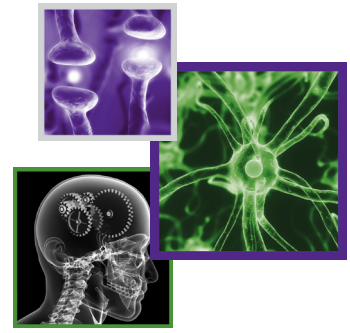
EDITORIAL

Neurodegenerative Disease Management



# Working memory and memory loss in neurodegenerative disease

"Basing cognitive rehabilitation on tested theoretical assumptions will increase the probability of managing the disabling cognitive symptoms that accompany neurodegenerative diseases."

Joshua Sandry*[,1,2]

**KEYWORDS**

• cognition • cognitive reserve • memory disorders • neurology • rehabilitation • translational research

Cognitive impairment is a troubling comorbid consequence of many neurodegenerative diseases that often negatively impacts day-to-day activities, results in unemployment and leads to reductions in quality of life. Long-term memory (LTM) is one commonly impaired system; however, there is significant variability across patients. Some individuals experience LTM loss while others with similar cerebral insults may not. The heterogeneity across patients has been accounted for, in part, by the theory of Cognitive Reserve (CR), which suggests that the behaviors that people engage in over the course of their lifetime may protect them from the negative cognitive consequences of neurodegeneration [1,2]. These findings have been frequently replicated in healthy aging and diseased populations. CR estimates that correlate with cognitive impairment include IQ, socioeconomic status and educational or occupational attainment, as well as participation in intellectually enriching cognitive leisure activities.

Given strong support for CR predictions, one unexplored next step is to identify the cognitive mechanisms and processes that underlie CR [3]. It may be that individuals with high CR are more efficient at processing information [4] or these individuals may use superior cognitive strategies [5,6]. Understanding these mechanisms and processes may serve as a specific cognitive biomarker useful for identifying who will and will not improve from cognitive rehabilitation. Additionally, this understanding may lead to novel treatments directed at increasing CR and rehabilitating impaired LTM. Drawing on theoretical models from cognitive psychology and using a translational approach will be one promising direction to better understand the mechanics of CR.

In recent work, my colleagues and I used a translational approach to test one possible underlying cognitive mechanism that could help to explain the relationship between CR and LTM impairment in neurological populations. We hypothesized that individual differences in working memory (WM) capacity, which is the cognitive system involved in the control,

"Revised accounts of the hippocampus implicate this brain region as an important structure for both working memory and long-term memory."

[1]Neuropsychology & Neuroscience Research, Kessler Foundation, 300 Executive Drive, Suite 70, West Orange, NJ 07052, USA

[2]Department of Physical Medicine & Rehabilitation, Rutgers New Jersey Medical School, Newark, NJ, USA

*Author for correspondence: JSandry@KesslerFoundation.org

Future Medicine part of fsg

regulation and maintenance [7] of only a limited amount of information [8], would mediate this relationship. Well-specified theoretical views from cognitive psychology offer a solid foundation for this prediction and provide support for this assumption. Individual differences in WM positively correlate with intelligence, efficiency in accessing or retrieving existing memory representations out of LTM and the binding or encoding of new information into LTM [9]. Using composite scores for CR, LTM and WM capacity, we tested and found support for this mediation hypothesis in separate samples of multiple sclerosis [10] and traumatic brain injury [11] patients. Importantly, the composite WM score in both studies included simple and complex span tasks, equating our estimates of WM more closely with traditional laboratory measures of WM that are frequently used in basic research [12]. Recently, similar evidence showed a WM-LTM relationship in a sample of healthy older adults and patients with amnestic mild cognitive impairment [13]. WM appears to be one cognitive mechanism that underlies CR.

"...many interpretations regarding the efficacy of cognitive training rely on experiments that recruit healthy individuals..."

Future work is needed to replicate these findings in other neurodegenerative populations, ideally using sensitive laboratory measures of WM capacity. Neural evidence related to the hippocampus may further support the CR–LTM–WM intercorrelation. Revised accounts of the hippocampus implicate this brain region as an important structure for both WM and LTM [14] and a region that may be functionally important for binding information [15]. The hippocampus is also related to CR; larger hippocampal volume is positively related to intellectual enrichment (a proxy of CR) and LTM functioning in multiple sclerosis [16]. The hippocampus may be one key anatomical structure that supports the CR–LTM–WM association and this may be a promising direction for future research. Now the prevailing question is what implications are there for WM as a CR mechanism and what does this mean for managing cognitive impairment that accompanies neurodegenerative disease? The answer may be multifaceted with implications for both compensatory and restorative treatment approaches.

## Managing LTM impairment

### • Implications for compensatory treatment

LTM impairment is not homogeneous across patients, thus, the nature of the patients' specific memory deficit should guide rehabilitation options; similar to how an oncologist would approach cancer treatment using a varied medicinal arsenal. For example, LTM-impaired patients may respond differently to internal or external compensatory rehabilitation. Internal compensatory strategies teach the patient a novel technique to learn and remember information (e.g., using an acronym to remember a grocery list). External compensatory strategies teach the patient to use some outside device to assist in retaining information (e.g., recording daily events on a notepad). The evidence supporting compensatory treatment is encouraging; however, treatments may not be uniformly effective across cognitively heterogeneous neurodegenerative disease populations. WM capacity may serve as a cognitive biomarker for who will and will not benefit from different LTM treatments. For example, high WM capacity patients may better understand and successfully implement compensatory strategies because they can efficiently process the treatment instructions. Alternatively, low WM capacity individuals may not efficiently process the compensatory strategy instructions, resulting in an ineffective treatment or even hindering performance. Additional predictions are also possible and the data may eventually suggest measurements of WM capacity will prove to be a clinically useful diagnostic tool to predict LTM treatment responsiveness. Using a translational approach may ultimately lead to patient-specific cognitive rehabilitation options.

### • Implications for restorative treatment

Identifying WM as a CR mechanism may have implications for attempts to increase CR, through cognitive training. Cognitive training is a restorative treatment. This differs from compensatory treatments in that restoration is designed to improve or alter cognition so that it operates similarly to the efficiency it was prior to neurodegeneration. Some assume this can be accomplished by requiring the patient to engage in repetitive cognitive exercises and that specific cognitive training will lead to generalized improvements in cognition, in other words, hypothesizing that training WM will lead to transferred improvements in LTM. Training programs are widely marketed and claims regarding cognitive changes caused by training are often quite extraordinary.

Unfortunately, the empirical evidence supporting transfer from cognitive training is highly mixed with discordant findings in the literature, including meta-analytic reports. Some suggest that cognitive training does not result in generalized changes in cognition [17,18] while others present evidence in favor of generalized and lasting cognitive changes [19,20]. Many claims regarding the efficacy of cognitive training may be premature, exaggerated and overly optimistic.

Importantly, many interpretations regarding the efficacy of cognitive training rely on experiments that recruit healthy individuals while evaluations of cognitive training programs in neurodegenerative disease patients have received less attention. Cognitively intact participants may exhibit near ceiling performance and it may be less feasible to improve cognition in these individuals. This healthy sampling bias limits the generalizability of these findings for cognitively impaired patients because impaired patients may be the most likely to benefit from training [10]. Unfortunately, many of the cognitive training studies in impaired patients suffer from critical methodological flaws including inappropriate enrollment criteria, inadequate control groups and unspecified treatments, etc. Currently, it may be too early to draw hard conclusions regarding the restorative benefits of cognitive training in neurological patients and whether training will ultimately increase CR.

Moving forward and adopting a translational approach will be valuable when designing and testing restorative treatments in impaired populations and WM may be a particularly important construct to target when trying to boost CR and improve impaired LTM. The lessons learned from ongoing cognitive research will provide a solid theoretical basis for testing restorative treatments in neurodegenerative disease patients. At this point, claims related to the benefits of cognitive training in neurological patients need to be evaluated using high-quality randomized controlled trials and preferably, the interventions will be theoretically informed. When it comes to restoration, only when treatment targets the appropriate overlapping cognitive subsystems should we expect an improvement in a related but separate system, for example, transfer between WM training and LTM improvement. It may be that only patients with WM and LTM deficits will show a LTM benefit from WM training. For example, some of the heterogeneity in LTM impairment might be explained by individual differences in WM capacity whereby patients with low capacity do not efficiently bind information into LTM. Other patients may have impairments in WM related to LTM retrieval. Taking translational steps early during design will strengthen the possibility of identifying successful cognitive rehabilitation treatments. Further, we may find that the most effective option will come from a synergistic effect between compensatory and restorative treatments.

## Conclusion & future perspective

Favorable progress in medicine often results from translating basic scientific research to practice, with treatments based on an understanding of the basic disease mechanisms. Similarly, understanding the basic mechanisms of cognition will inform cognitive rehabilitation treatment options. The massive literature on CR has demonstrated that there is a significant amount of heterogeneity among cognitive impairment in diseased populations and recent work suggests WM may be one mediating variable [10,11]. Existing memory theory is a rich source of information that can in turn be used to develop a strong foundation for treating cognitive impairment. As we identify the mechanisms underlying CR, researchers should draw from cognitive psychology theory to make predictions and understand different patient outcomes, a patient-specific individual differences approach to cognitive rehabilitation. Researchers should also draw from cognitive psychology theory to craft and test novel cognitive rehabilitation treatment strategies that target specific CR mechanisms. Basing cognitive rehabilitation on tested theoretical assumptions will increase the probability of managing the disabling cognitive symptoms that accompany neurodegenerative diseases.

## Financial & competing interests disclosure

*The author is supported by National Multiple Sclerosis Society Postdoctoral Fellowship Grant MB0024. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

*No writing assistance was utilized in the production of this manuscript.*

## References


1 Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J. Int. Neuropsychol. Soc.* 8(3), 448–460 (2002).

2 Stern Y. Cognitive reserve. *Neuropsychologia* 47(10), 2015–2028 (2009).

3 Barulli D, Stern Y. Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends Cogn. Sci.* 17(10), 502–509 (2013).

4 *Cognitive Reserve: Theory and Applications.* Stern Y (Ed.). Psychology Press, NY, USA (2013).

5 Barulli DJ, Rakitin BC, Lemaire P, Stern Y. The influence of cognitive reserve on strategy selection in normal aging. *J. Int. Neuropsychol. Soc.* 19(07), 841–844 (2013).

6 Czernochowski D, Fabiani M, Friedman D. Use it or lose it? SES mitigates age-related decline in a recency/recognition task. *Neurobiol. Aging* 29(6), 945–958 (2008).

7 Miyake A, Shah P. *Models of Working Memory: Mechanisms of Active Maintenance and Executive Control.* Cambridge University Press, NY, USA (1999).

8 Cowan N. The magical number 4 in short-term memory: a reconsideration of mental storage capacity. *Behav. Brain. Sci.* 24(1), 87–114 (2001).

9 Unsworth N, Fukuda K, Awh E, Vogel EK. Working memory and fluid intelligence: capacity, attention control, and secondary memory retrieval. *Cogn. Psychol.* 71, 1–26 (2014).

10 Sandry J, Sumowski JF. Working memory mediates the relationship between intellectual enrichment and long-term memory in multiple sclerosis: an exploratory analysis of cognitive reserve. *J. Int. Neuropsychol. Soc.* 20(8), 868–872 (2014).

11 Sandry J, Deluca J, Chiaravalloti N. Working memory capacity links cognitive reserve with long-term memory in moderate to severe TBI: a translational approach. *J. Neurol.* 262(1), 59–64 ( 2015).

12 Shelton JT, Elliott EM, Hill B, Calamia MR, Gouvier WD. A comparison of laboratory and clinical working memory tests and their prediction of fluid intelligence. *Intelligence* 37(3), 283–293 (2009).

13 Constantinidou F, Zaganas I, Papastefanakis E, Kasselimis D, Nidos A, Simos PG. Age-related decline in verbal learning is moderated by demographic factors, working memory capacity, and presence of amnestic mild cognitive impairment. *J. Int. Neuropsychol. Soc.* 20(8), 822–835 (2014).

14 Poch C, Campo P. Neocortical–hippocampal dynamics of working memory in healthy and diseased brain states based on functional connectivity. *Front. Hum. Neurosci.* 6(36) (2012).

15 Yonelinas AP. The hippocampus supports high-resolution binding in the service of perception, working memory and long-term memory. *Behav. Brain Res.* 254, 34–44 (2013).

16 Sumowski JF, Rocca MA, Leavitt VM *et al.* Searching for the neural basis of reserve against memory decline: intellectual enrichment linked to larger hippocampal volume in multiple sclerosis. *Eur. J. Neurol.* (2015) (In Press).

17 Melby-Lervåg M, Hulme C. Is working memory training effective? A meta-analytic review. *Dev. Psychol.* 49(2), 270 (2013).

18 Shipstead Z, Redick TS, Engle RW. Is working memory training effective? *Psychol. Bull.* 138(4), 628 (2012).

19 Au J, Sheehan E, Tsai N, Duncan G, Buschkuehl M, Jaeggi S. Improving fluid intelligence with training on working memory: a meta-analysis. *Psychon. Bull. Rev.* doi:10.3758/s13423-014-0699-x (2014) (Epub ahead of print).

20 Karbach J, Verhaeghen P. Making working memory work a meta-analysis of executive-control and working memory training in older adults. *Psychol. Sci.* 25(11), 2027–2037 (2014).