Skidmore, PhD, OTR/L**[b], **Howard Aizenstein, MD, PhD**[c], **Joseph Ricker, PhD**[d], and **Meryl Butters, PhD**[c]

[a]Department of Psychiatry and Department of Physical Medicine and Rehabilitation, School of Medicine, WPIC-BT 764, 3811 O'Hara St., Pittsburgh PA 15213

[b]Department of Occupational Therapy and Department of Physical Medicine and Rehabilitation, School of Medicine, University of Pittsburgh, Pittsburgh PA

[c]Department of Psychiatry, School of Medicine, University of Pittsburgh, Pittsburgh PA

[d]Department of Physical Medicine and Rehabilitation, School of Medicine, University of Pittsburgh, Pittsburgh PA

## Abstract

Cognitive impairment is a common sequela in acquired brain injury and one that predicts rehabilitation outcomes. There is emerging evidence that impairments in cognitive functions can be manipulated by both pharmacologic and nonpharmacologic interventions to improve rehabilitation outcomes. By using stroke as a model for acquired brain injury, we review the evidence that links cognitive impairment to poor rehabilitation outcomes and discuss possible mechanisms to explain this association. Furthermore, we examine nascent promising research that suggests that interventions that target cognitive impairments can lead to better rehabilitation outcomes.

## Introduction

Acquired brain injury, which includes both stroke and traumatic brain injury, is a leading cause of disability in the United States and worldwide. Fifteen to 30% of adult stroke survivors in the United States are permanently disabled, and 20% require institutional care at 3 months after stroke [1], whereas traumatic brain injury results in severe disability in 150–

Corresponding Author: Ellen M Whyte, MD, Department of Psychiatry and Department of Physical Medicine and Rehabilitation, School of Medicine, University of Pittsburgh, WPIC-BT 764, 3811 O'Hara St., Pittsburgh PA 15213, whyteem@upmc.edu.

**Disclosures**

Dr. Whyte reports funding through US PHS NICHD/NCMRR (R01 HD055525-01A2; PI: Whyte) and NINDS (subcontract through grant R44 NS 052948-02A2; PI: Fox); and through Forest Pharmaceuticals

Dr. Skidmore reports funding through US PHS NICHD/NCMRR (K12 HD055931; PI: Skidmore), NICHD/NCMRR(R01 HD055525-01A2; PI: Whyte) and through University of Pittsburgh Medical Center - Rehabilitation Institute.

Dr. Aizenstein has nothing to disclose.

Dr. Ricker has nothing to disclose.

Dr. Butters reports funding through US PHS NICHD/NCMRR (R01 HD055525-01A2; PI: Whyte) and NINDS (subcontract through grant R44 NS 052948-02A2; PI: Fox); and through MedTronic Inc.

200 per million people annually worldwide [2]. To combat this growing public health burden, it is imperative to develop interventions to increase the success of postinjury rehabilitation. The steps of such an endeavor would begin with identifying risk factors for poor rehabilitation outcomes. Risk factors precede the outcome of interest and divide a patient population into 2 groups: those with a high risk and those with a low risk of experiencing a particular outcome. The presence of a risk factor only increases the likelihood of a particular outcome; it does not guarantee or cause the outcome [3]. Risk factors can be considered markers or biomarkers that, in the spirit of "rehabilomics," not only predict rehabilitation outcomes but also may be targets that can be manipulated through interventions to improve rehabilitation outcomes.

There is evidence that cognitive function is an important marker that predicts rehabilitation outcomes after acquired brain injury and, more importantly, may be modified through targeted interventions and lead to improve rehabilitation outcomes. Clearly, cognitive function is not a unitary construct, and, therefore, care must be given to specifying which aspects of cognition may be useful as "rehabilomics" biomarkers. In this review, we will use stroke as a model for acquired brain injury to review the evidence that supports the association of impairment of specific aspects of cognitive function with poor rehabilitation outcomes and, in particular, will discuss how impairments in specific cognitive domains may moderate, or interfere with, the 2 pathways to recovery: remediation and adaptation. We also will discuss how impairment of or interference with implicit learning, an often overlooked cognitive function, may diminish recovery. Finally, we will describe nascent research investigating novel interventions that target impaired cognitive functions as a means to improve stroke rehabilitation outcomes.

## Cognitive Impairment and Functional Recovery after Stroke

Cognitive impairment is very common after stroke. Most studies have examined the prevalence of impairment at 3 months after stroke, because it is assumed that, by this point, any element of transient changes in cognition due to factors other than neurologic damage (eg, delirium or encephalopathy) have resolved. Among mixed-aged stroke survivors, 32%–56% of the population demonstrates cognitive impairment 3 months after stroke [4, 5, 6, 7, 8 and 9], whereas, among elderly stroke patients, almost all perform worse on most cognitive tests 3 months after stroke compared with nonstroke controls [8]. These 3-month estimates likely parallel the percentage of patients with cognitive impairment soon after stroke. These studies point to the dearth of research on cognition in the acute poststroke period and the poor understanding of the natural history of recovery of cognition in general or of specific cognitive domains over time. The cognitive functions most commonly impaired after stroke are attention and/or working memory, processing speed, and the executive functions [7, 10, 11 and 12]. Furthermore, the presence of impairments in executive functions best discriminated between stroke patients with any cognitive impairment (related to cerebrovascular disease) and those without cognitive impairment, whereas deficits in attention and concentration best discriminated patients with dementia from those with less-severe deficits [7].

Importantly, cognitive impairment is a risk factor of poor rehabilitation outcomes. Cognitive impairment presents immediately after stroke has been associated, with decreased likelihood of both being discharged to home and living at home 6 months later [13]. Indeed, results of numerous studies have demonstrated that cognitive impairment predicts poor functional outcomes after stroke, [14, 15 and 16], even after controlling for the level of physical impairment [4 and 17]. In particular, impairments in the executive functions [5, 18, 19 and 20], attention [21], and processing speed [7], which are the most common cognitive impairments after stroke, predict dependency in activities of daily living and instrumental activities of daily living. In elderly patients 3 months after stroke, impairments in attention and information processing speed have been associated with limitations in basic self-care (eg, dressing, toileting), whereas impairments in executive functions have been associated with impaired instrumental activities of daily living (eg, shopping, housework) [15].

## Impact of Cognitive Impairment on Pathways of Recovery

The effects of rehabilitation on recovery can be divided into adaptation and remediation [22]. Adaptation describes a person's ability to compensate for functional impairment and can be further divided into internal adaptation (eg, a person learns and internalizes cognitive strategies to account for lost abilities when performing daily activities) and external adaptation (eg, a person uses a paging system to remember to take medications at scheduled times to account for a memory impairment). Remediation is the actual regaining of a lost ability, for example, through intense repetitive practice, an individual demonstrates improvements in selected abilities (selective attention, limb function). Both of these approaches require learning (or relearning); therefore, both pathways may be inhibited by cognitive impairments.

### Adaptation

Cognitive impairments can inhibit therapy efforts that would promote adaptation. Adaptation describes a person's ability to compensate for residual impairments and hence is an important part of promoting functional outcomes. However, a person can adapt his or her environment and response only if he or she recognizes that there is a problem, conceptualizes the key issues that led to the problem, generates an array of potential solutions, tests the potential solutions, and continues to execute the most effective solution. Clearly, this process requires cognitive abilities in several different domains, including, but not limited to, attention, working memory, episodic memory, and executive functions.

### Remediation

Remediation, for patients with cortical and/or subcortical stroke, is based on the complex and not yet fully understood process of neuroplasticity [23, 24 and 25] through which functional ability is regained. For remediation to occur, the stroke survivor must engage in rehabilitation activities. The most robust stimulus of neural plasticity is experience [26 and 27]. Hence, rehabilitation tasks that promote remediation are based on repeated, patient-initiated, targeted skill-building activities. Although neuroplasticity appears to start soon after initiating rehabilitation, continued practice over days, weeks, and months is needed to consolidate the new neuronal pathways and ensure stability of the recovery [28]. Thus, there

is evidence that patients are more likely to regain lost ability and sustain favorable recovery by engaging in massed practice (ie, high-frequency repetitions in a concentrated period of time) of targeted activities [29 and 30] and by establishing routines that encourage patients to continue to engage in cognitively challenging activities on a regular basis after formal rehabilitation has concluded [31].

## Possible Pathways that Link Cognitive Function with Rehabilitation Outcomes

There are several possible explanations as to why cognitive impairment is associated with poor rehabilitation outcomes when considering both the adaptation and remediation pathways. One possible explanation involves rehabilitation participation. The extent to which patients fully engage or participate in rehabilitation therapies predict functional outcome at the conclusion of inpatient rehabilitation [32, 33, 34, 35, 36 and 37]. Persons with cognitive impairment are less likely to robustly engage in rehabilitation therapies [32]. In particular, impairment of executive functions after stroke is associated with poor engagement in rehabilitation activities [38]. Individuals with impaired executive functions may have difficulty initiating activities, maintaining consistency of response, and generalizing instructions to other tasks, and hence may have difficulty in fully participating in rehabilitation. In addition, persons with impairment in executive functions may have difficulty inhibiting impulsive behaviors; for these individuals, therapeutic activities may be limited due to safety concerns. The association of other cognitive domains with rehabilitation participation has not been investigated.

Beyond participation, cognitive impairments may lead to inferior rehabilitation outcomes through interference with rehabilitation practices. For example, stroke patients with impaired episodic memory and impaired executive functions are less able to achieve improvements in selected motor recovery outcomes than individuals without these impairments [39]. It is not difficult to imagine how impairments in episodic memory can limit a patient’s ability to remember the content of therapy instructions, thereby limiting “carry-over” from one therapy session to another. Although other specific cognitive domains have not been examined, we can imagine that attention and working memory can limit a patient’s ability to learn new information and perform exercises.

Another possible pathway through which cognitive impairment after stroke could lead to poor rehabilitation outcomes involves the disruption of implicit learning. Functional gains obtained through rehabilitation interventions (including both adaptation and remediation) ultimately reflect the creation of new neuronal connections, for example, the process of neuroplasticity. Although neuroplasticity is complex and not yet fully understood, the process through which it occurs likely includes implicit learning [40, 41 and 42], as well as explicit learning. Implicit learning is poorly operationalized, and there is no agreed upon definition [43]. Implicit learning involves learning new information or skills without awareness of the rules that govern performance or how it is being learned. Types of implicit learning include acquiring motor skills (procedural learning) as well as the ability to recognize perceptual features or categories. Learning to ride a bicycle is a protypical example of procedural learning, which highlights some of the key features of implicit

learning: the learning occurs gradually and automatically through repeated performance, and, unlike explicit learning, it does not require explicit recall of declarative knowledge [32]. Both remediation and adaptation interventions involve both implicit and explicit learning. Furthermore, there is evidence that implicit learning process [41] may benefit from optimally timed and dosed external and/or explicit feedback [44].

Although important clinically, the process of implicit learning is not typically assessed in clinical practice. In the research setting, a variety of behavioral tasks have been developed to study the different forms of implicit learning. One of the most commonly used tasks is the serial reaction time task [45]. In this task, individuals are asked to press 1 of 4 buttons as fast and accurately as they can in response to a sequence of asterisks that appear on the screen in 4 different locations. The subjects are not told ahead of time that the location of the asterisks follows a repeating pattern for most of the trials. Then, unbeknownst to the subject, the order of the asterisks is changed. Typically, despite not knowing that there was a sequence, the subjects perform with progressively greater accuracy and speed, until the order is changed, and then their performance drops. This drop in performance is a measure of implicit "sequence" learning, and, in this case, is distinguished from procedural "motor" learning. The motor learning component in this task is the nonspecific improvement in performance at pressing the buttons, which would occur with time when performing the task, even if the order were always random. There are other implicit learning tasks used experimentally, including artificial grammar learning [46] and probabilistic classification learning [47] as well as others. In the setting of stroke research, assessment of implicit learning in a person with motor impairment can be challenging, due to the co-occurrence of cognitive and motor control impairments. However, these tasks could be modified by allowing the individual to use the nonaffected side or by requiring a nonmotor (eg, verbal or ocular) response in place of the motor response, to permit assessment of the nonmotor aspects of implicit learning.

Because implicit learning is associated with motor recovery, impairment of or interference with implicit learning is likely associated with poor rehabilitation outcomes. In stroke, most evidence indicates that implicit learning ability remains intact with mild stroke but that implicit learning decreases as stroke severity increases [48]. In addition, there is evidence that implicit learning may be impeded during rehabilitation and thereby result in poor rehabilitation outcomes. For example, the provision of explicit instructions (eg, making an implicit process more explicit) as part of stroke rehabilitation may hinder procedural (implicit) learning [49], and reliance on explicit knowledge of a movement may inhibit performance (50–52). The extent of interference of explicit feedback may be dependent, in part, on both the content of and schedule of delivery for this information [53]. Furthermore, the presence of cognitive impairment may moderate the impact of explicit instructions. For example, persons with impaired episode memory or executive functions do not benefit from receiving explicit information on how to perform a specific motor task, and their motor recovery may actually be hindered by such explicit information [39].

## Cognitive Impairment as a Marker for an Altered Neurochemical Milieu

As discussed above, aspects of cognitive impairment may negatively impact the process of adaptation and remediation. It is hoped that altering the cognitive impairment may improve

the processes of remediation and adaptation. However, an alternate hypothesis must be considered; namely, that cognitive impairment is a proxy marker that indicates that the neurochemical milieu is not favorable for functional recovery. As an example, the neurotransmitter acetylcholine is thought to be involved in cognitive function as well as neuroplasticity of the motor cortex. Cognitive impairment in cerebrovascular disease is thought to be, in part, due to diminution of activity of the cholinergeric system [54, 55, 56, 57, 58 and 59]. Similarly, although many neurotransmitters are involved in neuroplasticity [60], results of animal studies suggest that the nucleus basalis and its cholinergic projections to the sensorimotor cortex are critical to experience-dependent plasticity, that is, the formation of new neuronal networks in response to rehabilitation activities [61]. Specifically, experience-dependent plasticity can be completely blocked by lesioning the cholinergic neurons in the nucleus basalis of Meynert with a selective immunotoxin in a rat model [62]. This finding parallels studies that suggest that anticholinergic drugs impair learning in humans [63, 64 and 65]. The exact mechanism by which acetylcholine is involved in experience-dependent plasticity under normal circumstances is unclear. It is hypothesized that acetylcholine potentiates cortical activity provoked by sensory stimulation [66 and 67]. By depleting cholinergic cortical stimulation, presynaptic and postsynaptic cortical activity could be altered to such an extent that n-methyl d-aspartate (NMDA) receptor dependent modification of synapses at the motor cortex cannot occur [ 62]. Hence, persons with cognitive impairment after stroke, especially involving memory or other functions supported by acetylcholine, may have a predilection for poor motor recovery due to a reduction of acetylcholine innervation of the motor cortex.

## Future Research Directions

We have described several ways through which impairment of specific cognitive functions impact rehabilitation from stroke. More importantly, specific cognitive functions may serve as a point of intervention to enhance recovery after stroke. Below, we provide several examples of recent and ongoing research studies to illustrate how cognitive interventions may be used in the future to promote rehabilitation.

One possible intervention would be to view cognitive functions as a “rehabilomic” marker that could be manipulated or enhanced to promote rehabilitation outcomes. Possible future interventions may focus on helping patients adapt in light of their cognitive impairment. For example, meta-cognitive strategy training may help patients with cognitive impairments, especially impairments of executive functions, actively engage in and even “steer” their rehabilitation programs [68 and 69] by teaching patients a strategy that can be used to increase awareness of impaired skills or processes (through self-assessment and self-monitoring), develop goals and plans to address areas of disability, and improve their ability to perform desired activities (thus reducing disability). Skidmore et al [72] recently reported a case study in which a stroke survivor with significant impairment in executive functions was able to use one such strategy, CO-OP (“cognitive orientation to daily occupational performance”) [69, 70 and 71] while undergoing inpatient rehabilitation. Through CO-OP, this patient learned a process that helped him identify, set, and address his own goals, and also provided skills to facilitate self-monitoring and self-directed learning during rehabilitation, despite impairments in executive functions.

Another possible intervention to enhance cognitive functions would be through the use of targeted pharmacotherapy. For example, we previously conducted a pilot study in which the results suggested that the drug donepezil, an acetylcholinesterase inhibitor approved for the treatment of Alzheimer dementia when paired with poststroke rehabilitation improved functional outcomes in older stroke patients who were cognitively impaired [73], and we are currently conducting a randomized controlled trial study to confirm this preliminary finding. There is evidence that in both impaired and normal subjects [74, 75, 76 and 77], acetylcholine esterase inhibitors can result in enhancement of cognitive function, even after a single dose [77]. We hypothesize that the use of acetylcholine esterase inhibitors, in the context of rehabilitation, modify cognition impairments (particularly impairments in working memory and/or executive functions and episodic memory), which leads to increased participation in rehabilitation therapies and, therefore, improved rehabilitation outcomes.

In a similar vein, one could view implicit learning as a “rehabilomic” marker that could be manipulated or enhanced to promote rehabilitation outcomes. One potential way to promote implicit learning is through the use of errorless learning with a concomitant reduction in the use of explicit learning. Currently, explicit techniques are frequently used in stroke rehabilitation. However, there is evidence that providing explicit instructions as part of stroke rehabilitation may hinder remediation [49] and that overreliance on explicit knowledge of a movement inhibits performance [50,51 and 52]. Hence, motor skills training may be enhanced by minimizing explicit learning and by promoting implicit learning. This can be accomplished through errorless learning strategies in which task training begins with a very easy condition (with little chance of error) to gradually involve more difficult conditions as the person masters the easier conditions [50]. By using an example provided by Orrell et al [50], current rehabilitation practices are explicit in nature, because therapists “teach” a person to stand from a sitting position by “talking them through” the task. However, to enhance implicit learning, the task presented to the patient may not be to stand from the sitting position but to reach for an object on a table. Over trials, the object would be placed farther and farther from the patient, which eventually necessitates the patient to stand to complete the reaching task. By starting with the object placed close to the patient at a distance that was achievable and by increasing the distance slowly, the patient would not have the opportunity to fail (or make an error) in the task.

Another potential way to maximize implicit learning is through pharmacologic augmentation of neurotransmitters thought to be important to implicit learning. Both dopamine [78] and acetylcholine [79] have been implicated in implicit learning. Dopamine augmentation (through use of levadopa) has been shown to promote experience-dependent encoding of simple motor memories in chronic stroke patients [80, 81 and 82]. More recently, levadopa augmentation was demonstrated to improve procedural learning in chronic stroke patients [83]. For acetylcholine, results of one study suggested that acetylcholinesterase inhibitors (such as donepezil, which increase the availability of acetylcholine) improve both implicit and explicit learning in Alzheimer disease [84], a disease characterized by loss of acetylcholine-producing neurons. Furthermore, although not designed to test a hypothesis regarding implicit learning, it is noteworthy that a small randomized controlled trial in which participants with significant residual upper-limb paresis

one year after stroke demonstrated a trend toward superior motor improvement when constraint-induced therapy was combined with donepezil, an acetylcholinesterase inhibitor [85]. At this time, the use of pharmacologic interventions to promote implicit learning per se is in its infancy. Many questions are unanswered and require further investigation, including the following: can a range of implicit learning aptitude among patients be reliably measured, does aptitude for implicit learning correlate with rehabilitation outcomes, can implicit learning aptitude be increased through intervention, and, finally, does such an intervention lead to improved rehabilitation outcomes?

One word of caution regarding the study of dopamergic or cholinergic agents in rehabilitation is that, in addition to implicit learning, dopamine and acetylcholine play an important role in neuroplasticity at the sensorimotor cortex. Hence, the use of dopamine or acetylcholine augmentation may promote neuroplasticity during experience-dependent learning directly at the level of the motor cortex and separately from improving the process of implicit learning. Dopamine is believed to have an important role in neuroplasticity at the sensorimotor cortex by strengthening experience-dependent synapses while suppressing experience irrelevant synapses [83]. Similarly, acetylcholine potentiates cortical activity provoked by sensory stimulation [66 and 67].

## Summary

In this report, we have provided an overview of the impact of cognitive impairment on rehabilitation outcomes in acquired brain injury. We propose that impairments of cognitive functions can be operationalized as “rehabilomic” markers that predict rehabilitation outcomes after stroke and, more importantly, may be modified through targeted interventions to lead to improved rehabilitation outcomes. Although we have focused on stroke, these concepts also may be applicable to neurorehabilitation after traumatic brain injury. Future research is needed to elucidate the relationship of specific domains of cognitive impairment with specific aspects of rehabilitation outcomes and to investigate unique novel interventions, including biologics, to enhance rehabilitation outcomes after acquired brain injury.

## Acknowledgments

Funding: None

## References

1. Thom, T.; Haase, N.; Rosamond, W., et al. Heart Disease and Stroke Statistics: 2006 Update. American Heart Association; http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.105.171600v1 [Accessed February 14, 2006]
2. Fleminger S, Ponsford J. Long term outcome after traumatic brain injury. BMJ. 2005; 17:1419–1420. [PubMed: 16356951]
3. Kazdin AE, Kraemer HC, Kessler RC, Kupfer DJ, Offord DR. Contributions of risk-factor research to developmental psychopathology. Clin Psychol Rev. 1997; 17:375–406. [PubMed: 9199858]
4. Tatemichi TK, Desmond DW, Stern Y, Paik M, Sano M, Bagiella E. Cognitive impairment after stroke: frequency, patterns, and relationship to functional abilities. J Neurol Neurosurg Psychiatry. 1994; 57:202–207. [PubMed: 8126506]

5. Pohjasvaara T, Leskela M, Vataja R, Kalska H, Ylikoski R, Hietanen M. Post-stroke depression, executive dysfunction and functional outcome. Eur J Neurol. 2002; 9:269–275. [PubMed: 11985635]
6. Patel M, Coshall C, Rudd AG, Wolfe CD. Natural history of cognitive impairment after stroke and factors associated with its recovery. Clin Rehabil. 2003; 17:158–166. [PubMed: 12625656]
7. Sachdev PS, Brodaty H, Valenzuela MJ. The neuropsychological profile of vascular cognitive impairment in stroke and TIA patients. 2004; 62:912–919.
8. Stephens S, Kenny RA, Rowan E. Neuropsychological characteristics of mild vascular cognitive impairment and dementia after stroke. Int J Geriatr Psychiatry. 2004; 19:1053–1057. [PubMed: 15481073]
9. Zhou DH, Wang JY, Li J, Deng J, Gao C, Chen M. Frequency and risk factors of vascular cognitive impairment three months after ischemic stroke in China: the Chongqing stroke study. Neuroepidemiology. 2004; 24:87–95. [PubMed: 15459515]
10. Ballard C, Stephens S, Kenny R, Kalaria R, Tovee M, O'Brien J. Profile of neuropsychological deficits in older stroke survivors without dementia. Dement Geriatr Cogn Disord. 2003; 16:52–56. [PubMed: 12714801]
11. Jaillard A, Naegele B, Trabucco-Miguel S, LeBas J, Hommel M. Hidden dysfunctioning in subacute stroke. Stroke. 2009; 40:2473–2479. [PubMed: 19461036]
12. Zinn S, Bosworth H, Hoenig H, Swartzwelder H. Executive function deficits in acute stroke. Arch Phys Med Rehabil. 2007; 88:173–180. [PubMed: 17270514]
13. Hénon H, Lebert F, Durieu I, et al. Confusional state in stroke: relation to preexisting dementia, patient characteristics, and outcome. Stroke. 1999; 30:773–779. [PubMed: 10187878]
14. Őzdemir F, Birtane M, Tabatabaei R, Ekuklu G, Kokino S. Cognitive evaluation and functional outcome after stroke. Am J Phys Med Rehabil. 2001; 80:410–415. [PubMed: 11399001]
15. Stephens S, Kenny RA, Rowan E. Association between mild vascular cognitive impairment and impaired activities of daily living in older stroke survivors without dementia. J Am Geriatr Soc. 2005; 53:103–107. [PubMed: 15667385]
16. vanZandvoort MJE, Kessels RPC, Nys GMS, deHaan EHF, Kapelle LJ. Early neuropsychological evaluation in patients with ischaemic stroke provides valid information. Clin Neurol Neurosurg. 2005; 107:385–392. [PubMed: 16023532]
17. Heruti RJ, Lusky A, Dankner R, et al. Rehabilitation outcome of elderly patients after a first stroke: effect of cognitive status at admission on the functional outcome. Arch Phys Med Rehabil. 2002; 83:742–749. [PubMed: 12048650]
18. Royall DR, Cabello M, Polk MJ. Executive dyscontrol: an important factor affecting the level of care received by older retirees. J Am Geriatr Soc. 1998; 46:1519–1524. [PubMed: 9848812]
19. Hanks RS, Rapport LJ, Millis SR, Deshpande SA. Measures of executive functioning as predictors of functional ability and social integration in a rehabilitation sample. Arch Phys Med Rehabil. 1999; 80:1030–1037. [PubMed: 10489004]
20. Mok VCT, Wong A, Lam WWM, et al. Cognitive impairment and functional outcome after stroke associated with small vessel disease. J Neurol Neurosurg Psychiatry. 2004; 75:560–566. [PubMed: 15026497]
21. Mysiw WJ, Beegan JG, Gatens PF. Prospective cognitive assessment of stroke patients before inpatient rehabilitation: The relationship of the neurobehavioral cognitive status examination to functional improvement. Am J Phys Med Rehabil. 1989; 68:168–171. [PubMed: 2765207]
22. Brockmann, RK.; Gillen, G. Treatment of cognitive-perceptual deficits: a function-based approach in stroke rehabilitation. 2. Gillen, G.; Burkhardt, RK., editors. Mosby; St Louis, MO: 2004.
23. Nudo RJ, Palutz EJ, Frost SB. Role of adaptive plasticity in recovery of function after damage to the motor cortex. Muscle Nerve. 2001; 24:1000–1019. [PubMed: 11439375]
24. Thickbroom GW, Byrnes ML, Archer SA, Mastaglia FL. Motor outcome after subcortical stroke correlates with the degree of cortical reorganization. Clin Neurophysiol. 2004; 115:2144–2150. [PubMed: 15294217]
25. Mark VW, Taub E, Morris DM. Neuroplasticity and constraint-induced movement therapy. Eura Medicophys. 2006; 42:269–284. [PubMed: 17039225]

26. Kaas JH, Merzenich MM, Killackey HP. The reorganization of somatosensory cortex following peripheral nerve damage in adult and developing mammals. Annu Rev Neurosci. 1983; 6:325–356. [PubMed: 6340591]
27. Feldman DE, Brecht M. Map plasticity in somatosensory cortex. Science. 2005; 310:810–815. [PubMed: 16272113]
28. Kreisel SH, Hennerici MG, Bäzner H. Pathophysiology of stroke rehabilitation: the natural course of clinical recovery, use-dependent plasticity and rehabilitative outcome. Cerebrovasc Dis. 2007; 23:243–255. [PubMed: 17192704]
29. Taub E, Uswatte G, King DK, Morris D, Crago JE, Chatterjee A. A placebo-controlled trial of constraint-induced movement therapy for upper extremity after stroke. Stroke. 2006; 37:1045–1049. [PubMed: 16514097]
30. Wolf SL, Winstein CJ, Miller JP, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: The EXCITE Randomized Clinical Trial. JAMA. 2006; 296:2095–2104. [PubMed: 17077374]
31. Cicerone K, Dahlberg C, Malec J, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. Arch Phys Med Rehabil. 2005; 86:1681–169. [PubMed: 16084827]
32. Lenze EJ, Munin MC, Dew MA, et al. Adverse effects of depression and cognitive impairment on rehabilitation participation and recovery from hip fracture. Int J Geriatr Psychiatry. 2004; 19:472–478. [PubMed: 15156549]
33. Lenze EJ, Munin MC, Quear T, et al. The Pittsburgh Rehabilitation Participation Scale: reliability and validity of a clinician-rated measure of participation in acute rehabilitation. Arch Phys Med Rehabil. 2004; 85:380–384. [PubMed: 15031821]
34. Horn W, Yoels W, Bartolucci A. Factors associated with patients' participation in rehabilitation services: a comparative injury analysis 12 months post-discharge. Disabil Rehabil. 2000; 22:358–362. [PubMed: 10896096]
35. Dorra HH, Lenze EJ, Kim Y, et al. Clinically relevant behaviors in elderly hip fracture inpatients. Int J Psychiatry Med. 2002; 32:249–259. [PubMed: 12489700]
36. Resnick B, Zimmerman SI, Magaziner J, Adelman A. Use of the apathy evaluation scale as a measure of motivation in elderly people. Rehabil Nurs. 1998; 23:141–147. [PubMed: 9697585]
37. Resnick B. Geriatric rehabilitation: the influence of efficacy beliefs and motivation. Rehabil Nurs. 2002; 27:152–159. [PubMed: 12116528]
38. Skidmore ER, Whyte EM, Holm MB, et al. Cognitive and affective predictors of rehabilitation participation after stroke. Arch Phys Med Rehabil. 2010; 91:203–207. [PubMed: 20159122]
39. Cirstea CM, Ptito A, Levin MF. Feedback and cognition in arm motor skill reacquisition after stroke. Stroke. 2006; 37:1237–1242. [PubMed: 16601218]
40. Hallett, M.; Pascual-Leone, A.; Topka, H. Adaptation and skill learning: evidence for different neural substrates. In: Bloedel, JR.; Ebner, TJ.; Wise, S., editors. The acquisition of motor behavior in vertebrates. MIT Press; Cambridge: 1996. p. 289-302.
41. Krebs HI, Volpe B, Hogan N. A working model of stroke recovery from rehabilitation robotics practitioners. J Neuroeng Rehabil. 2009; 25:6. [PubMed: 19243615]
42. Doyon J, Benali H. Reorganization and plasticity in the adult brain during learning of motor skills. Curr Opin Neurobiol. 2005; 15:161–167. [PubMed: 15831397]
43. Frensch, P. One concept, multiple meanings: how to define the concept of implicit learning. In: Stadler, MA.; Frensch, PA., editors. Handbook of implicit learning. Sage Publications; Thousand Oaks, CA: 1998. p. 47-104.
44. Subramanian SK, Massie CL, Malcolm MP, Levin MF. Does provision of extrinsic feedback result in improved motor learning in the upper limb poststroke?: A systematic review of the evidence. Neurorehabil Neural Repair. 2010; 24:113. [PubMed: 19861591]
45. Nissen MJ, Bullemer P. Attentional requirements of learning: evidence from performance measures. Cognit Psychol. 1987; 19:1–32.
46. Reber AS. Implicit learning of artificial grammars. J Verbal Learn Verbal Behav. 1967; 6:855–863.

47. Gluck MA, Bower GH. From conditioning to category learning: an adaptive network model. J Exp Psychol Gen. 1988; 117:227–247. [PubMed: 2971760]
48. Boyd LA, Quaney BM, Pohl PS, Winstein CJ. Learning implicitly: effects of task and severity after stroke. Neurorehabil Neural Repair. 2007; 21:444–454. [PubMed: 17416874]
49. Boyd L, Winstein C. Explicit information interferes with implicit motor learning of both continuous and discrete movement tasks after stroke. J Neurol Phys Ther. 2006; 30:46–57. [PubMed: 16796767]
50. Orrell AJ, Eves FF, Masters RS. Motor learning of a dynamic balancing task after stroke: implicit implications for stroke rehabilitation. Phys Ther. 2006; 86:369–380. [PubMed: 16506873]
51. Boyd LA, Winstein CJ. Impact of explicit information on implicit motor-sequence learning following middle cerebral artery stroke. Phys Ther. 2003; 83:976–989. [PubMed: 14577825]
52. Boyd LA, Winstein CJ. Providing explicit information disrupts implicit motor learning after basal ganglia stroke. Learn Mem. 2004; 11:388–396. [PubMed: 15286181]
53. van Vliet PM, Wulf G. Extrinsic feedback for motor learning after stroke: what is the evidence? Disabil Rehabil. 2006; 28:831–840. [PubMed: 16777770]
54. Court JA, Perry EK. Neurotransmitter abnormalities in vascular dementia. Inter Psychogeriatr. 2003; 15(Suppl 1):81–87.
55. Gottfries CG, Blennow K, Karlsson I, Wallin A. The neurochemistry of vascular dementia. Dement. 1994; 5:163–167.
56. Kristofikova Z, Fales E, Majer E, Klaschka J. (3H) hemicholinium-3 binding sites in postmortem brains of human patients with Alzhemier's disease and multi-infarct dementia. Exp Gerontol. 1995; 30:125–136. [PubMed: 8591807]
57. Martin-Ruiz C, Court J, Lee M, et al. Nicotinic receptors in dementia of Alzheimer, Lewy body and vascular types. Acta Neurol Scand Suppl. 2000; 176:34–41. [PubMed: 11261803]
58. Nordberg, Alafuzoff I, Winblad B. Nicotinic and muscarinic sub-types in the human brain: changes with aging and dementia. J Neurosci Res. 1992; 31:103–111. [PubMed: 1613816]
59. Tohgi H, Abe T, Kimura M, Saheki M, Takahashi S. Cerebrospinal fluid acetylcholine and choline in vascular dementia of Binswanger and multiple small infarct types as compared with Alzheimer-type dementia. J Neural Transm. 1996; 103:1211–1220. [PubMed: 9013408]
60. Berends HI, Nijlant JM, Movig KL, Van Putten MJ, Jannink MJ, Ijzerman MJ. The clinical use of drugs influencing neurotransmitters in the brain to promote motor recovery after stroke; a Cochrane systematic review. Eur J Phys Rehabil Med. 2009; 45:621–630. [PubMed: 20032921]
61. Richardson RT, DeLong MR. A reappraisal of the functions of the nucleus basalis of Meynert. Trends Neurosci. 1988; 11:264–267. [PubMed: 2465623]
62. Baskerville KA, Schweitzer JB, Herron P. Effects of cholinergic depletion on experience-dependent plasticity in the cortex of the rat. Neuroscience. 1997; 80:1159–1169. [PubMed: 9284068]
63. Gelenberg AJ, Van Putten T, Lavori PW, et al. Anticholinergic effects on memory: benztropine versus amantadine. J Clin Psychopharmacol. 1989; 9:180–185. [PubMed: 2661606]
64. McEvoy JP, Freter S. The dose-response relationship for memory impairment by anticholinergic drugs. Compr Psychiatry. 1989; 30:135–138. [PubMed: 2920548]
65. Mulsant BH, Pollock BG, Kirshner M, Shen C, Dodge H, Ganguli M. Serum anticholinergic activity in a community-based sample of older adults: relationship with cognitive performance. Arch Gen Psychiatry. 2003; 60:198–203. [PubMed: 12578438]
66. Rasmusson DD, Dykes RW. Long-term enhancement of evoked potentials in cat somatosensory cortex produced by co-activation of the basal forebrain and cutaneous receptors. Exp Brain Res. 1988; 70:276–286. [PubMed: 3384031]
67. Rasmusson DD. Cholinergic modulation of sensory information. Prog Brain Res. 1993; 98:357–364. [PubMed: 8248524]
68. Kennedy MRT, Coelho C, Turkstra L, et al. Intervention for executive functions after traumatic brain injury: a systematic review, meta-analysis and clinical recommendations. Neuropsychol Rehabil. 2008; 18:257–299. [PubMed: 18569745]

69. McEwen SE, Polatajko HJ, Davis JA, Huijbregts MPH, Ryan JD. “There’s a real plan here, and I am responsible for that plan”: participant experiences with a novel cognitive-based treatment approach for adults living with chronic stroke. Disabil Rehabil. 2010; 32:541–550.
70. Dawson D, Gaya A, Hunt A, Levine B, Lemsky C, Polatajko H. Using the cognitive orientation to occupational performance (CO-OP) with adults with executive dysfunction following traumatic brain injury. Can J Occup Ther. 2009; 76:74–86.
71. Polatajko, HJ.; Mandich, A. Enabling occupation in children: the cognitive orientation to daily occupational performance (CO-OP) approach. CAOT Publications; Ottawa, ON, Canada: 2004.
72. Skidmore ER, Holm MB, Whyte EM, Dew MA, Dawson D, Becker JT. The feasibility of meta-cognitive strategy training in acute inpatient stroke rehabilitation: case report. Neuropsych Rehabil. 2011; 21:208–223.
73. Whyte EM, Lenze EJ, Butters M, et al. An open-label pilot study of acetylcholinesterase inhibitors to promote functional recovery in elderly cognitively impaired stroke patients. Cerebrovasc Dis. 2008; 26:317–321. [PubMed: 18667813]
74. Yesavage JA, Mumenthaler MS, Taylor JL, et al. Donepezil and flight simulator performance: effects on retention of complex skills. Neurology. 2002; 59:123–125. [PubMed: 12105320]
75. Beglinger LJ, Gaydos BL, Kareken DA, Tangphao-Daniels O, Siemers ER, Mohs RC. Neuropsychological test performance in healthy volunteers before and after donepezil administration. J Psychopharmacol. 2004; 18:102–108. [PubMed: 15107192]
76. Grön G, Kirstein M, Thielscher A, Riepe MW, Spitzer M. Cholinergic enhancement of episodic memory in healthy young adults. Psychopharmacology. 2005; 182:170–179. [PubMed: 16021483]
77. Wezenberg E, Verkes RJ, Sabbe BGC, Ruigt GSF, Hulstijn W. Modulation of memory and visuspatial processes by biperiden and rivastigmine in elderly healthy subjects. Psychopharmacology. 2005; 181:582–594. [PubMed: 16041534]
78. Karabanov, Cervenka S, de Manzano O, Forssberg H, Farde L, Ullén F. Dopamine D2 receptor density in the limbic striatum is related to implicit but not explicit movement sequence learning. Proc Natl Acad Sci U S A. 2010; 107:7574–7579. [PubMed: 20368439]
79. Thiel CM. Cholinergic modulation of learning and memory in the human brain as detected with functional neuroimaging. Neurobiol Learn Mem. 2003; 80:234–244. [PubMed: 14521866]
80. Flöel, Breitenstein C, Hummel F, et al. Dopaminergic influences on formation of a motor memory. Ann Neurol. 2005; 58:121–130. [PubMed: 15984008]
81. Flöel, Hummel F, Breitenstein C, Knecht S, Cohen LG. Dopaminergic effects on encoding of a motor memory in chronic stroke. Neurology. 2005; 65:472–474. [PubMed: 16087920]
82. Meintzschel F, Ziemann U. Modification of practice-dependent plasticity in human motor cortex by neuromodulators. Cereb Cortex. 2006; 16:1106–1115. [PubMed: 16221926]
83. Rösser N, Heuschmann P, Wersching H, Breitenstein C, Knecht S, Flöel A. Levodopa improves procedural motor learning in chronic stroke patients. Arch Phys Med Rehabil. 2008; 89:1633–1641. [PubMed: 18760148]
84. Winstein CJ, Bentzen KR, Boyd L, Schneider LS. Does the cholinesterase inhibitor, donepezil, benefit both declarative and non-declarative processes in mild to moderate Alzheimer’s disease? Curr Alzheimer Res. 2007; 4:273–4276. [PubMed: 17627484]
85. Nadeau SE, Behrman AL, Davis SE, et al. Donepezil as an adjuvant to constraint-induced therapy for upper-limb dysfunction after stroke: an exploratory randomized clinical trial. J Rehabil Res Dev. 2004; 41:525–534. [PubMed: 15558381]