

# Evidence booklet

## Effectiveness studies



### Effectiveness through comparability

A large number of studies show evidence for the efficacy of Cognitive Rehabilitation Therapy.

A few years ago, the development team of the market leader RehaCom started to create HeadApp. Based on 30 years of experience and accompanied by science, we built a modern system to make therapy even more effective and entertaining.

The results of the studies are transferable to HeadApp, as the same methods and recent paradigms have been applied and implemented in HeadApp.

For this reason, studies are now ongoing to show the benefits of the new system.

In 2019, HeadApp was enhanced with the NEUROvitalis therapy system (release in 2020). The effectiveness of NEUROvitalis has been proven in several studies.

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# Table of Content

<b>NEUROVITALIS STUDIES (HEADAPP CONTENT, RELEASE 2020)</b>	<b>3</b>
<b>NEW STUDIES</b>	<b>6</b>
<b>CEREBRAL LESIONS</b>	<b>10</b>
<b>MULTIPLE SCLEROSIS</b>	<b>15</b>
<b>DEMENTIA / ALZHEIMER</b>	<b>18</b>
<b>SCHIZOPHRENIA</b>	<b>19</b>
<b>ADHD</b>	<b>22</b>
<b>DEPRESSION</b>	<b>23</b>
<b>AGING AND PREVENTION</b>	<b>24</b>
<b>METASTUDIES</b>	<b>25</b>

## NEUROvitalis studies (HeadApp content, release 2020)

### **Cognitive stimulation in individuals with Parkinson's disease dementia living in a specialized Parkinson care unit: A randomized cross-over pilot study.**

Folkerts AK, Dorn M, Roheger M, Maassen M, Koerts J, Tucha O, Altgassen M, Sack AT, Smit D, Haarmann L, Kalbe E (submitted). Parkinson's Disease. <https://pubmed.ncbi.nlm.nih.gov/30631420/>

### **Effects of cognitive training in Parkinson's disease: a randomized controlled trial.**

Petrelli A, Kaesberg S, Barbe MT, Timmermann L, Fink GR, Kessler J, Kalbe E.; Parkinsonism Relat Disord. 2014 Nov;20(11):1196-202. doi: 10.1016/j.parkreldis.2014.08.023. Epub 2014 Sep 16.; <https://pubmed.ncbi.nlm.nih.gov/25242806/>

„A neuropsychological test battery was performed before and after the training. RESULTS: Compared to the CG, patients from the "NEUROvitalis" group improved in short-term memory (word list learning "Memo":  $p < .01$ ) and working memory (digit span reverse from "DemTect" ..."

### **Cognitive training in Parkinson's disease reduces cognitive decline in the long term.**

Petrelli A, Kaesberg S, Barbe MT, Timmermann L, Rosen JB, Fink GR, Kessler J, Kalbe E.; Eur J Neurol. 2015 Apr;22(4):640-7. doi: 10.1111/ene.12621. Epub 2014 Dec 22. <https://pubmed.ncbi.nlm.nih.gov/25534579/>

"METHODS: One-year follow-up data (T2 ) of a randomized controlled trial evaluating two 6-week cognitive trainings - a structured (NEUROvitalis, NV) and an unstructured (mentally fit, MF) program - compared with a waiting list control group (CG) in non-demented PD patients ..."

### **Prognostic factors for change in memory test performance after memory training in healthy older adults: a systematic review and outline of statistical challenges.**

Roheger M, Folkerts AK, Krohm F, Skoetz N, Kalbe E.; Diagn Progn Res. 2020 May 21;4:7. doi: 10.1186/s41512-020-0071-8. eCollection 2020. <https://pubmed.ncbi.nlm.nih.gov/32478173/>

### **Enhancement of Executive Functions but Not Memory by Multidomain Group Cognitive Training in Patients with Parkinson's Disease and Mild Cognitive Impairment: A Multicenter Randomized Controlled Trial.**

Kalbe E, Folkerts AK, Ophey A, Eggers C, Elben S, Dimenshteyn K, Sulzer P, Schulte C, Schmidt N, Schlenstedt C, Berg D, Witt K, Wojtecki L, Liepelt-Scarfone I.; Parkinsons Dis. 2020 Nov 30;2020:4068706. doi: 10.1155/2020/4068706. eCollection 2020. <https://pubmed.ncbi.nlm.nih.gov/33312495/>

### **Memory enhancement by multidomain group cognitive training in patients with Parkinson's disease and mild cognitive impairment: long-term effects of a multicenter randomized controlled trial.**

Schmidt N, Tödt I, Berg D, Schlenstedt C, Folkerts AK, Ophey A, Dimenshteyn K, Elben S, Wojtecki L, Liepelt-Scarfone I, Schulte C, Sulzer P, Eggers C, Kalbe E, Witt K., J Neurol. 2021 Dec;268(12):4655-4666. doi: 10.1007/s00415-021-10568-9. Epub 2021 Apr 27. <https://pubmed.ncbi.nlm.nih.gov/33904966/>

### **Prognostic Factors and Models for Changes in Cognitive Performance After Multi-Domain Cognitive Training in Healthy Older Adults: A Systematic Review**

Mandy Roheger, Hannah Liebermann-Jordanidis, Fabian Krohm, Anne Adams, Elke Kalbe; Front Hum Neurosci. 2021 Apr 27;15:636355. doi: 10.3389/fnhum.2021.636355. eCollection 2021. <https://pubmed.ncbi.nlm.nih.gov/33986652/>

**Cognitive training with and without additional physical activity in healthy older adults: effects of a randomized controlled trial on cognition one year after intervention.**

Kalbe E, Roheger M, Paluszak K, Meyer J, Becker J, Fink GR, Kukulja J, Rahn A, Szabados F, Wirth B, Kessler J

**Cognitive Training in Healthy Older People: A Scientifically based Structured Training yields best Results, and the ApoE4 State and Baseline Level influence Training Benefits.**

Roheger M, Kessler J, Kalbe E. *Frontiers in Human Neuroscience*.

**Cognitive Stimulation for People with Dementia in Long-term Care Facilities: Baseline cognitive level predicts cognitive gains, moderated by depression. Evidence from a Randomized Controlled Trial.**

Middelstädt J, Folkerts AK, Blawath S, Kalbe E (2016). *Journal of Alzheimer's disease*, 54, 253-68. <https://pubmed.ncbi.nlm.nih.gov/27497474/>

**One-year follow-up of cognitive training in Parkinson's disease.**

Petrelli A, Kaesberg S, Barbe MT, Timmermann L, Rosen J, Fink GR, Kessler J, Kalbe E (2015). *European Journal of Neurology*, 22, 640-647.

**Cognitive training with and without additional physical activity in healthy older adults: cognitive effects, neurobiological mechanisms, and prediction of training success.**

Rahe J, Becker J, Fink GR, Kessler J, Kukulja J, Rahn A, Rosen JB, Szabados F, Wirth B, Kalbe E (2015). *Frontiers in Aging Neuroscience*, 7, 187. <https://pubmed.ncbi.nlm.nih.gov/26528177/>

**Sex differences in cognitive training effects of patients with amnesic mild cognitive impairment.**

Rahe J, Liesk J, Rosen JB, Petrelli A, Kaesberg S, Onur OA, Kessler J, Fink GR, Kalbe E (2015). *Aging, Neuropsychology, and Cognition*, 22, 620-638. <https://pubmed.ncbi.nlm.nih.gov/25818876/>

**Effects of cognitive training with additional physical activity compared to pure cognitive training in healthy older adults.**

Rahe J, Petrelli A, Kaesberg S, Fink GR, Kessler J, Kalbe E (2015). *Clinical Interventions in Aging*, 19, 297-310. <https://pubmed.ncbi.nlm.nih.gov/25632227/>

**Cognitive stimulation and music intervention in inpatients with dementia. A pilot study, problems & perspectives.**

Liesk J, Hartogh T, Kalbe E (2014). *Zeitschrift für Gerontologie und Geriatrie*, 48, 275-281.

### **Effects of cognitive training in patients with Parkinson´s disease: a randomized controlled trial.**

Petrelli A, Kaesberg S, Kessler J, Barbe MT, Fink GR, Timmermann L, Kalbe E (2014). Parkinsonism & Related Disorders, 20, 1196-1202.

### **NEUROvitalis literature from German journals (not listed in PubMed)**

#### **Cognitive training effects of neuropsychological program NEUROvitalis in combination with physical activity.**

Rahe J, Petrelli A, Kaesberg S, Baller G, Kessler J, Kalbe E (2012). Neurologie & Rehabilitation, 18, 187.

#### **Structured training NEUROvitalis versus brain jogging in patients with mild cognitive disorders and healthy elderly: a randomized, controlled trial.**

Kalbe E, Kaesberg S, Petrelli A, Baller G, Fink GR & Kessler J (2011). Zeitschrift für Neuropsychologie, 22, 194.

#### **Non-pharmacological intervention in patients with multiple sclerosis - effects of neuropsychological training NEUROvitalis.**

Müller K, Kaesberg S, Petrelli A, Kalbe E, Baller G, Sack AT, Kessler J (2011). Zeitschrift für Neuropsychologie, 22, 228.

#### **Basic cognitive level and propensity for the training success of patients with idiopathic Parkinson's syndrome in neuropsychological group training NEUROvitalis.**

Petrelli A, Kaesberg S, Barbe MT, Timmermann L, Kessler J, Baller G, Fink GR, Kalbe E (2011). Zeitschrift für Neuropsychologie, 22, 230.

#### **NEUROvitalis®: effects of a new neuropsychological training in healthy elderly as well as in patients with mild cognitive impairment and onset of Alzheimer's dementia.**

Kaesberg S, Mayer A, Schlegel M, Baller G, Fink G, Kessler J, Kalbe E (2010). Zeitschrift für Neuropsychologie, 21, 221.

#### **NEUROvitalis®: effects of a new neuropsychological training in healthy elderly individuals as well as patients suffering from Mild Cognitive Impairment and early-stage Alzheimer's Disease.**

Kaesberg S, Kalbe E, Mayer A, Baller G, Sack A, Kessler J (2009). Alzheimer's and Dementia, 5, 332.

#### **NeuroVitalis®: effects of a new neuropsychological training in patients with mild cognitive disorders and patients with Alzheimer's disease.**

Kalbe E, Kaesberg S, Mayer A, Schlegel M, Baller G, Fink GR, Kessler J (2009). Aktuelle Neurologie, 36, 149.

For details on each study please contact us on [science@headapp.com](mailto:science@headapp.com).

## New Studies

### Beneficial Effect of Multidomain Cognitive Training on the Neuropsychological Performance of Patients with Early-Stage Alzheimer's Disease

Nousia A, Siokas V, Aretouli E, Messinis L, Aloizou AM, Martzoukou M, Karala M, Koumpoulis C, Nasios G, Dardiotis E Hindawi, *Neural Plasticity*, Volume **2018**, Article ID 2845176, <https://doi.org/10.1155/2018/2845176>

**Background and Purpose:** There is an increasing interest in the effect of nonpharmacological interventions on the course of patients with Alzheimer's disease (AD). The objective of the present study is to determine the benefits of a structured, multidomain, mostly computer-based, cognitive training (MCT) on the cognitive performance of patients with early-stage AD.

**Method:** Fifty patients with early-stage AD participated in the study. Patients were randomly allocated either to the training program group (n=25) or to a wait list control group (n=25). The training program group received computer-assisted MCT and linguistic exercises utilizing pen and paper supplemented by cognitive-linguistic exercises for homework. The duration of the MCT intervention program was 15 weeks, and it was administered twice a week. Each session lasted for approximately one hour. Objective measures of episodic memory, delayed memory, word recognition, attention, executive function, processing speed, semantic fluency, and naming were

assessed at baseline and after the completion of the program in both groups. Results. Analysis showed that in controls, delayed memory and executive function had deteriorated over the observation period of 15 weeks, while the training group improved their performance in word recognition, Boston Naming Test (BNT), semantic fluency (SF), clock-drawing test (CDT), digit span forward (DSF), digit span backward (DSB), trail-making test A (TMT A), and trail-making test B (TMT B). Comparison between the training group and the controls showed that MCT had a significant beneficial effect in delayed memory, naming, semantic fluency, visuospatial ability, executive functions, attention, and processing speed. Conclusions. The study provides evidence of a beneficial effect of MCT with an emphasis on cognitive-language performance of patients with early-stage AD. Considering the limited efficacy of current pharmacological therapies in AD, concurrent computer-based MCT may represent an additional enhancing treatment option in early-stage AD patients.

### The implementation of cognitive remediation interventions in Campania

Palumbo D, Patriarca S, Mucci A, De Angelis M, Di Crosta I, Piegari G, Galderisi S *JOURNAL OF PSYCHOPATHOLOGY*, **2018**; 24:98-103

Cognitive impairment is considered a core aspect of schizophrenia and an important therapeutic target for its negative impact on real-life functioning of affected people. Psychotropic drugs commonly used in the treatment of schizophrenia do not improve and might even worsen cognitive dysfunctions. In contrast, cognitive remediation (CR) was found to improve cognitive deficits and real-life functioning of subjects with schizophrenia. The present paper aims to provide a brief review of the theoretical basis of different CR programs and to illustrate the implementation of two

such programs in Campania. In particular, the Social Skills And Neurocognitive Individualized Training (SSANIT) and the Computerized Interactive Remediation of Cognition - Training for Schizophrenia (CIRCuiTS) will be illustrated. SSANIT is an integrated program, including individualized computerized CR and social skills trainings. CIRCuiTS is a stand-alone computerized CR program targeting the development of metacognitive skills. Factors informing the choice of a specific CR program for individual subjects are also illustrated.

### Improving Everyday Memory Performance After Acquired Brain Injury: An RCT on Recollection and Working Memory Training

Richter KM, Mödden C, Eling P, Hildebrandt H  
Online First Publication, April 26, 2018. <http://dx.doi.org/10.1037/neu0000445>

**Objective:** To show the effectiveness of a combined recognition and working memory training on everyday memory performance in patients suffering from organic memory disorders.

**Method:** In this double-blind, randomized controlled Study 36 patients with organic memory impairments, mainly attributable to stroke, were assigned to either the experimental or the active control group. In the experimental group a working memory training was combined with a recollection training based on the repetition-lag procedure. Patients in the active control group received the memory therapy usually provided in the rehabilitation center. Both groups received nine hours of therapy. Prior (T0) and subsequent (T1) to the therapy, patients were evaluated on an everyday memory test (EMT) as well as on a neuropsychological test battery. Based on factor analysis of the neuro-

psychological test scores at T0 we calculated composite scores for working memory, verbal learning and word fluency.

**Results:** After treatment, the intervention group showed a significantly greater improvement for WM performance compared with the active control group. More importantly, performance on the EMT also improved significantly in patients receiving the recollection and working memory training compared with patients with standard memory training.

**Conclusion:** Our results show that combining working memory and recollection training significantly improves performance on everyday memory tasks, demonstrating far transfer effects. The present study argues in favor of a process-based approach for treating memory impairments. (PsycINFO Database Record (c) 2018 APA, all rights reserved)

### Effectiveness of a Computer-Based Training Program of Attention and Memory in Patients with Acquired Brain Damage

Fernandez E, Bergado Rosado JA, Rodriguez Perez D, Salazar Santana S, Torres Aguilar M, Bringas ML Behavioral Sciences (Basel). 2017 Dec 30;8(1). pii: E4. doi: 10.3390/bs8010004

Many training programs have been designed using modern software to restore the impaired cognitive functions in patients with acquired brain damage (ABD). The objective of this study was to evaluate the effectiveness of a computer-based training program of attention and memory in patients with ABD, using a two-armed parallel group design, where the experimental group (n = 50) received cognitive stimulation using RehaCom software, and the control group (n = 30) received the standard cognitive stimulation (non-computerized) for eight weeks. In order to assess the possible cognitive changes after the treatment, a post-pre experimental design was employed using the following

neuropsychological tests: Wechsler Memory Scale (WMS) and Trail Making test A and B. The effectiveness of the training procedure was statistically significant ( $p < 0.05$ ) when it established the comparison between the performance in these scales, before and after the training period, in each patient and between the two groups. The training group had statistically significant ( $p < 0.001$ ) changes in focused attention (Trail A), two subtests (digit span and logical memory), and the overall score of WMS. Finally, we discuss the advantages of computerized training rehabilitation and further directions of this line of work.

### **New aspects of symptomatic MS treatment: Part 6 – cognitive dysfunction and rehabilitation**

Henze T, Feneberg W, Flachenecker P, Seidel D, Albrecht H, Starck M, Meuth SG  
Der Nervenarzt, April **2018**, Volume 89, Issue 4, pp 453–459

The symptomatic treatment of multiple sclerosis (MS) is nowadays of similar importance as immunotherapy within a comprehensive treatment concept of this chronic disease. It makes a considerable contribution to the reduction of disabilities in activities of daily living as well as social and occupational life. Moreover, symptomatic treatment is of great importance for amelioration of the quality of life. Since our last survey of symptomatic MS treatment in 2004 and publication of the guidelines of the German Neurological Society and the Clinical

Competence Network Multiple Sclerosis in 2014 several developments within the topics of mobility, bladder and sexual function, vision, fatigue, cognition and rehabilitation have taken place. These new findings together with further aspects of disease measurement methods and overall treatment strategies of the respective symptoms, as well as treatment goals are introduced in several individual contributions. In this article the symptoms of cognitive disorders and the growing impact of rehabilitation are discussed.

### **Stress-related cortisol responsivity modulates prospective memory**

Glienke K, Piefke M  
Journal of Neuroendocrinology **2017** Dec;29(12). doi: 10.1111/jne.12544.

It is known that there is inter-individual variation in behavioral and physiological stress reactions to the same stressor. The present study aimed to examine the impact of cortisol responsivity on performance in a complex real life-like prospective memory (PM) paradigm by a re-analysis of data published previously, with a focus on the taxonomy of cognitive dimensions of PM. Twenty-one male subjects were stressed with the Socially Evaluated Cold Pressor Test (SECPT) before the planning of intentions. Another group of 20 males underwent a control procedure. Salivary cortisol was measured to assess the intensity of the biological stress response. Additionally, participants rated the subjective experience of stress on a 5-point rating scale. Stressed participants were post-hoc differentiated in high (n = 11) and low cortisol responders (n = 10). Cortisol level differed significantly between the two groups, whereas subjective

stress ratings did not. PM performance of low cortisol responders was stable across time and the PM performance of controls declined. High cortisol responders showed a nominally weaker PM retrieval across the early trials and significantly improved only on the last trial. The data demonstrate for the first time that participants with a low cortisol responsivity may benefit from stress exposure before the planning phase of PM. PM performance of high cortisol responders shows a more inconsistent pattern, which may be interpreted in the sense of a recency effect in PM retrieval. Alternatively, high cortisol responses may have a deteriorating effect on PM retrieval, which disappeared on the last trials of the task as a result of the decrease of cortisol levels across time. Importantly, the data also demonstrate that the intensity of cortisol responses does not necessarily correspond to the intensity of the mental experience of stress.



## **Efficacy of a Computer-Assisted Cognitive Rehabilitation Intervention in Relapsing-Remitting Multiple Sclerosis Patients: A Multicenter Randomized Controlled Trial**

Messinis L, Nasios G, Kosmidis MH, Zampakis P, Malefaki S, Ntoskou K, Nousia A, Bakirtzis C, Grigoriadis N, Gourzis P, Papathanasopoulos P  
Behavioural Neurology, Vol. **2017**, Article ID 5919841, doi.org/10.1155/2017/5919841

Cognitive impairment is frequently encountered in multiple sclerosis (MS) affecting between 40–65% of individuals, irrespective of disease duration and severity of physical disability. In the present multi-center randomized controlled trial, fifty-eight clinically stable RRMS patients with mild to moderate cognitive impairment and relatively low disability status were randomized to receive either computer-assisted (RehaCom) functional cognitive training with an emphasis on episodic memory, information processing speed/attention, and executive functions for 10 weeks (IG; n = 32) or standard clinical care (CG; n = 26). Outcome measures included a flexible comprehensive neuropsychological battery of tests sensitive to MS patient deficits and feedback regarding

personal benefit gained from the intervention on four verbal questions. Only the IG group showed significant improvements in verbal and visuospatial episodic memory, processing speed/attention, and executive functioning from pre- to post-assessment. Moreover, the improvement obtained on attention was retained over 6 months providing evidence on the long-term benefits of this intervention. Group by time interactions revealed significant improvements in composite cognitive domain scores in the IG relative to the demographically and clinically matched CG for verbal episodic memory, processing speed, verbal fluency, and attention. Treated patients rated the intervention positively and were more confident about their cognitive abilities following treatment.

## Cerebral Lesions

### Clinical Efficacy of Acupuncture Treatment in Combination with RehaCom Cognitive Training for Improving Cognitive Function in Stroke: A 2 x 2 Factorial Design Randomized Controlled Trial

Jiang C, Yang S, Tao J, Huang J, Li Y, Ye H, Chen S, Hong W, Chen L; J Am Med Dir Assoc. 2016 Aug 31. pii: S1525-8610(16)30299-7. doi: 10.1016/j.jamda.2016.07.021. Epub 2016 Aug 31

**Objective:** The aim of this study was to identify the clinical efficacy of acupuncture in combination with RehaCom cognitive training in post-stroke patients with cognitive dysfunction.

**Methods/Design:** This study was a 2 x 2 factorial design randomized controlled trial comparing acupuncture, computer-assisted cognitive rehabilitation, and the usual treatment by per-protocol analysis. The trial was completed by 204 stroke patients, including 49 patients in a control group, 52 patients in an acupuncture treatment group, 51 patients in a RehaCom training group, and 52 patients in an acupuncture combined with RehaCom group. All of the patients accepted basic treatment and health education. The interventions continued for 12 weeks (30 minutes per day, 5 days per week). The relative cognitive and functional outcomes were measured at baseline and 12 weeks (at the end of intervention) using the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Functional Independence Measure (FIM) scales.

**Results:** After 12 weeks of treatment, the functional statuses of the patients in each of the 4 groups showed varying degrees of

improvement. Multiple comparisons of the changes in the MMSE, MoCA, and FIM scores indicated that acupuncture combined with RehaCom cognitive training (ACR) had enhanced therapeutic effects on the functional statuses of the stroke patients ( $P < .05$ ). In addition, ACR had similar therapeutic effects on the functional statuses of the stroke patients according to each of the assessment scales applied ( $P_{\Delta}$  change value MMSE = 0.399,  $P_{\Delta}$ MoCA = 0.794,  $P_{\Delta}$ FIM = 0.862). The interaction effect values between acupuncture and RehaCom training (acceptance or non-acceptance) were as follows:  $\Delta$ MMSE:  $F = 6.251$ ,  $P = .013$ ;  $\Delta$ MoCA:  $F = 4.991$ ,  $P = .027$ ; and  $\Delta$ FIM:  $F = 6.317$ ,  $P = .013$ . Further, the main effect values for acupuncture and RehaCom training were both significant ( $P < .05$ ).

**Conclusions:** There is an interaction effect in the treatment of stroke patients using ACR. The use of acupuncture in combination with RehaCom training has better therapeutic effects on the functional statuses of post-stroke patients than the use of either treatment alone, demonstrating the clinical significance of this combination therapy.

### Effects of neurofeedback and computer-assisted cognitive rehabilitation on relative brain wave ratios and activities of daily living of stroke patients: a randomized control trial

Cho HY, Kim KT, Jung JH

J Phys Ther Sci. **2016** Jul; 28(7): 2154–2158. Published online 2016 Jul 29. doi: 10.1589/jpts.28.2154

**Purpose:** This study investigated the effects of neurofeedback (NFB) and computer-assisted cognitive rehabilitation (CACR) on the relative brain wave ratios and activities of daily living (ADL) of stroke patients.

**Subjects and methods:** Forty-four participants were randomly allocated to the NFB (n=14), CACR (n=14), or control (CON) (n=16) groups. Two expert therapists provided the NFB, CACR, and CON groups with traditional rehabilitation therapy in 30-minute sessions, 5 times a week, for 6 weeks. NFB training was provided only to the NFB group and CACR training was provided only to the CACR group. The CON group received

traditional rehabilitation therapy only. Before and after 6 weeks of intervention, brain wave and ADL evaluations were performed, and the results were analyzed.

**Results:** The relative ratio of beta waves, only showed a significant increase in the frontal and parietal areas of the NFB group. Significant changes in ADL were shown by all three groups after the intervention. However, there were no significant differences between the NFB and CACR groups and the CON group.

**Conclusions:** Our results suggest that CACR and NFB are effective at improving cognitive function and ADL of stroke patients.

### Effect of computerized cognitive rehabilitation program on cognitive function and activities of living in stroke patients

Yoo C, Yong M, Chung J, Yang, J; Phys Ther Sci. 2015 Aug; 27(8): 2487–2489. Published online **2015** Aug 21. doi: 10.1589/jpts.27.2487

**Purpose:** The objective of this study was to examine the effect of cognitive rehabilitation using a computer on cognitive function and activities of daily living in stroke patients presenting impairment of cognitive function.

**Subjects:** Forty-six stroke patients were divided into two groups (a training group and control group) through random assignment.

**Methods:** The training group received rehabilitation therapy and an additional computerized cognitive rehabilitation program using the RehaCom software 30 minutes/day, 5 times/week for 5 weeks. The control group received only rehabilitation therapy including physical and occupational therapy. A comparative analysis on all subjects was conducted before and after the experiment

using a cognitive test and activities of daily living test.

**Results:** After 5 weeks of therapy, the training group presented statistically significant improvement in cognitive function assessment items of digit span, visual span, visual learning, auditory continuous performance, visual continuous performance, and others compared with the control group but did not present statistically significant improvement in activities of daily living.

**Conclusion:** It was revealed through this study that computerized cognitive rehabilitation with the RehaCom program results in improvement in cognitive function and can be used as a treatment tool beneficial to stroke patients presenting cognitive impairment.

### Recovery after brain damage: Is there any indication for generalization between different cognitive functions?

Richter KM, Mödden C, Hanken K, Hildebrandt H  
Clin Exp Neuropsychol. **2015**; 37(6):571-80. doi: 10.1080/13803395.2015.1030358.  
Epub 2015 Jun 10.

**Introduction:** The question whether recovery in various cognitive functions is supported by one or two more fundamental functions (for instance, attentional or working memory functions) is a longstanding problem of cognitive rehabilitation. One possibility to answer this question is to analyze the recovery pattern in different cognitive domains and to see whether improvement in one domain is related to performance in another domain.

**Method:** Ninety-two inpatients with stroke or other brain lesions (Barthel Index >75) were included. Neuropsychological assessment was done at the beginning and the end of a rehabilitation stay. Cognitive performance was analyzed at test and at domain level using conceptually and statistically defined composite scores for attention, immediate and delayed memory, working memory, prospective memory, and word fluency. We

used regression analysis to look for generalization between cognitive domains.

**Results:** Effect sizes of improvement varied largely (from  $d = 0.18$  in attention and  $d = 1.36$  in episodic memory). Age, gender, and time since injury had no impact on recovery. Impaired patients showed significantly more improvement than non-impaired patients. Regression analysis revealed no effect of initial performance in one cognitive domain on improvements in other cognitive domains.

**Conclusion:** Significant recovery in impaired cognitive domains can be expected during neuro-psychological rehabilitation. It depends more or less exclusively on improvement in the specific functions itself, and there was no evidence for generalization between cognitive domains.

### Working memory training and semantic structuring improves remembering future events, not past events

Richter KM, MSc, Mödden C, MSc, Eling P, PhD, Hildebrandt H, Prof.  
Neurorehabil Neural Repair. **2015** Jan; 29(1):33-40. doi: 10.1177/1545968314527352.  
Epub 2014 Apr 2.

**Objectives:** Memory training in combination with practice in semantic structuring and word fluency has been shown to improve memory performance. This study investigated the efficacy of a working memory training combined with exercises in semantic structuring and word fluency and examined whether training effects generalize to other cognitive tasks.

**Methods:** In this double-blind randomized control study, 36 patients with memory impairments following brain damage were allocated to either the experimental or the active control condition, with both groups receiving 9 hours of therapy. The experimental group received a computer-based working memory training and exercises in word fluency and semantic structuring. The control group

received the standard memory therapy provided in the rehabilitation center. Patients were tested on a neuropsychological test battery before and after therapy, resulting in composite scores for working memory; immediate, delayed, and prospective memory; word fluency; and attention.

**Results:** The experimental group improved significantly in working memory and word fluency. The training effects also generalized to prospective memory tasks. No specific effect on episodic memory could be demonstrated.

**Conclusion:** Combined treatment of working memory training with exercises in semantic structuring is an effective method for cognitive rehabilitation of organic memory impairment.

### Clinical Impact of RehaCom Software for Cognitive Rehabilitation of Patients with Acquired Brain Injury

Fernández E, Bringas ML, Salazar S, Rodríguez D, García ME, Torres M. MEDICC Rev. **2012** Oct; 14(4):32-5.

We describe the clinical impact of the RehaCom computerized cognitive training program instituted in the International Neurological Restoration Center for rehabilitation of brain injury patients. Fifty patients admitted from 2008 through 2010 were trained over 60 sessions. Attention and memory functions were assessed with a pre-

and post-treatment design, using the Mini-Mental State Examination, Wechsler Memory Scale and Trail Making Test (Parts A and B). Negative effects were assessed, including mental fatigue, headache and eye irritation. The program's clinical usefulness was confirmed, with 100% of patients showing improved performance in trained functions.

### A Randomized Controlled Trial Comparing 2 Interventions for Visual Field Loss with Standard Occupational Therapy During Inpatient Stroke Rehabilitation

Mödden C, Behrens M, Damke I, Eilers N, Kastrup A, Hildebrandt H  
Neurorehabil Neural Repair. **2012** Jun;26 (5):463-9. doi: 10.1177/1545968311425927.  
Epub 2011 Dec 2.

**Background and purpose:** Compensatory and restorative treatments have been developed to improve visual field defects after stroke. However, no controlled trials have compared these interventions with standard occupational therapy (OT).

**Methods:** A total of 45 stroke participants with visual field defect admitted for inpatient rehabilitation were randomized to restorative computerized training (RT) using computer-based stimulation of border areas of their visual field defects or to a computer based compensatory therapy (CT) teaching a visual search strategy. OT, in which different compensation strategies were used to train for activities of daily living, served as standard treatment for the active control group. Each treatment group received 15 single sessions of 30 minutes distributed over 3 weeks. The primary outcome measures were visual field

expansion for RT, visual search performance for CT, and reading performance for both treatments. Visual conjunction search, alertness, and the Barthel Index were secondary outcomes.

**Results:** Compared with OT, CT resulted in a better visual search performance, and RT did not result in a larger expansion of the visual field. Intragroup pre- post comparisons demonstrated that CT improved all defined outcome parameters and RT several, whereas OT only improved one.

**Conclusions:** CT improved functional deficits after visual field loss compared with standard OT and may be the intervention of choice during inpatient rehabilitation. A larger trial that includes lesion location in the analysis is recommended.

### Is the Neuropsychological Treatment of Memory Specific or Unspecific? – Comparing Treatment Effects on Memory and Attention

Spahn V, Kulke H, Kunz M, Thöne-Otto A, Schupp W, Lautenbacher S; Zeitschrift für Neuropsychologie : ZNP ; zugleich Organ der GNP; mit Mitteilungen der DGNKN. - 21 (2010), 4, 239 – 245

**Primary objective and research design:** In order to analyze whether neuropsychological memory therapy acts specifically on the memory domain or in a more generalized fashion on further cognitive domains, 27 patients with organic memory deficits due to different etiologies (cerebrovascular, traumatic, infectious, etc.) were randomly assigned to two different memory treatment programs and investigated for changes in memory and attention.

**Methods and procedures:** Patients treated by a specific computer-based training of story recall (Training of Verbal Memory, TVM) were compared to a group in which compensational strategies for everyday memory problems were trained (Memory Therapy in Groups, MTG).

Both therapies were conducted over 12 to 15 sessions, 4-5 times per week, in addition to standard program of neurorehabilitation. Training effects were assessed for verbal and figural memory (Verbal Learning Test, Nonverbal Learning Test) and for attention (Alertness and Divided Attention in Test Battery of Attentional Performance).

**Results and conclusions:** Both treatment groups resulted in improvement in tests of memory but not attention. This finding provides good evidence for the assumption of specificity of effects in neuropsychological treatment of memory.

### Attention remediation following traumatic brain injury in childhood and adolescence

Galbiati S, Recla M, Pastore V, Liscio M, Bardoni A, Castelli E, Strazzer S *Neuropsychology*. 2009 Jan;23(1):40-9. doi: 10.1037/a0013409.

Traumatic brain injury (TBI) frequently affects both the basic and the superordinate components of attention; deficits vary according to patient age. This study evaluated the efficacy of a specific remediation intervention for attention. Sixty-five TBI patients (aged 6-18 years) with attention deficit were assessed at baseline and at 1-year follow-up: 40 patients received attention-specific neuropsychological training for 6 months, and the control group comprised 25 patients. Cognitive assessment included a Wechsler Intelligence Scale (e.g., A. Orsini, 1993) and the Continuous Performance Test II (CPT II; C. K. Conners, 2000). The Vineland

Adaptive Behavior Scales (VABS; S. Sparrow, D. Balla & D. V. Cicchetti, 1984) was administered to assess the treatment's ecological validity. At baseline, all patients presented with a mild intellectual disability and pathological scores on the CPT II. At follow-up, significant differences were found between the 2 groups on the CPT II and VABS: The clinical group improved more than the control group. Specific remediation training for attention, including a combination of a process-specific approach and metacognitive strategies, significantly improved attention performance. Improvement in attention skills also affected adaptive skills positively.

## Multiple Sclerosis

### A Randomised Controlled Trial of Efficacy of Cognitive Rehabilitation in Multiple Sclerosis: A Cognitive, Behavioural, and MRI Study

Campbell J, Langdon D, Cercignani M, Rashid W  
Hindawi Publishing Corporation Neural Plasticity Volume 2016, Article ID 4292585, 9 pages

**Aim:** To explore the efficacy of home-based, computerized, cognitive rehabilitation in patients with multiple sclerosis using neuropsychological assessment and advanced structural and functional magnetic resonance imaging (fMRI).

**Methods:** 38 patients with MS and cognitive impairment on the Brief International Cognitive Assessment for MS (BICAMS) were enrolled. Patients were randomized to undergo 45 minutes of computerized cognitive rehabilitation using RehaCom software ( $n = 19$ ) three times weekly for six weeks or to a control condition ( $n = 19$ ). Neuropsychological and MRI data were obtained at baseline (time1), following the 6-week intervention (time 2), and after a further twelve weeks (time 3). Cortical activations were explored

using fMRI and microstructural changes were explored using quantitative magnetization transfer (QMT) imaging.

**Results:** The treatment group showed a greater improvement in SDMT gain scores between baseline and time 2 compared to the control group ( $p = 0.005$ ). The treatment group exhibited increased activation in the bilateral prefrontal cortex and right temporoparietal regions relative to control group at time 3 ( $p < 0.05$ FWE corrected). No significant changes were observed on QMT.

**Conclusion:** This study supports the hypothesis that home-based, computerized, cognitive rehabilitation may be effective in improving cognitive performance in patients with MS.

### Cognitive Rehabilitation in Multiple Sclerosis: The Role of Plasticity

Chiaravalloti ND, Genova HM, DeLuca J  
Front Neurol. 2015; 6: 67. Published online 2015 Apr 2. doi: 10.3389/fneur.2015.00067

Cognitive deficits are common in multiple sclerosis (MS), documented at many stages of the disease. Both structural and functional neuroimaging have demonstrated a relationship with cognitive abilities in MS. Significant neuroplasticity of cognitive functions in individuals with MS is evident. Homologous region adaptation, local activation expansion, and extra-region recruitment all occur in an effort to maintain cognitive functioning. While much of this neuroplasticity is adaptive, it may also be maladaptive, particularly in individuals that are demonstrating significant cognitive impairment and/or with disease progression. This maladaptive neuroplasticity may come at the cost of other cognitive functions. Studies of cognitive rehabilitation efficacy have also recently applied neuroimaging techniques to establish outcome. Researchers have

successfully applied various neuroimaging techniques to study the effects of cognitive rehabilitation in MS including task-based fMRI and resting state functional connectivity across multiple realms of cognition including episodic memory, executive functioning, attention, and processing speed. These studies have demonstrated neuroplasticity in the brains of persons with MS through the documentation of changes at the level of the cerebral substrate from before to after non-invasive, non-pharmacological, behavioral treatment for deficits in cognition. Future research should seek to identify adaptive versus maladaptive neuroplasticity associated with specific cognitive rehabilitation programs within all MS phenotypes to foster the validation of the most effective cognitive rehabilitation interventions for persons with MS.

## Multiple Sclerosis

### Computer-Assisted Cognitive Rehabilitation of Attention Deficits for Multiple Sclerosis: A Randomized Trial With fMRI Correlates

Cerasa A, Gioia MC, Valentino P, Nisticò R, Chiriaco C, Pirritano D, Tomaiuolo F, Mangone G, Trotta M, Talarico T, Bilotti G, Quattrone A.  
Neurorehabil Neural Repair. **2013** May; 27(4):284-95. doi: 10.1177/1545968312465194.  
Epub 2012 Nov 27.

**Background:** Although a growing body of evidence has highlighted the role of cognitive rehabilitation (CR) in the management of cognitive dysfunctions in multiple sclerosis (MS), there is still no evidence for a validated therapeutic approach.

**Objective:** We propose a new therapeutic strategy characterized by a computer-based intensive attention training program in MS patients with predominant attention deficits. We aim to investigate the effectiveness of our rehabilitation procedure, tailored for those with impaired abilities, using functional magnetic resonance imaging (fMRI).

**Methods:** Using a double-blind randomized controlled study, we enrolled 12 MS patients, who underwent a CR program (experimental group), and 11 age-gender-matched MS patients, who underwent a placebo intervention (control group). fMRI was recorded during the execution of a cognitive task broadly used for assessing attention

abilities in MS patients (paced visual serial addition test).

**Results:** Significant effects were detected both at a phenotypic and at an intermediate phenotypic level. After CR, the experimental group, in comparison with the control group, showed a specific enhanced performance in attention abilities as assessed by the Stroop task with an effect size of 0.88, which was associated with increased activity in the posterior cerebellar lobule and in the superior parietal lobule.

**Conclusions:** Our study demonstrates that intensive CR tailored for those with impaired abilities affects neural plasticity and improves some aspects of cognitive deficits in MS patients. The reported neurophysiological and behavioral effects corroborate the benefits of our therapeutic approach, which might have a reliable application in the clinical management of cognitive deficits in MS.

### Cognitive Rehabilitation in Multiple Sclerosis

Barbosa F, Sousa C, Nogueira-Silva L, José Sá M Sinapse, Vol. 11, No. 1, May **2011**

**Background:** Recent studies have shown that 45%-65% of MS patients have deficits in the cognitive function area that contributes to a significant decrease in their quality of life. Through cognitive assessment is possible the early identification and subsequent planning of rehabilitation and follow up of cognitive deficits in these patients. In order to improve health care in their cognition, cognitive rehabilitation uses different techniques and strategies integrating a dynamic process of restoration for a highest level of performance in their physical, psychological and social life.

**Purpose:** The main aim of this work is to evaluate the success of cognitive rehabilitation in MS patients with cognitive impairment.

**Methods:** 28 patients (20 females, 8 males), with diagnosis of mild to moderate (<25) cognitive impairment, with indication for immunomodulatory therapy followed in the MS

Clinic of a University Hospital, are part of this study. At first, the cognitive function of these patients was assessed using the Neuropsychological Test battery for MS (Rao et al., 1991) as a composite screening tool of the major cognitive areas.

Subsequently, patients underwent weekly sessions for a period of 12 months on a program of cognitive rehabilitation: the RehaCom, an instrument consisting of several software programs for different areas: attention and concentration, topology memories, reactive behavior and verbal memory. After the completion of the cognitive rehabilitation program, the effectiveness of the whole process was assessed through a new evaluation with above battery of tests comparing the previous results as a pre-post design methodology.



## Multiple Sclerosis

**Results:** Significant improvements in cognitive functions after cognitive rehabilitation program were acquired. The cognitive area with major improvements was the spatial memory.

**Discussion:** This study demonstrates that cognitive rehabilitation, preceded by the neuropsychological evaluation, is an important tool in MS because it may stabilize or enhance improvements in cognitive deficits and thereby improve the quality of life for patients.

### Efficacy and Specificity of intensive cognitive Rehabilitation of Attention and executive Functions in Multiple Sclerosis

Mattioli F, Stampatori C, Zanotti D, Parrinello G, Capra R  
J Neurol Sci. 2010 Jan 15; 288(1-2):101-5. doi: 10.1016/j.jns.2009.09.024. Epub 2009 Oct 13.

**Objective:** To evaluate the efficacy of a computer- based intensive training program of attention, information processing and executive functions in patients with clinically-stable relapsing-remitting (RR) multiple sclerosis (MS) and low levels of disability.

**Design, Patients and Interventions:** A total of 150 patients with RR MS and an Expanded Disability Status Scale (EDSS) score of < or =4 were examined. Information processing, working memory and attention were assessed by the Paced Auditory Serial Addition Test (PASAT) and executive functions by the Wisconsin Card Sorting Test (WCST). Twenty patients who scored below certain cut-off measures in both tests were included in this double-blind controlled study. Patients were casually assigned to a study group (SG) or a control group (CG) and underwent neuropsychological evaluation at baseline and after 3 months. Patients in the SG received intensive computer-assisted cognitive rehabilitation of attention, information processing and executive functions for 3

months; the CG did not receive any rehabilitation.

**Setting:** Ambulatory patients were sent by the MS referral center.

**Outcome Measures:** Improvement in neuropsychological test and scale scores.

**Results:** After rehabilitation, only the SG significantly improved in tests of attention, information processing and executive functions (PASAT 3" p=0.023, PASAT 2" p=0.004, WCSTte p=0.037), as well as in depression scores (MADRS p=0.01). Neuropsychological improvement was unrelated to depression improvement in regression analysis.

**Conclusions:** Intensive neuropsychological rehabilitation of attention, information processing and executive functions is effective in patients with RR MS and low levels of disability, and also leads to improvement in depression.

## Dementia / Alzheimer

### The Effects of Cognitive Rehabilitation Training on Cognitive Function of Elderly Dementia Patients

Oh BH, Kim YK, Kim JH, Shin YS  
J Korean Neuropsychiatr. Assoc. **2003**, Vol 42, No 4, 514-519

**Objectives:** This study was to evaluate the effects of cognitive rehabilitation training on the cognitive decline of elderly dementia patients.

**Methods:** Each of 20 subjects received 16 sessions of repeated training with computer-aided cognitive rehabilitation program (REHACOM). Cognitive function of all subjects were evaluated by K-DRS, K-BNT, K-MMSE and GDS before and after the training.

**Results:** Significant improvement of attention and memory was observed following RehaCom. There was no significant change in visuospatial memory, executive function, and conceptualization.

**Conclusion:** It is suggested that cognitive rehabilitation training with elderly dementia patients can be useful to ameliorate the cognitive decline and to enhance motivation and self-esteem.

## Schizophrenia

### Preliminary study of a rehabilitation program based on attentional processes to treat auditory hallucinations

López-Luengo B, Muela-Martínez JA  
Cogn Neuropsychiatry. 2016 Jul;21(4):315-334. Epub 2016 Jul 18.

**Introduction:** Despite the effectiveness of pharmacological treatment, residual hallucinations do not completely resolve in some medicated patients. The aim of this study was to investigate the efficacy of attention training for reducing hallucinations in individuals with psychosis.

**Methods:** A randomized controlled trial was performed in which 20 individuals suffering auditory hallucinations received auditory stimulation similar to their internal voices, which was integrated into the RehaCom program of attention training. An equal number of individuals suffering auditory hallucinations did not receive this training. Cognitive and symptomatologic variables were evaluated before and after the intervention period in both groups.

**Results:** Only data of 16 subjects were analyzed. Auditory hallucinations no longer occurred by the end of the training program in five of eight individuals, whereas their frequency, intensity and negative content and associated anxiety were significantly reduced in the remaining three. No changes in hallucinations were observed in the control group. Attentional processes and executive functions were significantly better in patients who underwent the training than in those who did not at the end of the intervention period.

**Conclusions:** Attention training can help people with auditory hallucinations develop an ability to ignore them, which can reduce or eliminate them entirely.

### The effectiveness of computerized cognitive rehabilitation training program in improving cognitive abilities of schizophrenia clients

Mohammadi MR, Keshavarzi Z, Talepasand S Iran J Psychiatry. 2014 Oct;9(4):209-15.

**Objective:** The aim of this study was to evaluate the efficacy of a computer-based training program of attention, memory and executive functions in enhancing neuropsychological performances as well as functional outcome in clients with schizophrenia.

**Method:** A total of 15 clinically stable out patients with Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for schizophrenia, diagnosed with different types of schizophrenia: paranoid, disorganized, residual, based on DSM- IV-TR were selected to participate in this study. All patients were randomly selected using a conventional sampling method and assigned to 60 hours individual sessions of computer - assisted cognitive remediation (CACR). This was a pre-experimental study with pretest and posttest in a single group. Cognitive functions were checked with Continuous Performance Test (CPT), Wechsler Adult Intelligence Scale (Wds) and Prospective and Retrospective Memory Questionnaire (PRMQ). The symptoms of

patients were measured with the Positive and Negative Syndrome Scale (PANSS). Remediation was performed utilizing the RehaCom software. Patients received the cognitive remediation program including attention, concentration and working memory. All participants were followed up after an interval of one month and three months. Data were analyzed using repeated measures analysis.

**Result:** After 3 months, the findings showed that patient's scores improved in the time factor. Also, a significant improvement favoring cognitive remediation was found in several cognitive measures including Reaction Time ( $F = 4015, p < .05, \eta^2 = 0.242$ ), Wds ( $F = 11.806, p < .05, \eta^2 = .48$ ) PRMQ1 ( $F = 3.314, p < .05, \eta^2 = 0.20$ ) PRMQ7 ( $F = 2.85, p < .05, \eta^2 = 0.18$ ).

**Conclusion:** Computer-assisted cognitive remediation training program was effective in improving the performance of schizophrenic

## Schizophrenia

patients. CACR did not have any effects on the positive and negative symptoms. Long-term

follow-up studies are needed to confirm the maintenance of such improvements.

### **The efficacy of cognitive neurorehabilitation with RehaCom program in schizophrenia patients**

Mak M, Tybura P, Bieńkowski P, Karakiewicz B, Samochowicz J. *Psychiatr Pol.* **2013** Mar-Apr;47(2):213-23

Schizophrenic patients present cognitive dysfunctions which are currently regarded to be one of endophenotypic markers predisposing to schizophrenia. This indicates neuro-structural changes underlying schizophrenia, which can be treated as a neuro-degenerative and neuro-developing disease.

**Aim:** The purpose of this study was to assess the possibility of neuropsychological rehabilitation in schizophrenia.

**Methods:** 41 participants and 40 control subjects were randomly selected and did not show differences in gender, age and illness duration. Both groups had the diagnosis of paranoid schizophrenia according to ICD-10 criteria and were treated with antipsychotic drugs. Cognitive functions were checked with Wisconsin Card Sorting Test (WCST), Trail Making Test (TMT), and Stroop Color -Word Interference Test (SCWT) in the beginning and in the end of the experiment. In the research group each patient was trained with the rehabilitation programs that focused on

attention and concentration and topological memory. This group was compared with the control group that was not trained with RehaCom.

**Results:** RehaCom procedures apparently can be useful in neuropsychological rehabilitation of cognitive dysfunctions in patients with diagnosed schizophrenia. Every participant from the research group showed a significant improvement in the training programs, especially in attention/concentration procedure. The analysis of parameters obtained in the neuropsychological tests showed some improvement in neuropsychological assessment in both groups.

**Conclusions:** Cognitive rehabilitation produces moderate improvement in cognitive functioning. A comprehensive treatment using also new technologies supporting pharmacological treatments and other therapies should result in increased cognitive functioning and as a consequence improvement of quality of patient's life.

## How can cognitive remediation therapy modulate brain activations in schizophrenia? An fMRI study

Bor J, Brunelin J, d'Amato T, Costes N, Suaud-Chagny M, Saoud M, Poulet E June 30, **2011** Volume 192, Issue 3, Pages 160–166

Cognitive remediation therapy (CRT) is a non-bio- logical treatment that aims to correct cognitive deficits through repeated exercises. Its efficacy in patients with schizophrenia is well recognized, but little is known about its effect on cerebral activity. Our aim was to explore the impact of CRT on cerebral activation using functional magnetic resonance imaging (fMRI) in patients with schizophrenia. Seventeen patients and 15 healthy volunteers were recruited. Patients were divided into two groups: one group received CRT with RehaCom software (n=8), while a control group of patients (non-CRT group) received no additional treatment (n=9). The three groups underwent two fMRI sessions with an interval

of 3 months: they had to perform a verbal and a spatial n-back task at the same performance level. Patients were additionally clinically and cognitively assessed before and after the study. After CRT, the CRT group exhibited brain over-activations in the left inferior/middle frontal gyrus, cingulate gyrus and inferior parietal lobule for the spatial task. Similar but nonsignificant over-activations were observed in the same brain regions for the verbal task. Moreover, CRT patients significantly improved their behavioral performance in attention and reasoning capacities. We conclude that CRT leads to measurable physiological adaptation associated with improved cognitive ability.

## A randomized, controlled trial of computer-assisted cognitive remediation for schizophrenia

d'Amato T, Bation R, Cochet A, Jalenques I, Galland F, Giraud-Baro E, Pacaud-Troncin M, Augier-Astolfi F, Llorca PM, Saoud M, Brunelin J.; Schizophr Res. **2011** Feb; 125(2-3):284-90. doi: 10.1016/j.schres.2010.10.023. Epub 2010 Nov 19.

**Objective:** There is considerable interest in cognitive remediation for schizophrenia. Our study aimed to evaluate, in a large sample of patients with schizophrenia, the interest of a computer-assisted cognitive remediation program on cognitive performances of patients as well as in clinical and functional outcome.

**Method:** Seventy-seven patients with remitted schizophrenia were randomly assigned to 14 2-hours individual sessions of computer-assisted cognitive remediation (n=39) or a control condition (n=38). Remediation was performed using RehaCom software. Four procedures were chosen to train four cognitive functions involved in different stages of the information processing: attention/concentration, working memory, logic, and executive functions. Primary outcomes were remediation exercise metrics, neuropsychological composites (episodic memory, working memory, attention,

executive functioning, and processing speed), clinical and community functioning measures.

**Results:** Cognitive performances concerning attention/vigilance, verbal working memory and verbal learning memory and reasoning/problem solving improved significantly in the remediation condition when no difference was reported in the control condition between the 2 assessments. However, there were no significant benefits of cognitive remediation on non-verbal working memory and learning and speed of processing or functional outcome measures.

**Conclusions:** Cognitive remediation for people with schizophrenia was effective in improving performance, but the benefits of training did not generalize to functional outcome measures. Long term follow-up studies are needed to confirm the maintenance of such improvements.

## ADHD

### Evaluation of a computer-based neuropsychological Training in Children with Attention-Deficit Hyperactivity Disorder (ADHD)

Amonn F, Frölich J, Breuer D, Banaschewski T, Doepfner M NeuroRehabilitation. **2013**;32(3):555-62. doi: 10.3233/NRE-130877

**Background:** We report the effects of a computer-based neuropsychological training in children with Attention-Deficit Hyperactivity Disorder (ADHD). We hypothesized that a specific training focusing on attentional dysfunction would result in an improvement of inattention, observable in test performance, behavior and performance during experimental school lessons and in parent and teacher ratings of the related core symptom.

**Method:** We chose a within-subject-control-design with a 4-week baseline period and subsequent 12 to 15 weekly training-sessions. 30 children (6 to 13 years old) with a diagnosis of ADHD (ICD 10: F 90.0) and no other comorbidities participated in the study.

**Results:** The training revealed significant improvement in training parameters of the neuropsychological training and in the symptoms of inattention and department as rated during experimental school lessons. However, generalization of training effects as measured by parent and teacher ratings was not detected.

**Conclusions:** We conclude that neuropsychological training could be helpful as one adjunct module in the complex treatment of ADHD but to prove clinical value, similar training programs must focus more strongly on individually existing neuropsychological deficits. Training programs should be more intensive and should eventually be combined with home-based training access.

## Depression

### **Efficacy of Neurocognitive Remediation Therapy During an Acute Depressive Episode and Following Remission: Results from Two Randomised Pilot Studies**

Semkovska M, Ahern E, Lonergain D.O, Lambe S, McLaughlin D.M.  
European Psychiatry, Volume 30, Supplement 1, 28–31 March 2015, Pages 403

**Introduction:** Major depression is the most prevalent psychiatric disorder with high relapse rates. Following usual treatment, mood may improve but neurocognitive difficulties often persist, preventing full return to normal social function. These deficits worsen with repeated depressive episodes and are a significant predictor of relapse. The efficacy of neurocognitive remediation therapy (NCRT) to rehabilitate cognition has been demonstrated in several neurological and psychiatric populations but randomized controlled trials (RCT) have not been conducted in depression.

**Objective:** Conduct two randomized controlled pilot studies to determine the feasibility and obtain preliminary efficacy data of NCRT in (1) acutely depressed, hospitalized patients; and (2) community-living remitters from recurrent depression.

**Methods:** In Pilot 1, 24 inpatients hospitalized for major depression were randomized to computerized NCRT or playing computer games for five weeks with four one-hour

individual sessions weekly. NCRT targeted divided attention, working memory and planning. In Pilot 2, 20 community-living remitters from recurrent depression were randomized to the same intervention arms, but their administration was home-based from the program start. In both studies, before the intervention start and within a week of the final session, standardized assessments of cognition and depression severity were conducted.

**Results:** The feasibility assessment demonstrated good recruitment and compliance rates, excellent acceptance of randomization. Preliminary outcome data showed improvement in 80% of the targeted cognitive domains following NCRT comparatively to the control condition.

**Conclusions:** These pilot studies support the feasibility and value of conducting an RCT of computerized NCRT for neurocognitive deficits in both acutely depressed and remitted individuals.

## Aging and prevention

### Acute social stress before the planning phase improves memory performance in a complex real life-related prospective memory task

Glienke K, Piefke M

Neurobiol Learn Mem. 2016 Sep;133:171-81. doi: 10.1016/j.nlm.2016.06.025. Epub 2016 Jun 28.

Successful execution of intentions, but also the failure to recall are common phenomena in every-day life. The planning, retention, and realization of intentions are often framed as the scientific concept of prospective memory. The current study aimed to examine the influence of acute stress on key dimensions of complex „real life“ prospective memory. To this end, we applied a prospective memory task that involved the planning, retention, and performance of intentions during a fictional holiday week. Forty healthy males participated in the study. Half of the subjects were stressed with the Socially Evaluated Cold Pressor Test (SECPT) before the planning of intentions, and the other half of the participants underwent a control procedure at the same time. Salivary cortisol was used to measure the effectiveness of the SECPT stress induction. Stressed participants did not differ from controls in planning accuracy. However, when we compared stressed participants with controls during prospective memory retrieval, we found

statistically significant differences in PM across the performance phase. Participants treated with the SECPT procedure before the planning phase showed improved prospective memory retrieval over time, while performance of controls declined. Particularly, there was a significant difference between the stress and control group for the last two days of the holiday week. Interestingly, control participants showed significantly better performance for early than later learned items, which could be an indicator of a primacy effect. This differential effect of stress on performance was also found in time- and event-dependent prospective memory. Our results demonstrate for the first time, that acute stress induced before the planning phase may improve prospective memory over the time course of the performance phase in time- and event-dependent prospective memory. Our data thus indicate that prospective memory can be enhanced by acute stress.

### Memory enhancement in healthy older adults using a brain plasticity- based training program: a randomized, controlled study

Mahncke HW, Connor BB, Appelman J, Ahsanuddin ON, Hardy JL, Wood RA, Joyce NM, Boniske T, Atkins SM, Merzenich MM. Proc Natl Acad Sci U S A. 2006 Aug 15;103(33):12523-8. Epub 2006 Aug 3.

Normal aging is associated with progressive functional losses in perception, cognition, and memory. Although the root causes of age-related cognitive decline are incompletely understood, psychophysical and neuropsychological evidence suggests that a significant contribution stems from poorer signal- to-noise conditions and down-regulated neuro- modulatory system function in older brains. Because the brain retains a lifelong capacity for plasticity and adaptive reorganization, dimensions of negative reorganization should be at least partially reversible through the use of an appropriately designed training program. We report here results from such a training program targeting age-related cognitive decline. Data from a randomized, controlled trial using standardized

measures of neuropsychological function as outcomes are presented. Significant improvements in assessments directly related to the training tasks and significant generalization of improvements to nonrelated standardized neuro- psychological measures of memory (effect size of 0.25) were documented in the group using the training program. Memory enhancement appeared to be sustained after a 3-month no-contact follow-up period. Matched active control and no-contact control groups showed no significant change in memory function after training or at the 3-month follow-up. This study demonstrates that intensive, plasticity- engaging training can result in an enhancement of cognitive function in normal mature adults.



## Metastudies

### Can impaired working memory functioning be improved by training? A meta-analysis with a special focus on brain injured patients

Weicker J, Villringer A, Thöne-Otto A  
Neuropsychology. 2016 Feb;30(2):190-212. doi: 10.1037/neu0000227

**Objective:** Deficits in working memory (WM) are commonly observed after brain injuries and cause severe impairments in patient's everyday life. It is still under debate if training can enhance or rehabilitate WM in case of malfunction. The current meta-analysis investigates this issue from a clinical point of view. It addresses under which conditions and for which target group WM training may be justifiable.

**Method:** Relevant WM training studies were identified by searching electronic literature databases with a comprehensive search term. In total, 103 studies, which added up to 112 independent group comparisons (N = 6,113 participants), were included in the analysis.

**Results:** Overall, WM training caused a moderate and long-lasting improvement in untrained WM tasks. Moreover, improvement of WM functioning led to sustainable better evaluation of everyday life functioning,

however, effect sizes were small. Concerning transfer effects on other cognitive domains, long-lasting improvements with small effect sizes were observed in cognitive control and reasoning/intelligence. In contrast, small immediate, but no long-term effects were found for attention and long-term memory. Studies with brain injured patients demonstrated long-lasting improvements in WM functions with moderate to large effect sizes. A main moderator variable of intervention efficacy is the number of training sessions applied.

**Conclusion:** WM training produces long-lasting beneficial effects which are strongly pronounced in patients with acquired brain injuries. This finding supports the application of WM training in clinical settings. To determine optimal training conditions, future studies must systematically investigate the characteristics of interventions as they are at present inevitably confounded.

### Computerized Cognitive Training in Older Adults with Mild Cognitive Impairment or Dementia: A Systematic Review and Meta-Analysis

Hill NT, Mowszowski L, Naismith SL, Chadwick VL, Valenzuela M, Lampit A  
The American journal of psychiatry 2017 Apr 1;174(4):329-340. doi: 10.1176/appi.ajp.2016.16030360

**Objective:** Previous meta-analyses indicate that computerized cognitive training (CCT) is a safe and efficacious intervention for cognition in older adults. However, efficacy varies across populations and cognitive domains, and little is known about the efficacy of CCT in people with mild cognitive impairment or dementia.

**Method:** The authors searched Medline, Embase, PsychINFO, CINAHL, and CENTRAL through July 1, 2016, for randomized controlled trials of CCT in older adults with mild cognitive impairment or dementia. Overall cognition, individual cognitive domains, psychosocial function, and activities of daily living were pooled separately for mild cognitive impairment and dementia trials.

**Results:** The overall effect on cognition in mild cognitive impairment across 17 trials was moderate (Hedges'  $g=0.35$ , 95% CI=0.20–0.51). There was no evidence of publication bias or difference between active- and passive-controlled trials. Small to moderate effects were found for global cognition, attention, working memory, learning, and memory, with the exception of nonverbal memory, and for psychosocial functioning, including depressive symptoms. In dementia, statistically significant effects were found on overall cognition ( $k=11$ ,  $g=0.26$ , 95% CI=0.01–0.52) and visuospatial skills, but these were driven by three trials of virtual reality or Nintendo Wii.

## Metastudies

**Conclusions:** CCT is efficacious on global cognition, select cognitive domains, and psychosocial functioning in people with mild cognitive impairment. This intervention therefore warrants longer-term and larger-

scale trials to examine effects on conversion to dementia. Conversely, evidence for efficacy in people with dementia is weak and limited to trials of immersive technologies.

### Cognitive training in Parkinson disease: A systematic review and meta-analysis

Leung IH, Walton CC, Hallock H, Lewis SJ, Valenzuela M, Lampit A  
Neurology published online October 30, 2015 DOI 10.1212/WNL.0000000000002145

**Objective:** To quantify the effects of cognitive training (CT) on cognitive and behavioral outcome measures in patients with Parkinson disease (PD).

**Methods:** We systematically searched 5 databases for randomized controlled trials (RCTs) of CT in patients with PD reporting cognitive or behavioral outcomes. Efficacy was measured as standardized mean difference (Hedges  $g$ ) of post-training change.

**Results:** Seven studies encompassing 272 patients with Hoehn & Yahr Stages 1–3 were included. The overall effect of CT over and above control conditions was small but statistically significant (7 studies:  $g = 0.23$ , 95% confidence interval [CI] 0.014–0.44,  $p = 0.037$ ). True heterogeneity across studies was low ( $I^2 = 0\%$ ) and there was no evidence of publication bias. Larger effect sizes were noted

on working memory (4 studies:  $g = 0.74$ , CI 0.32–1.17,  $p = 0.001$ ), processing speed (4 studies:  $g = 0.31$ , CI 0.01–0.61,  $p = 0.04$ ), and executive function (5 studies:  $g = 0.30$ , CI 0.01–0.58,  $p = 0.042$ ), while effects on measures of global cognition (4 studies), memory (5 studies), visuospatial skills (4 studies), and depression (5 studies), as well as attention, quality of life, and instrumental activities of daily living (3 studies each), were not statistically significant. No adverse events were reported.

**Conclusions:** Though still small, the current body of RCT evidence indicates that CT is safe and modestly effective on cognition in patients with mild to moderate PD. Larger RCTs are necessary to examine the utility of CT for secondary prevention of cognitive decline in this population.

## The efficacy of cognitive training programs in children and adolescents: a meta-analysis

Karch D, Albers L, Renner G, Lichtenauer N, von Kries R  
Deutsches Ärzteblatt Int. 2013 Sep;110(39):643-52. doi: 10.3238/arztebl.2013.0643. Epub 2013 Sep 27.

**Background:** Cognitive therapies are intended to improve basic cognitive functions, whatever the cause of the deficiency may be. Children and adolescents with various cognitive deficits are treated with behavioral therapeutic and computer-supported training programs. We here report the first meta-analysis of the efficacy of such programs.

**Methods:** We systematically searched the Medline, Embase, PsycINFO, PSYINDEX, and ERIC databases to find pertinent publications for a meta-analysis of cognitive training programs that are used in children and adolescents to improve attention, memory, and executive performance (primary goals) as well as behavior/psychopathology, intelligence, and school performance (secondary goals). The mean differences between the treatment and control groups are given here as standard deviation (SD) scores.

**Results:** 1661 potentially relevant publications were found, including 22 studies that were

considered in the meta-analysis, 17 of which were randomized controlled trials. The target variables were measured with more than 90 different testing techniques. The overall effects of cognitive training on attention (SD 0.18, 95% CI 0.11-0.47) and executive function (SD 0.17, 95% CI 0.12-0.46) were consistently small. A relatively strong effect was found on memory performance (0.65 SD, 95% CI 0.12-1.42), albeit with marked heterogeneity ( $I^2 = 82\%$ ) owing to two studies. The largest effect was found in the area of behavior and psychopathology (SD 0.58, 95% CI 0.31-0.85), but this last figure is derived mainly from studies that lacked an active control group.

**Conclusion:** Cognitive therapies for children and adolescents have generally favorable, but probably nonspecific effects on behavior. On the other hand, the specific effects, however, were weak overall. Therapeutic benefit has been demonstrated only for certain individual types of therapy for specific indications.

## Evidence-Based Cognitive Rehabilitation: Updated Review of the Literature From 2003 Through 2008

Cicerone KD, Langenbahn DM, Braden C, Malec JF, Kalmar K, Fraas M, Felicetti T, Laatsch L, Harley JP, Bergquist T, Azulay J, Cantor J, Ashman T.; Arch Phys Med Rehabil. **2011**;92: 519-30.

**Objective:** To update our clinical recommendations for cognitive rehabilitation of people with traumatic brain injury (TBI) and stroke, based on a systematic review of the literature from 2003 through 2008.

**Data sources:** PubMed and Infotrieve literature searches were conducted using the terms attention, awareness, cognitive, communication, executive, language, memory, perception, problem solving, and/or reasoning combined with each of the following terms: rehabilitation, remediation, and training for articles published between 2003 and 2008. The task force initially identified citations for 198 published articles.

**Study selection:** One hundred forty-one articles were selected for inclusion after our initial screening. Twenty-nine studies were excluded after further detailed review. Excluded articles included 4 descriptive studies without data, 6 nontreatment studies, 7 experimental manipulations, 6 reviews, 1 single case study not related to TBI or stroke, 2 articles where the intervention was provided to caretakers, 1 article redacted by the journal, and 2 reanalyses of prior publications. We fully reviewed and evaluated 112 studies.

**Data extraction:** Articles were assigned to 1 of 6 categories reflecting the primary area of

intervention: attention; vision and visuospatial functioning; language and communication skills; memory; executive functioning, problem solving and awareness; and comprehensive-holistic cognitive rehabilitation. Articles were abstracted and levels of evidence determined using specific criteria.

**Data synthesis:** Of the 112 studies, 14 were rated as class I, 5 as class Ia, 11 as class II, and 82 as class III. Evidence within each area of intervention was synthesized and recommendations for Practice Standards, Practice Guidelines, and Practice Options were made.

**Conclusions:** There is substantial evidence to support interventions for attention, memory, social communication skills, executive function, and for comprehensive-holistic neuropsychologic rehabilitation after TBI. Evidence supports visuospatial rehabilitation after right hemisphere stroke, and interventions for aphasia and apraxia after left hemisphere stroke. Together with our prior reviews, we have evaluated a total of 370 interventions, including 65 class I or Ia studies. There is now sufficient information to support evidence-based protocols and implement empirically-supported treatments for cognitive disability after TBI and stroke.

### Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002

Cicerone KD, Dahlberg C, Malec JF, Langenbahn DM, Felicetti T, Kneipp S, Ellmo W, Kalmar K, Giacino JT, Harley JP, Laatsch L, Morse PA, Catanese J; Arch Phys Med Rehabil. **2005** Aug; 86(8):1681-92.

**Objective:** To update the previous evidence-based recommendations of the Brain Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine for cognitive rehabilitation of people with traumatic brain injury (TBI) and stroke, based on a systematic review of the literature from 1998 through 2002.

**Data sources:** PubMed and Infotrieve literature searches were conducted using the terms attention, awareness, cognition, communication, executive, language, memory, perception, problem solving, and reasoning combined with each of the terms rehabilitation, remediation, and training. Reference lists from identified articles were reviewed and a bibliography listing 312 articles was compiled.

**Study selection:** One hundred eighteen articles were initially selected for inclusion. Thirty-one studies were excluded after detailed review. Excluded articles included 14 studies without data, 6 duplicate publications or follow-up studies, 5 non-treatment studies, 4 reviews, and 2 case studies involving diagnoses other than TBI or stroke.

**Data extraction:** Articles were assigned to 1 of 7 categories reflecting the primary area of intervention: attention; visual perception; apraxia; language and communication; memory; executive functioning, problem solving and awareness; and comprehensive-holistic cognitive rehabilitation. Articles were abstracted and levels of evidence determined using specific criteria.

**Data synthesis:** Of the 87 studies evaluated, 17 were rated as class I, 8 as class II, and 62 as class III. Evidence within each area of intervention was synthesized and recommendations for practice standards, practice guidelines, and practice options were made.

**Conclusions:** There is substantial evidence to support cognitive-linguistic therapies for people with language deficits after left hemisphere stroke. New evidence supports training for apraxia after left hemisphere stroke. The evidence supports visuospatial rehabilitation for deficits associated with visual neglect after right hemisphere stroke. There is substantial evidence to support cognitive rehabilitation for people with TBI, including strategy training for mild memory impairment, strategy training for post-acute attention deficits, and interventions for functional communication deficits. The overall analysis of 47 treatment comparisons, based on class I studies included in the current and previous review, reveals a differential benefit in favor of cognitive rehabilitation in 37 of 47 (78.7%) comparisons, with no comparison demonstrating a benefit in favor of the alternative treatment condition. Future research should move beyond the simple question of whether cognitive rehabilitation is effective, and examine the therapy factors and patient characteristics that optimize the clinical outcomes of cognitive rehabilitation.