Cognitive Enhancement:

A Practical Scientific Guide

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Drugs and Dietary Supplements

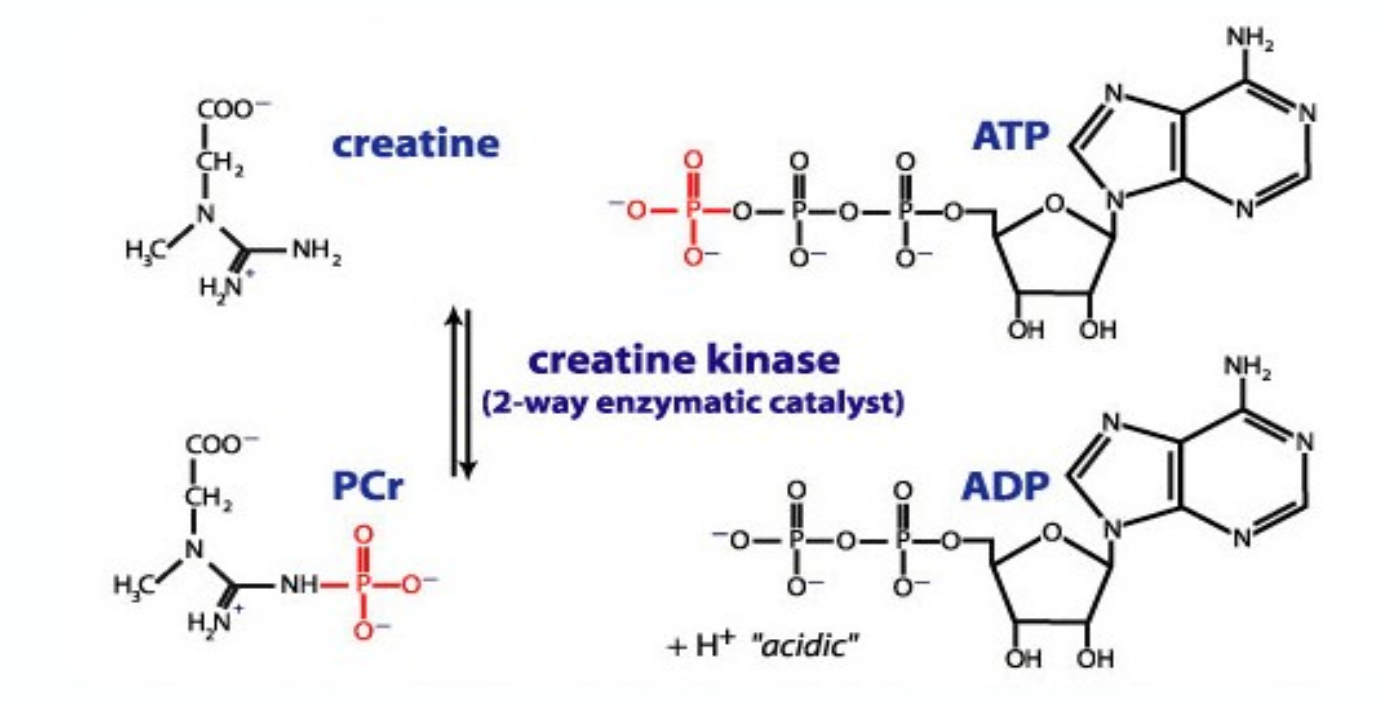
- Creatine
- Modafinil (Provigil®)
- Piracetam
- Magnesium L-threonate
- Kynurenic acid inhibition
- Uridine + choline + ω-3 fatty acids

Creatine

- Used in muscle and nervous tissue to store energy:

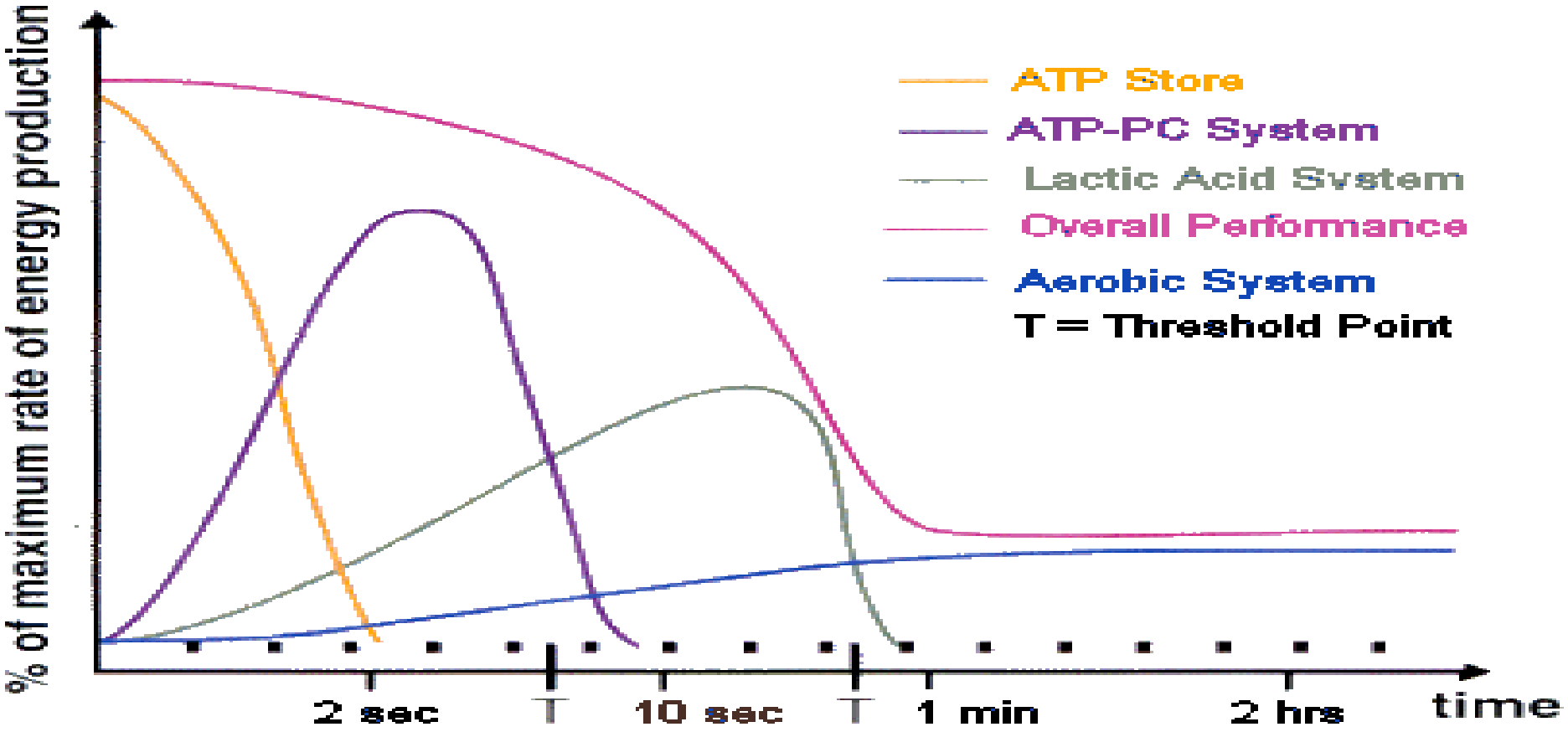
  creatine + ATP <=> phosphocreatine + ADP

- When [ATP] is high, phosphocreatine is produced. When [ATP] is low, ATP is produced.
- This reaction is very fast



Creatine

Creatine's importance peaks after a few seconds of high energy usage



Creatine in Vegetarian Undergrads

Oral creatine monohydrate supplementation improves brain performance: a double-blind, placebo-controlled, cross-over trial

Caroline Rae[1*], Alison L. Digney[1], Sally R. McEwan[1] and Timothy C. Bates[2]

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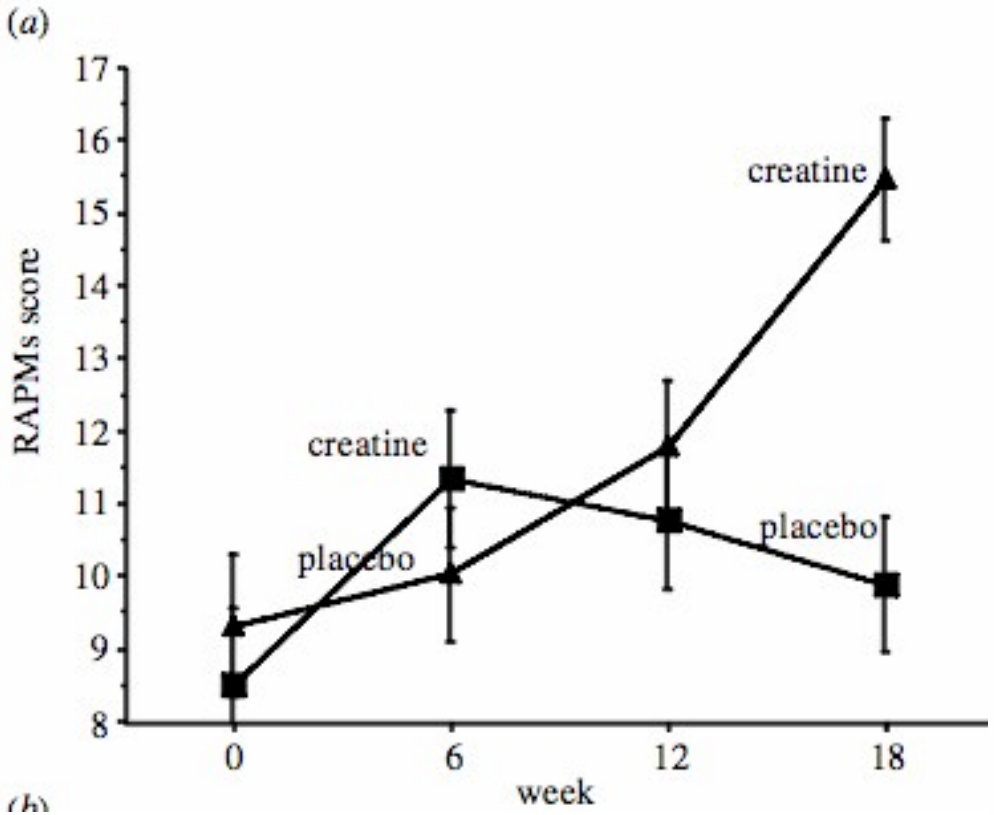
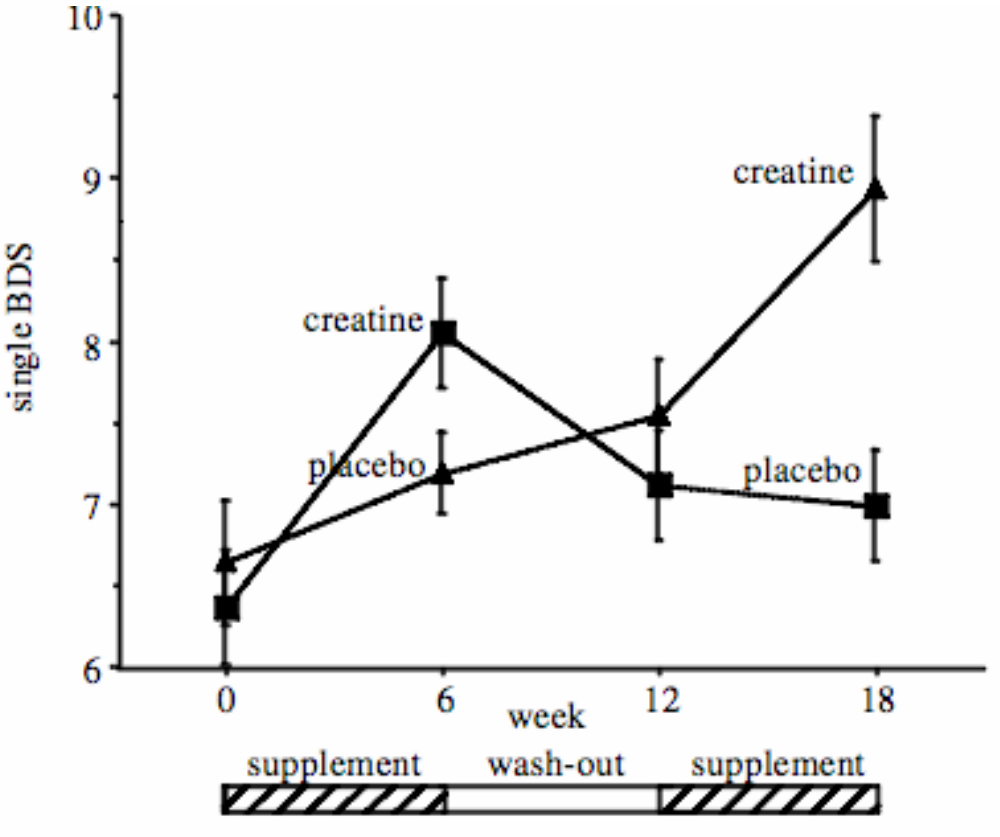
Creatine supplementation is in widespread use to enhance sports–fitness performance, and has been trialled successfully in the treatment of neurological, neuromuscular and atherosclerotic disease. Creatine plays a pivotal role in brain energy homeostasis, being a temporal and spatial buffer for cytosolic and mitochondrial pools of the cellular energy currency, adenosine triphosphate and its regulator, adenosine diphosphate. In this work, we tested the hypothesis that oral creatine supplementation (5 g d^{-1} for six weeks) would enhance intelligence test scores and working memory performance in 45 young adult, vegetarian subjects in a double-blind, placebo-controlled, cross-over design. Creatine supplementation had a significant positive effect ($p < 0.0001$) on both working memory (backward digit span) and intelligence (Raven's Advanced Progressive Matrices), both tasks that require speed of processing. These findings underline a dynamic and significant role of brain energy capacity in influencing brain performance.

Keywords: creatine; oral supplementation; intelligence; memory; brain bioenergetics

Rae et al., 2003

Creatine in Vegetarian Undergrads





Rae et al., 2003

Creatine in Omnivorous Undergrads

- 34 subjects (12 female)
- 5 cognitive tests, including one IQ test (iqtest.dk)
- 5 g/day of creatine ethyl ester for 2 weeks (or placebo)
- Creatine improved performance on 4 of the 5 tests
  - Placebo group's IQ scores: 112 before, 112 after
  - Creatine groups IQ scores: 108 before, 120 after ($p < .01$)

Ling et al., 2009

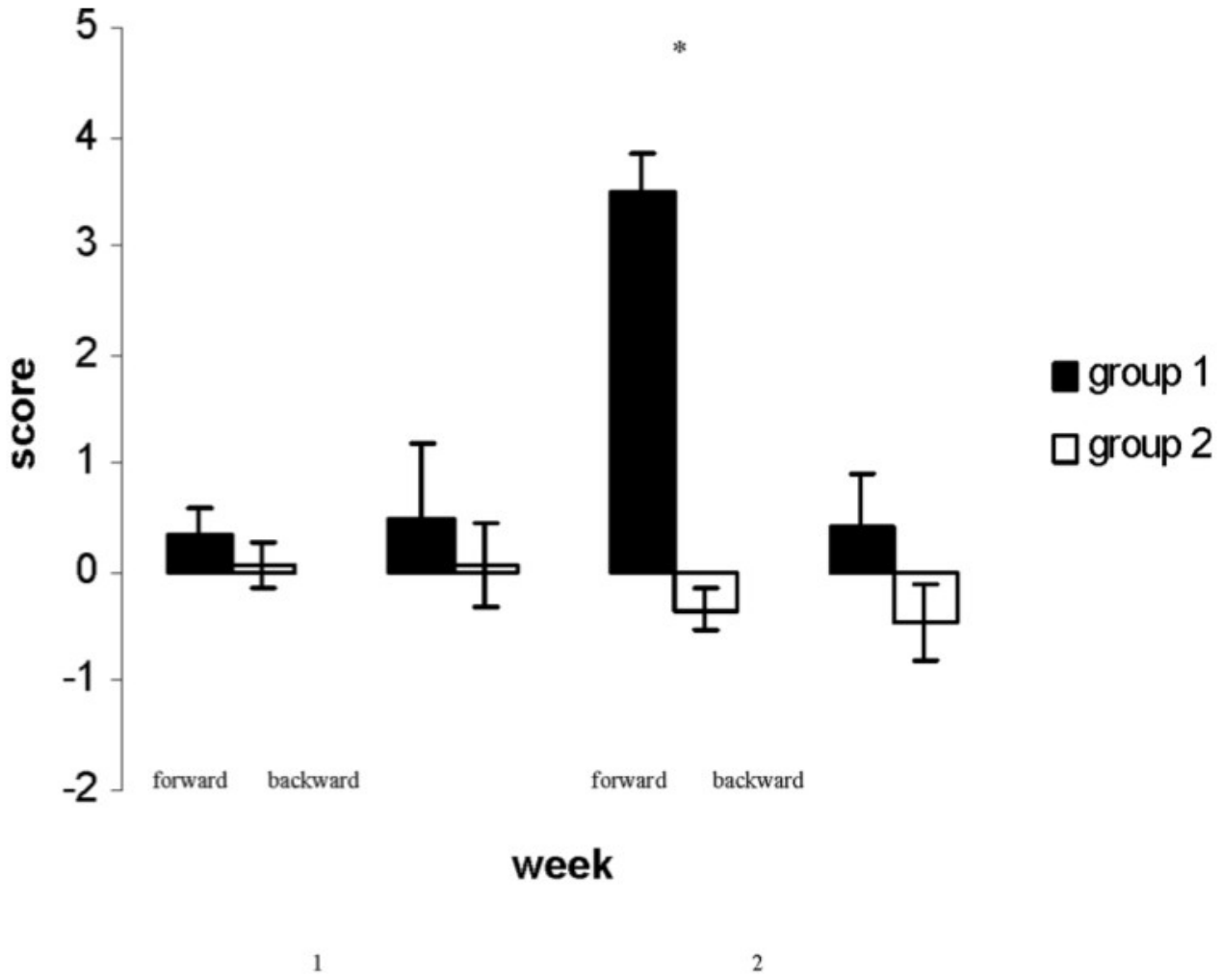
Other Creatine Studies

- McMorris (2006): creatine improves working memory in the elderly
- Rawson (2008): creatine does nothing for cognition

  (But their study was poorly designed)
- Watanabe (2002): Creatine reduces mental fatigue

Creatine in the Aged – Digit Span

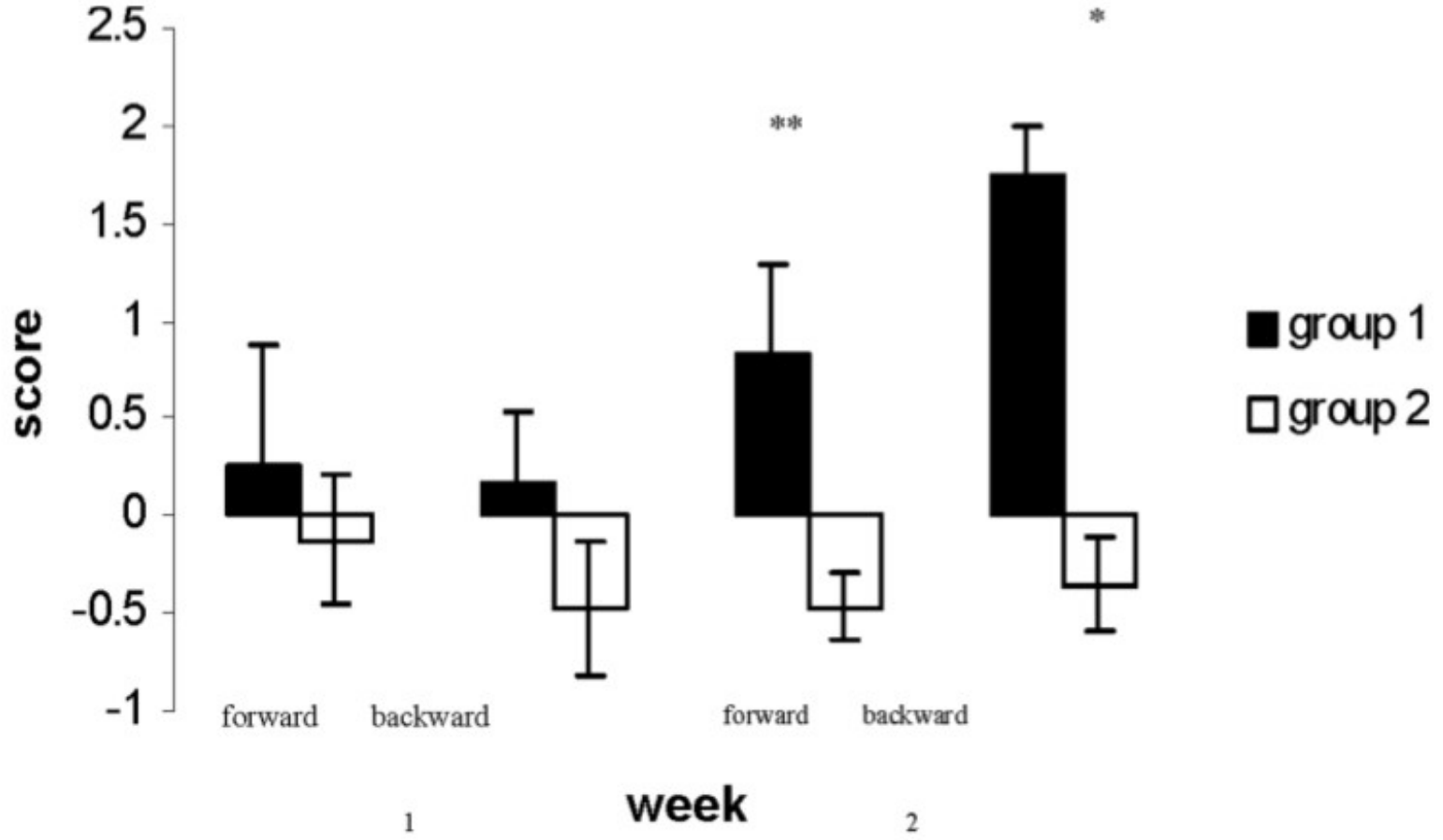
FIGURE 1. Mean (*SE*) Δ scores at weeks 1 and 2 for both groups on the forward and backward number recall tests.



McMorris et al., 2006

Creatine in the Aged – Spatial Span

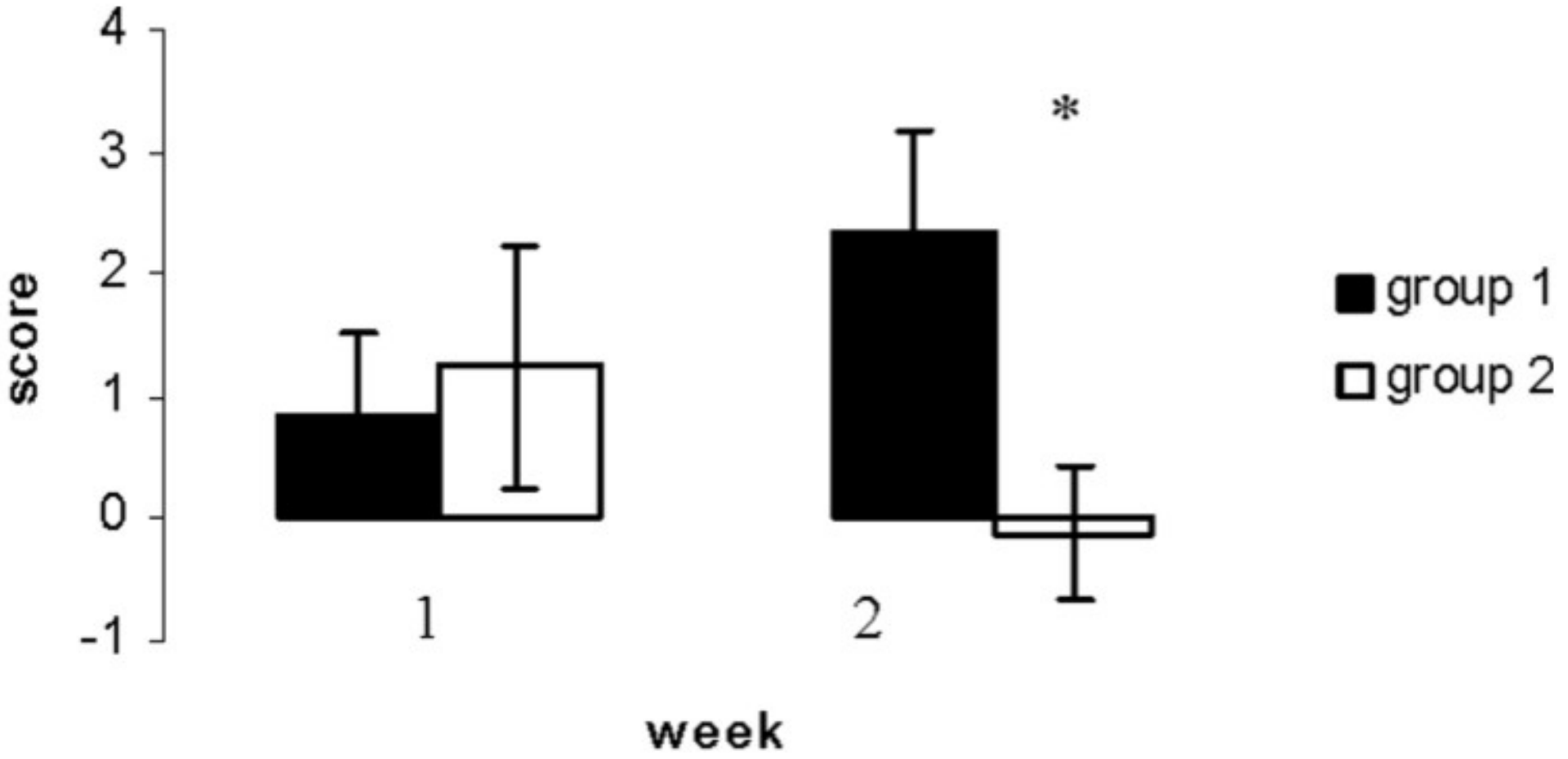
FIGURE 2. Mean (*SE*) Δ scores at weeks 1 and 2 for both groups on the forward and backward spatial recall tests.



McMorris et al., 2006

Creatine in the Aged – LTM

FIGURE 3. Mean (*SE*) Δ scores at weeks 1 and 2 for both groups on the long-term memory test.



McMorris et al., 2006

Creatine in the Rest of Us

Creatine supplementation does not improve cognitive function in young adults

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ABSTRACT

Creatine supplementation has been reported to improve certain aspects of cognitive and psychomotor function in older individuals and in young subjects following 24 and 36 h of sleep deprivation. However, the effects of creatine supplementation on cognitive processing and psychomotor performance in non-sleep deprived young adults have not been assessed with a comprehensive battery of neurocognitive tests. The primary objective of this study was to examine the effects of creatine supplementation on cognitive processing and psychomotor performance in young adults. Twenty-two subjects (21 ±2 yr) ingested creatine (0.03 g/kg/day) or placebo for 6 weeks in a double-blind placebo-controlled fashion. Subjects completed a battery of neurocognitive tests pre- and post-supplementation, including: simple reaction time (RT), code substitution (CS), code substitution delayed (CSD), logical reasoning symbolic (LRS), mathematical processing (MP), running memory (RM), and Sternberg memory recall (MR). There were no significant effects of group, no significant effects of time, and no significant group by time interactions for RT, CS, CSD, LRS, MP, RM, and MR (all $p>0.05$), indicating that there were no differences between creatine and placebo supplemented groups at any time. These results suggest that six weeks of creatine supplementation (0.03/g/kg/day) does not improve cognitive processing in non-sleep deprived young adults. Potentially, creatine supplementation only improves cognitive processing and psychomotor performance in individuals who have impaired cognitive processing abilities.

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Rawson et al., 2008

Creatine in the Rest of Us: Criticisms of Rawson 2008

- Rawson used 22 subjects vs. Rae's 45
- Rawson was not a crossover study
- Rawson's test battery (the ANAM) is not very good

Caveat emptor: I want this study to be wrong

Rawson et al., 2008

Modafinil

Modafinil

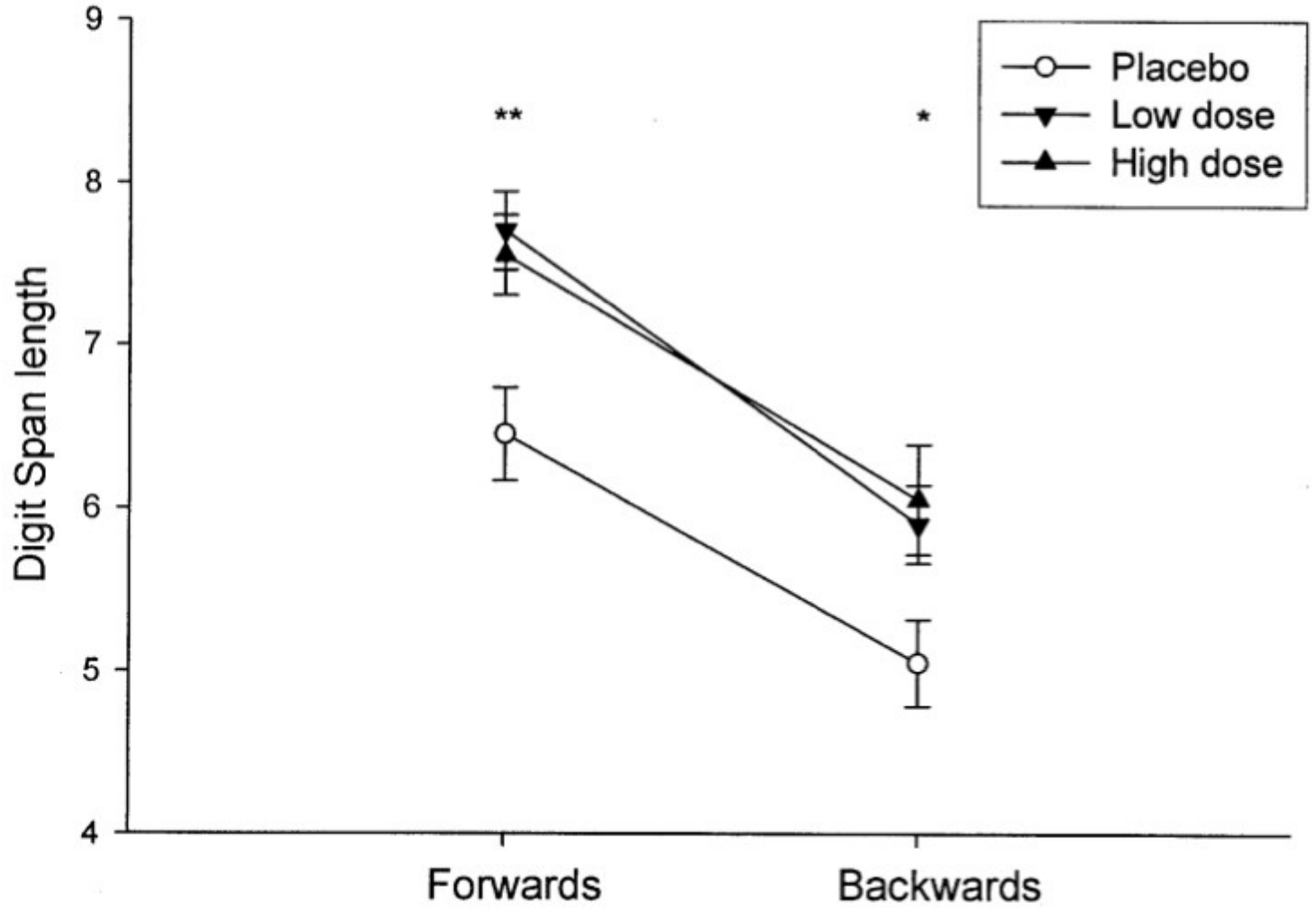
Danielle C. Turner · Trevor W. Robbins · Luke Clark · Adam R. Aron · Jonathan Dowson · Barbara J. Sahakian

Cognitive enhancing effects of modafinil in healthy volunteers

Abstract *Rationale:* Modafinil, a novel wake-promoting agent, has been shown to have a similar clinical profile to that of conventional stimulants such as methylphenidate. We were therefore interested in assessing whether modafinil, with its unique pharmacological mode of action, might offer similar potential as a cognitive enhancer, without the side effects commonly experienced with amphetamine-like drugs. *Objectives:* The main aim of this study was to evaluate the cognitive enhancing potential of this novel agent using a comprehensive battery of neuropsychological tests. *Methods:* Sixty healthy young adult male volunteers received either a single oral dose of placebo, or 100 mg or 200 mg modafinil prior to performing a variety of tasks designed to test memory and attention. A randomised double-blind, between-subjects design was used. *Results:* Modafinil significantly enhanced performance on tests of digit span, visual pattern recognition memory, spatial planning and stop-signal reaction time. These performance improvements were complemented by a slowing in latency on three tests: delayed matching to sample, a decision-making task and the spatial planning task. Subjects reported feeling more alert, attentive and energetic on drug. The effects were not clearly dose dependent, except for those seen with the stop-signal paradigm. In contrast to previous findings with methylphenidate, there were no significant effects of drug on spatial memory span, spatial working memory, rapid visual information processing or attentional set-shifting. Additionally, no effects on paired associates learning were identified. *Conclusions:* These data indicate that modafinil selectively improves neu-

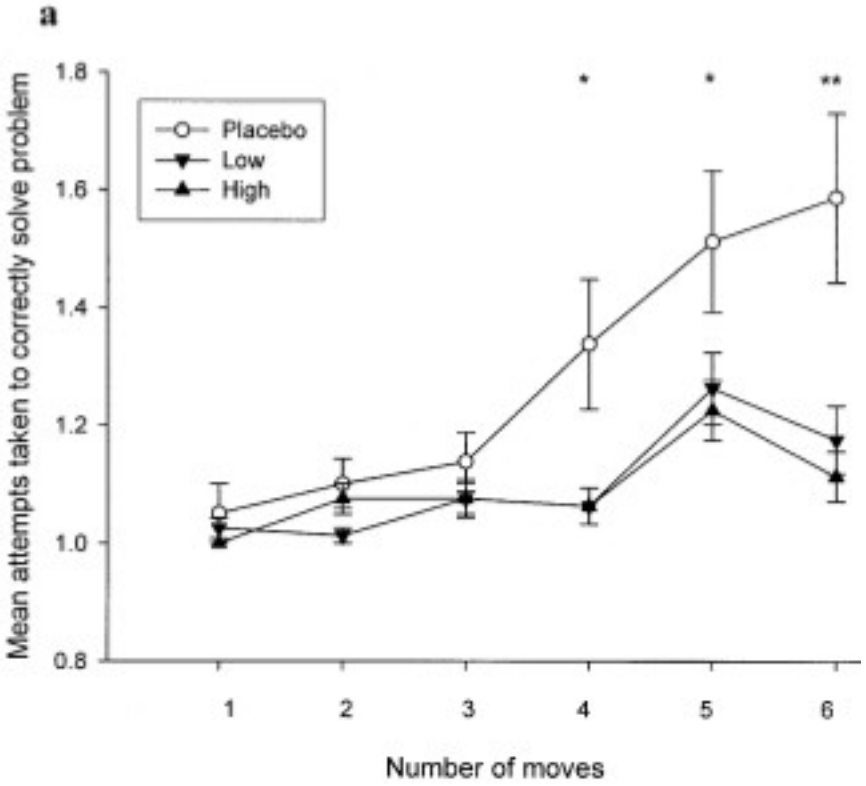
Turner et al., 2002

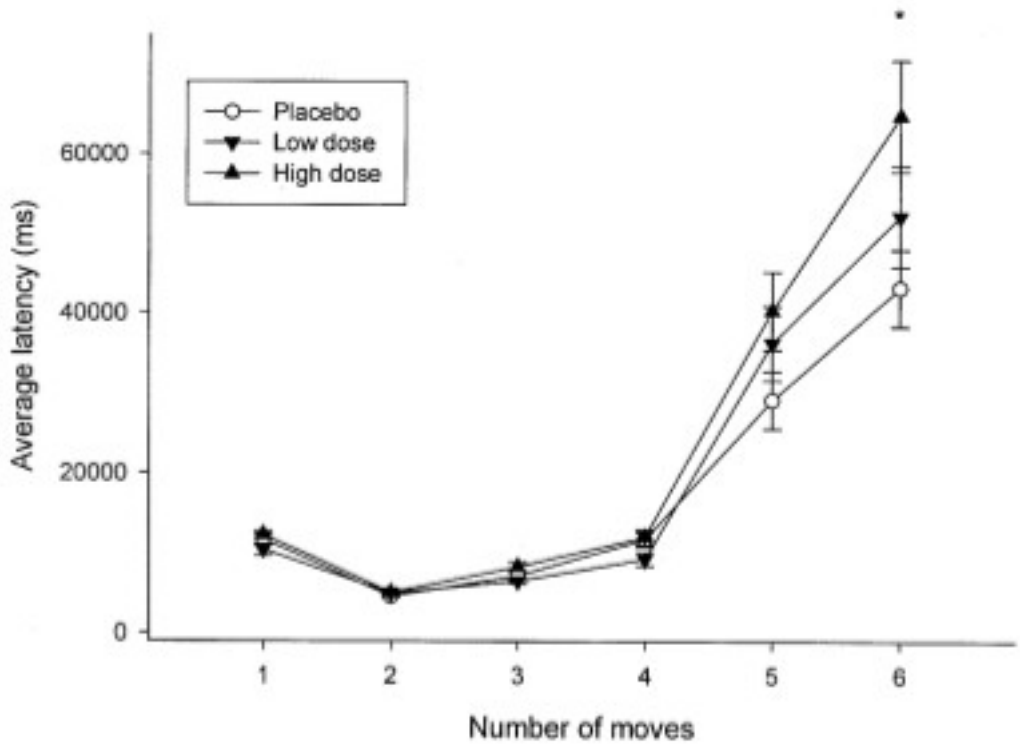
Modafinil



Turner et al., 2002

Modafinil





Turner et al., 2002

Piracetam

Piracetam

Dimond and Brouwers (1976):

- Healthy university students given piracetam or placebo for 14 days
- Piracetam group showed improved verbal learning
- No effect on a pursuit motor task

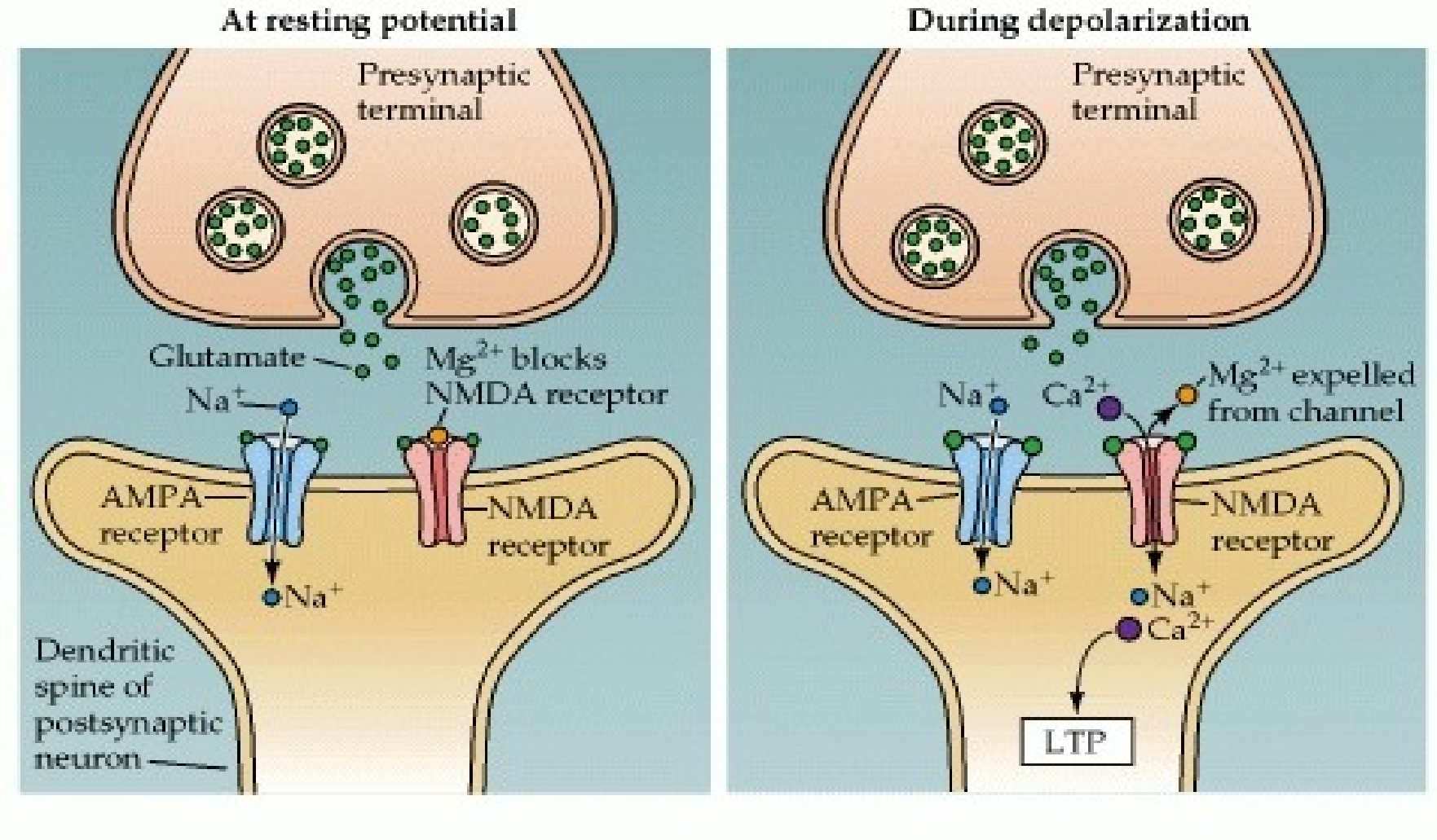
Piracetam

Wilsher, Atkins and Manfield (1979):

- 16 dyslexics, 14 normal volunteers received 4.8g/day (double-blind, placebo controlled)
- Piracetam accelerated rote-learning in both normals and dyslexics vs. placebo

NMDA Receptor

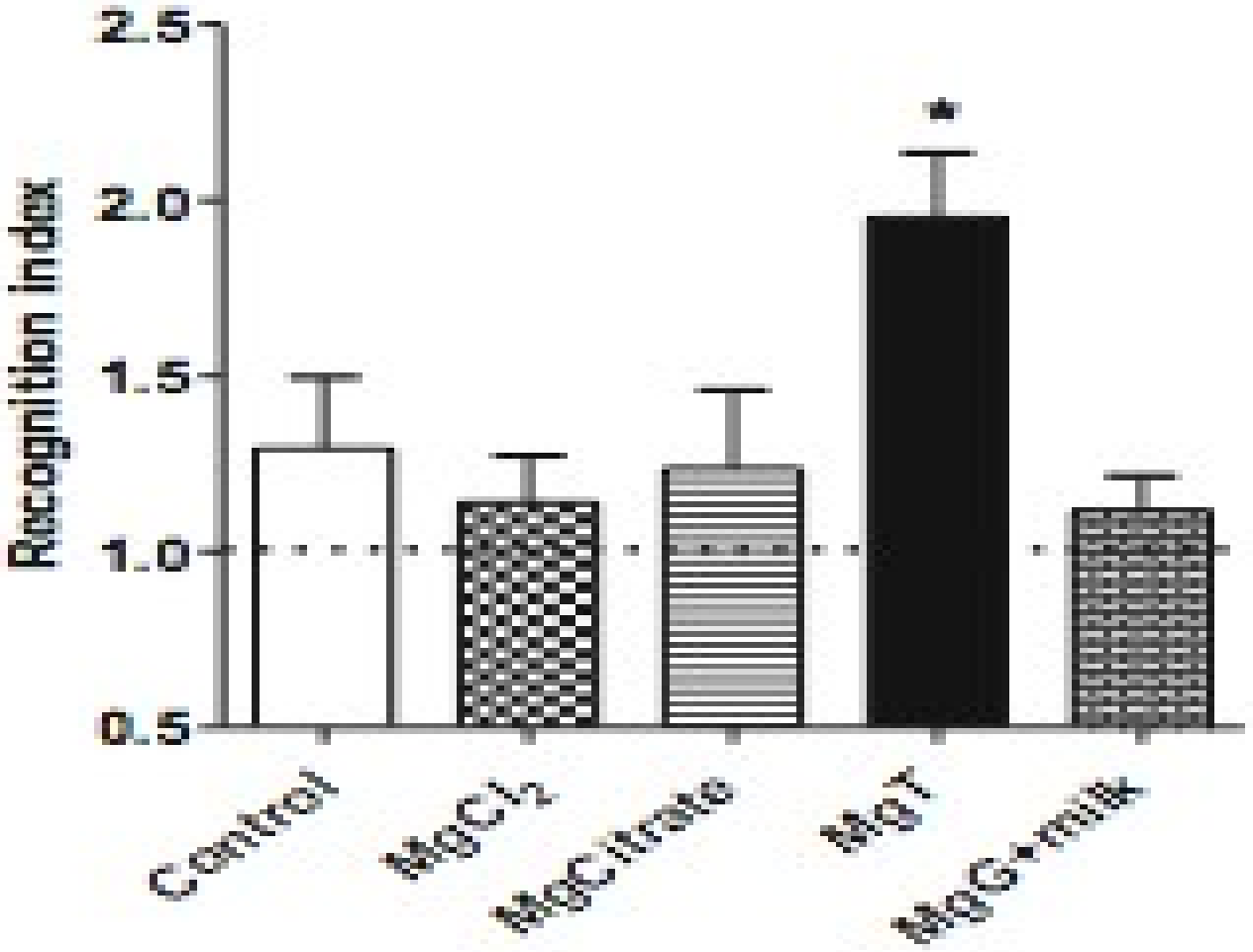
NMDA Receptor



Magnesium L-Threonate

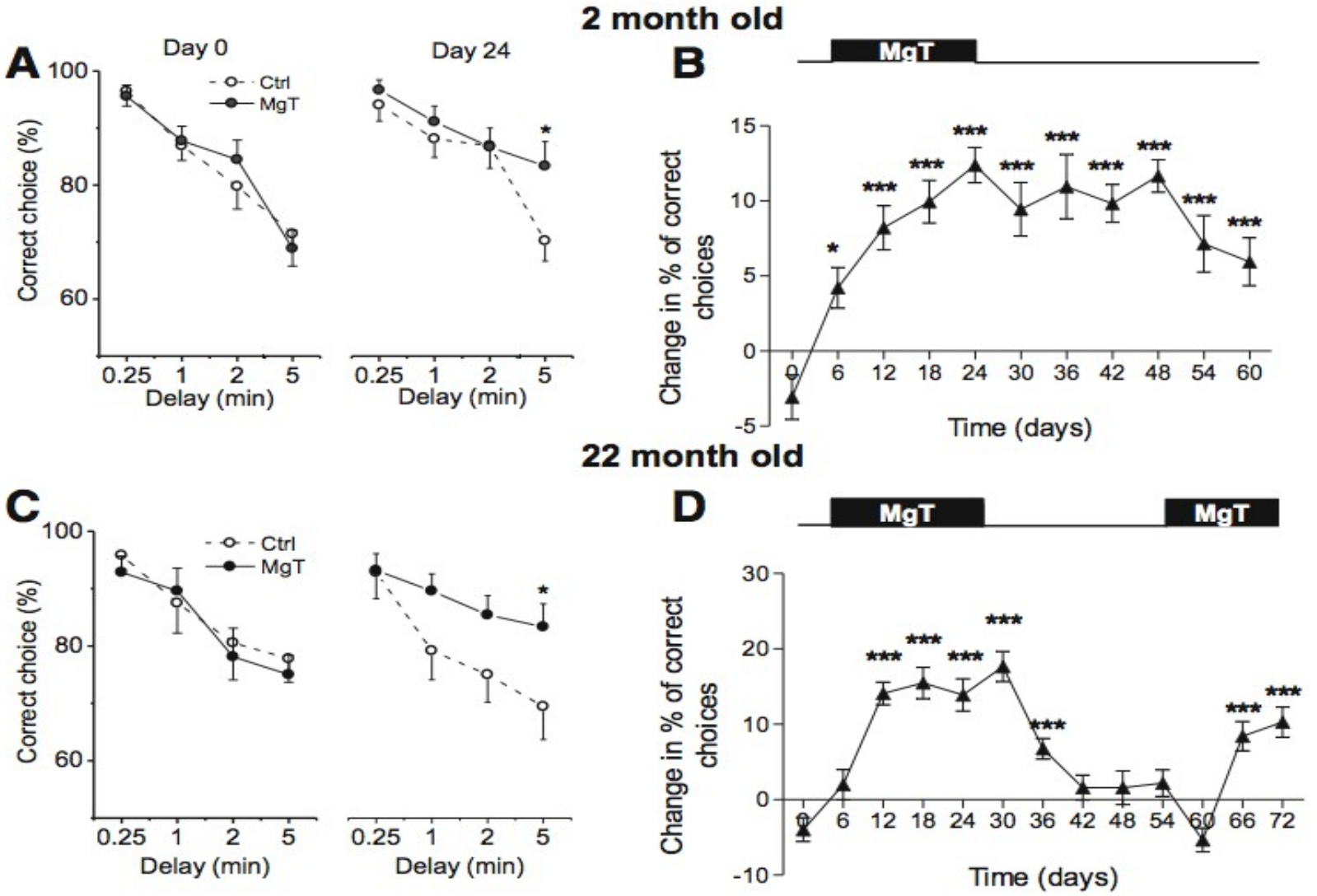
Slutsky et al., 2002

Magnesium L-Threonate



Slutsky et al., 2002

Magnesium L-Threonate

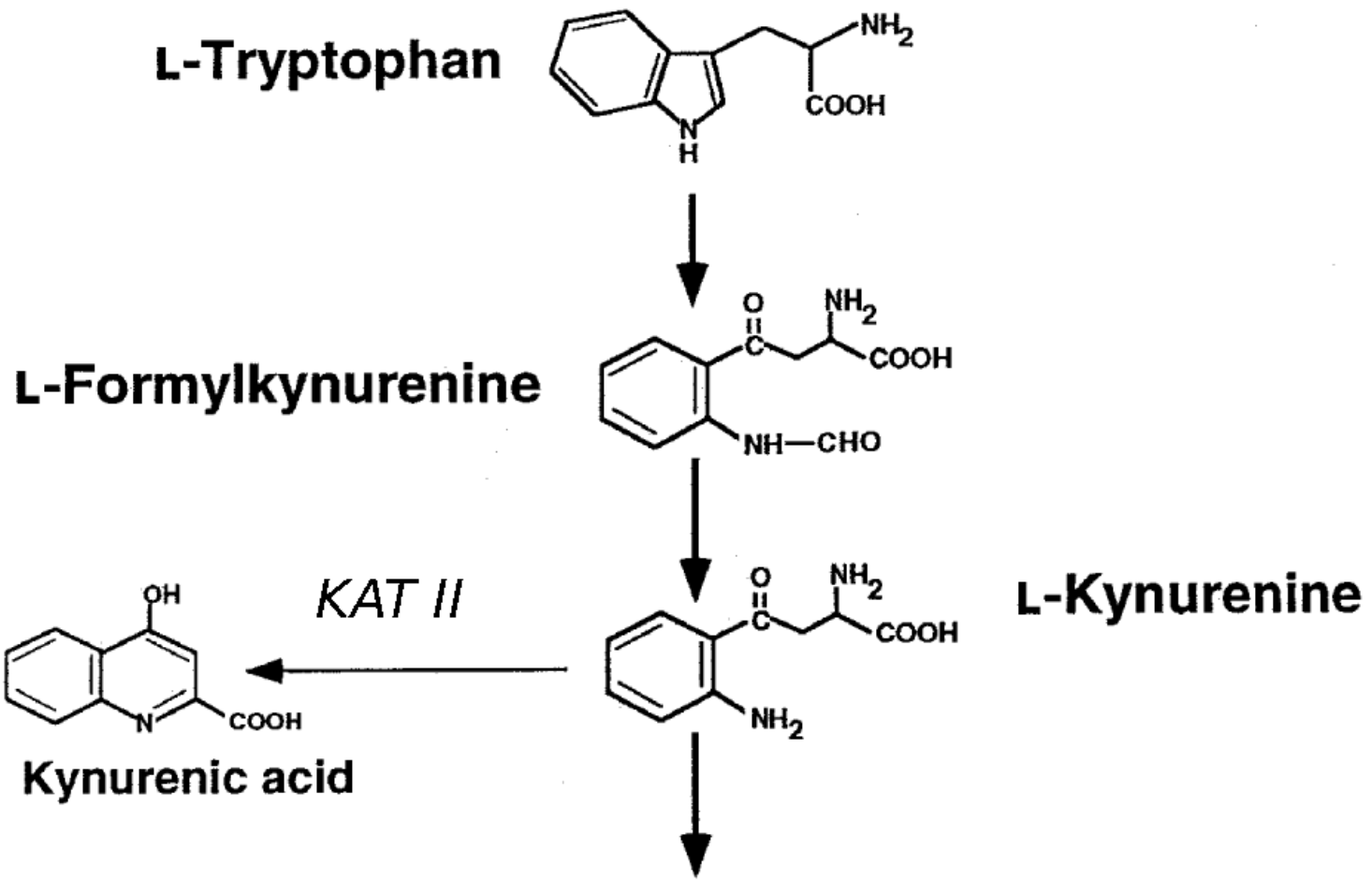


Slutsky et al., 2002

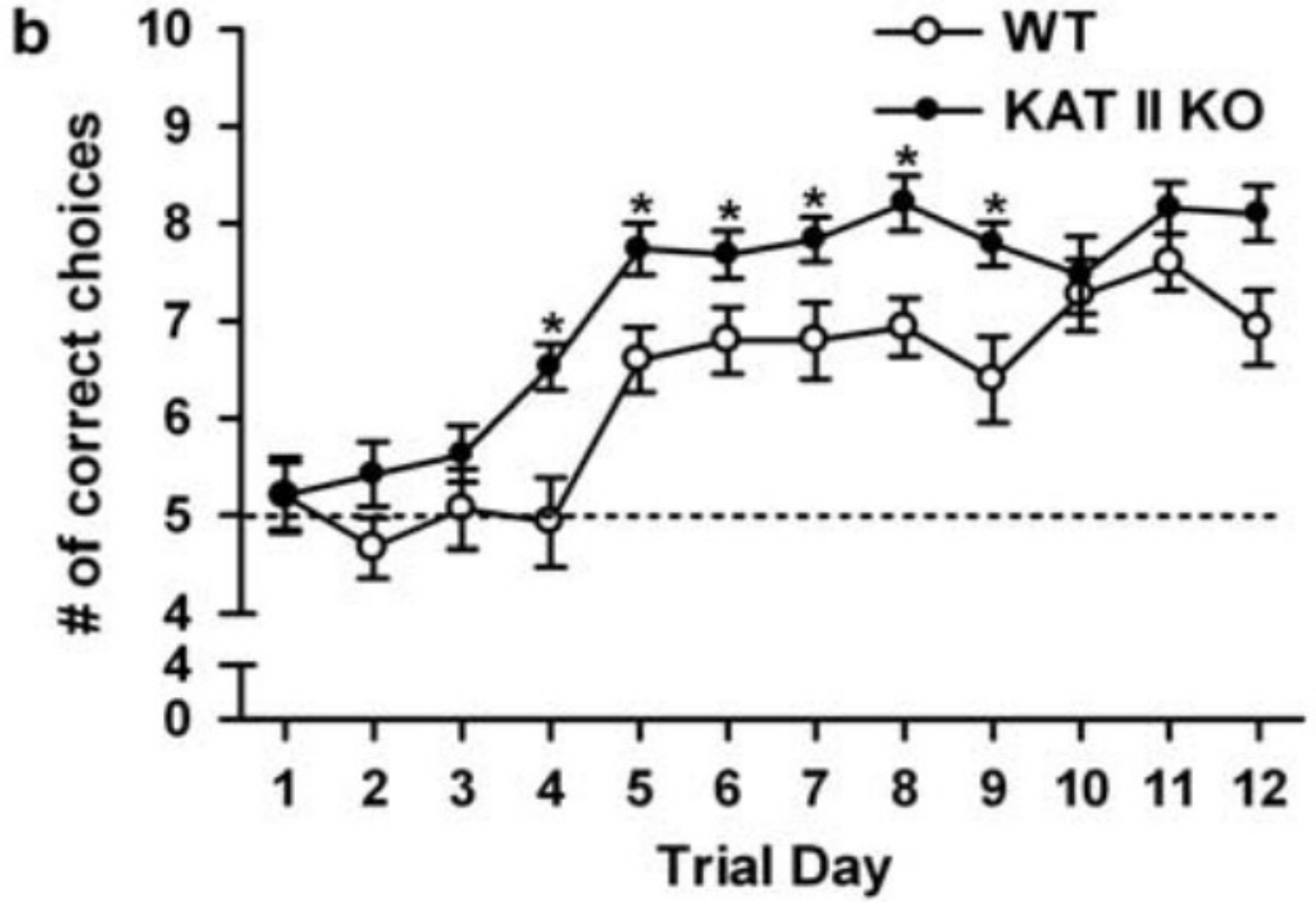
Kynurenic acid

- Natural byproduct of L-tryptophan metabolism
- Inhibits NMDA receptors and nicotinic acetylcholine receptors
- Reduces neural learning (LTP)

Kynurenic acid



Reducing Kynurenic Acid: T-Maze



Kynurenic acid

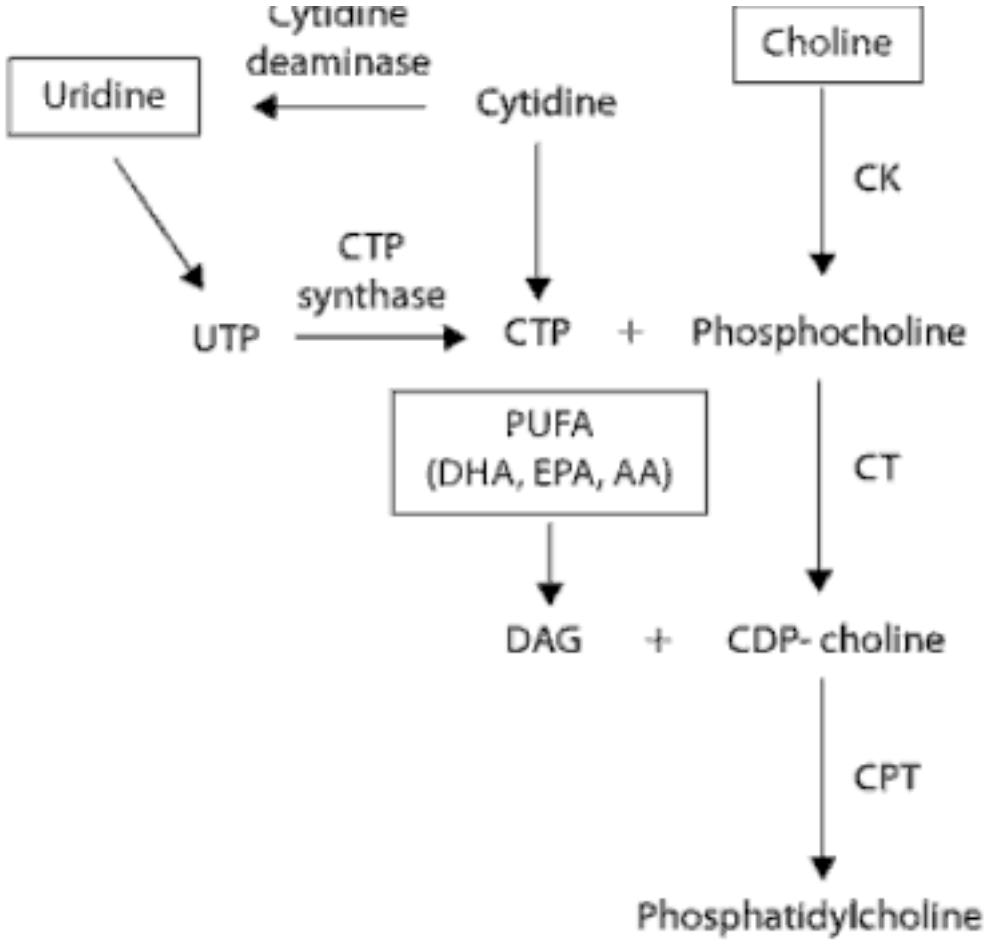
- Inhibition of KAT II is possible with:
  - Deleting the gene (no thanks)
  - Making a drug for it (in progress, “BFF122”)
  - “Distracting” KAT II with other molecules – yes!

Kynurenic acid

- KAT II also metabolizes alpha-aminoadipic acid (AAAA) – Fukuwatari
- AAAA is a byproduct of lysine metabolism

ω-3 Fatty Acids

Omega-3 Fatty Acids and the Kennedy Cycle



The FASEB Journal • Research Communication

Dietary uridine enhances the improvement in learning and memory produced by administering DHA to gerbils

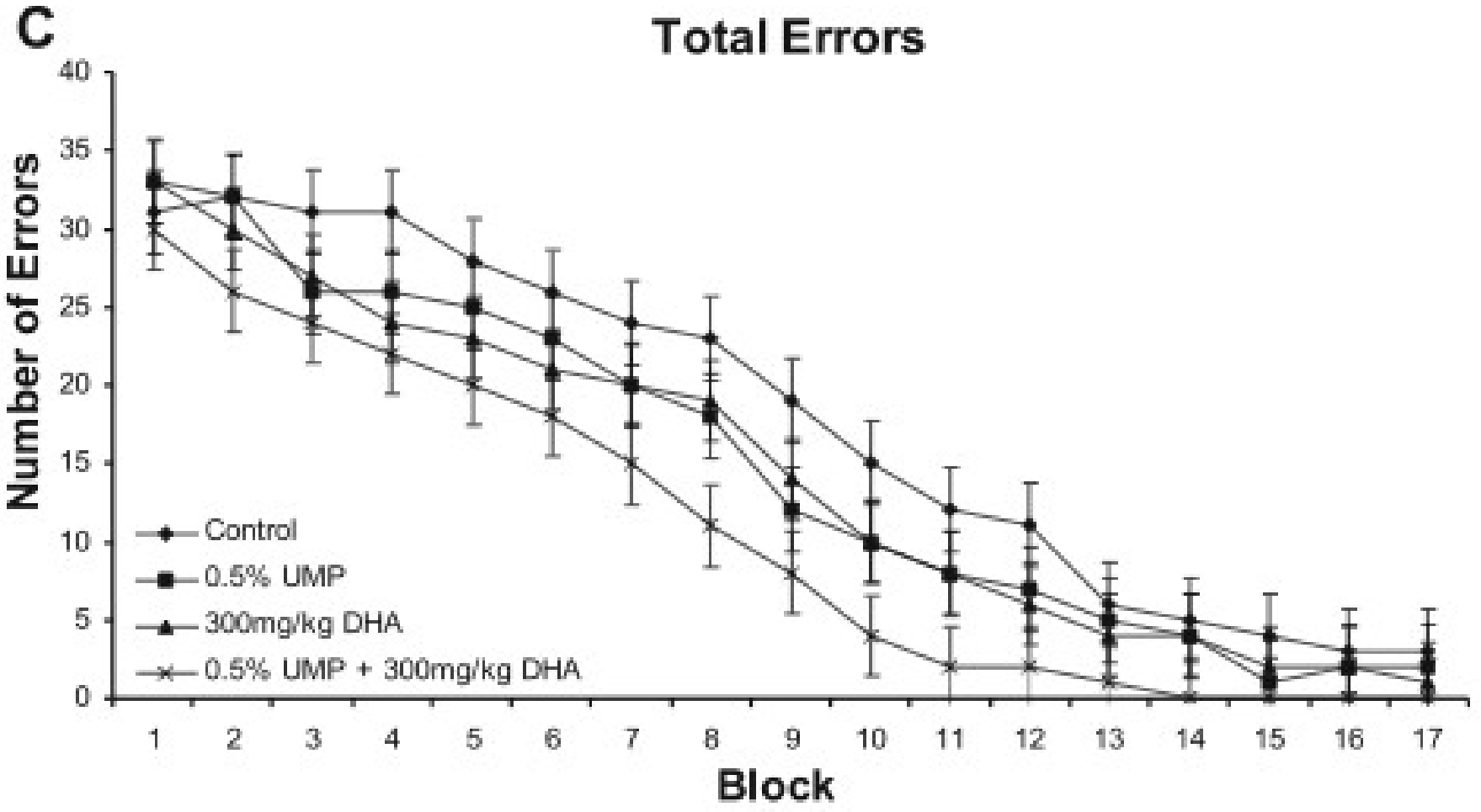
Sarah Holguin, Joseph Martinez, Camille Chow, and Richard Wurtman[1]

Massachusetts Institute of Technology, Department of Brain and Cognitive Sciences, Cambridge, Massachusetts, USA

ABSTRACT **This study examined the effects on cognitive behaviors of giving normal adult gerbils three compounds, normally in the circulation, which interact to increase brain phosphatides, synaptic proteins, dendritic spines, and neurotransmitter release. Animals received supplemental uridine (as its monophosphate, UMP; 0.5%) and choline (0.1%) *via* the diet, and docosahexaenoic acid (DHA; 300 mg/kg/day) by gavage, for 4 wk, and then throughout the subsequent period of behavioral training and testing. As shown previously, giving all three compounds caused highly significant ($P<0.001$) increases in total brain phospholipids and in each major phosphatide; giving DHA or UMP (plus choline) produced smaller increases in some of the phosphatides. DHA plus choline improved**

where. Oral administration of uridine monophosphate (UMP), a source of circulating and brain uridine (8), also promotes the synthesis of synaptic phosphatides and proteins (6), acting *via* its phosphorylated products uridine triphosphate (UTP) (which stimulates P2Y receptors; ref. 9) and cytidine triphosphate (CTP) (which is rate limiting in phosphatide synthesis *via* the Kennedy cycle; 10). Moreover, the effects on phosphatide synthesis of giving UMP to animals also receiving DHA and choline tend to be substantially greater than the sum of the increases observed after either treatment alone (6). Local application of UMP into the hippocampus 30 min prior to acquisition of the Y maze reportedly improved performance, as examined 48 h later (11). A UMP-enriched diet can reverse the mem-

Uridine + (Choline + ω-3 Fatty Acids)



Training

Dual N-Back

PNAS PNAS PNAS

Improving fluid intelligence with training on working memory

Susanne M. Jaeggi*†‡, Martin Buschkuehl*†‡, John Jonides*, and Walter J. Perrig†

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Edited by Edward E. Smith, Columbia University, New York, NY, and approved March 18, 2008 (received for review February 7, 2008)

Fluid intelligence (*Gf*) refers to the ability to reason and to solve new problems independently of previously acquired knowledge. *Gf* is critical for a wide variety of cognitive tasks, and it is considered one of the most important factors in learning. Moreover, *Gf* is closely related to professional and educational success, especially in complex and demanding environments. Although performance on tests of *Gf* can be improved through direct practice on the tests themselves, there is no evidence that training on any other regimen yields increased *Gf* in adults. Furthermore, there is a long history of research into cognitive training showing that, although performance on trained tasks can increase dramatically, transfer of this learning to other tasks remains poor. Here, we present evidence for transfer from training on a demanding working memory task to measures of *Gf*. This transfer results even though the trained task is entirely different from the intelligence test itself. Furthermore, we demonstrate that the extent of gain in intelligence critically depends on the amount of training: the more training, the more improvement in *Gf*. That is, the training effect is dosage–dependent. Thus, in contrast to many previous studies, we conclude that it is possible to improve *Gf* without practicing the testing tasks themselves, opening a wide range of applications.

Jaeggi et al., 2008

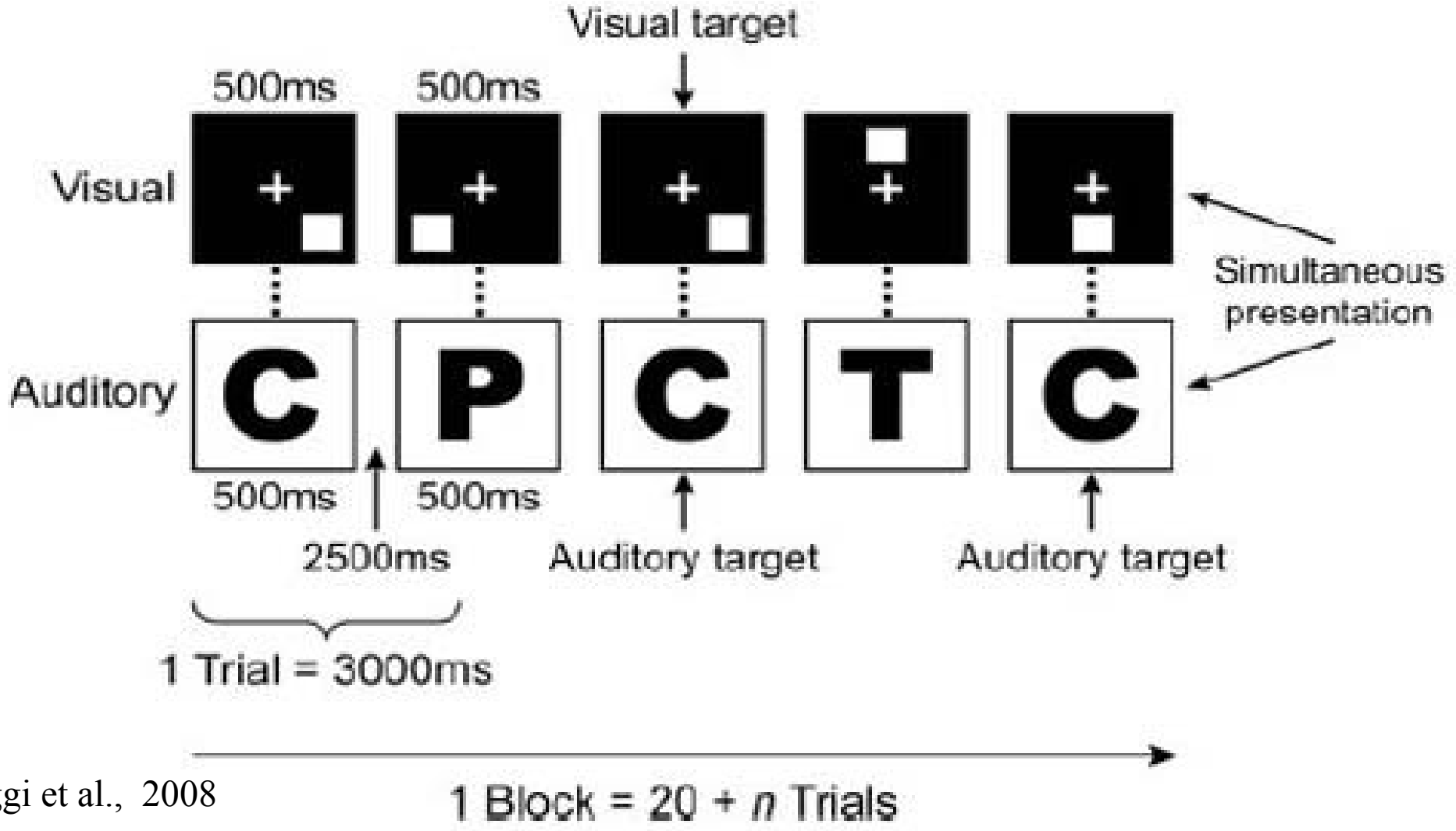
cognitive training | transfer | individual differences | executive processes | control processes

dramatically, transfer of this learning to other tasks or domains remains shockingly rare (18–21).

Despite the many failures to find transfer in any domain, the sheer importance of identifying tasks that can lead to improvement in other tasks recommends continued investigation of transfer effects. With respect to *Gf*, the issue is whether one can identify a task that shares many of the features and processes of *Gf* tasks, but that is still different enough from the *Gf* tasks themselves to avoid mere practice effects. A recently proposed hypothesis by Halford *et al.* (22) might serve as a useful framework for the design of a transfer study in which one would like to improve *Gf* by means of a working memory task. Their claim is that working memory and intelligence share a common capacity constraint. This capacity constraint can be expressed either by the number of items that can be held in working memory or by the number of interrelationships among elements in a reasoning task. The reason for a common capacity limitation is assumed to lie in the common demand for attention when temporary binding processes are taking place to form representations in reasoning tasks (22). Other authors came to a related conclusion, stating that *Gf* and working memory are primarily related through attentional control processes (23, 24). Furthermore, Carpenter *et al.* (1) have proposed that the ability to derive abstract relations and to maintain a large set of possible goals in working memory accounts for individual differences in typical

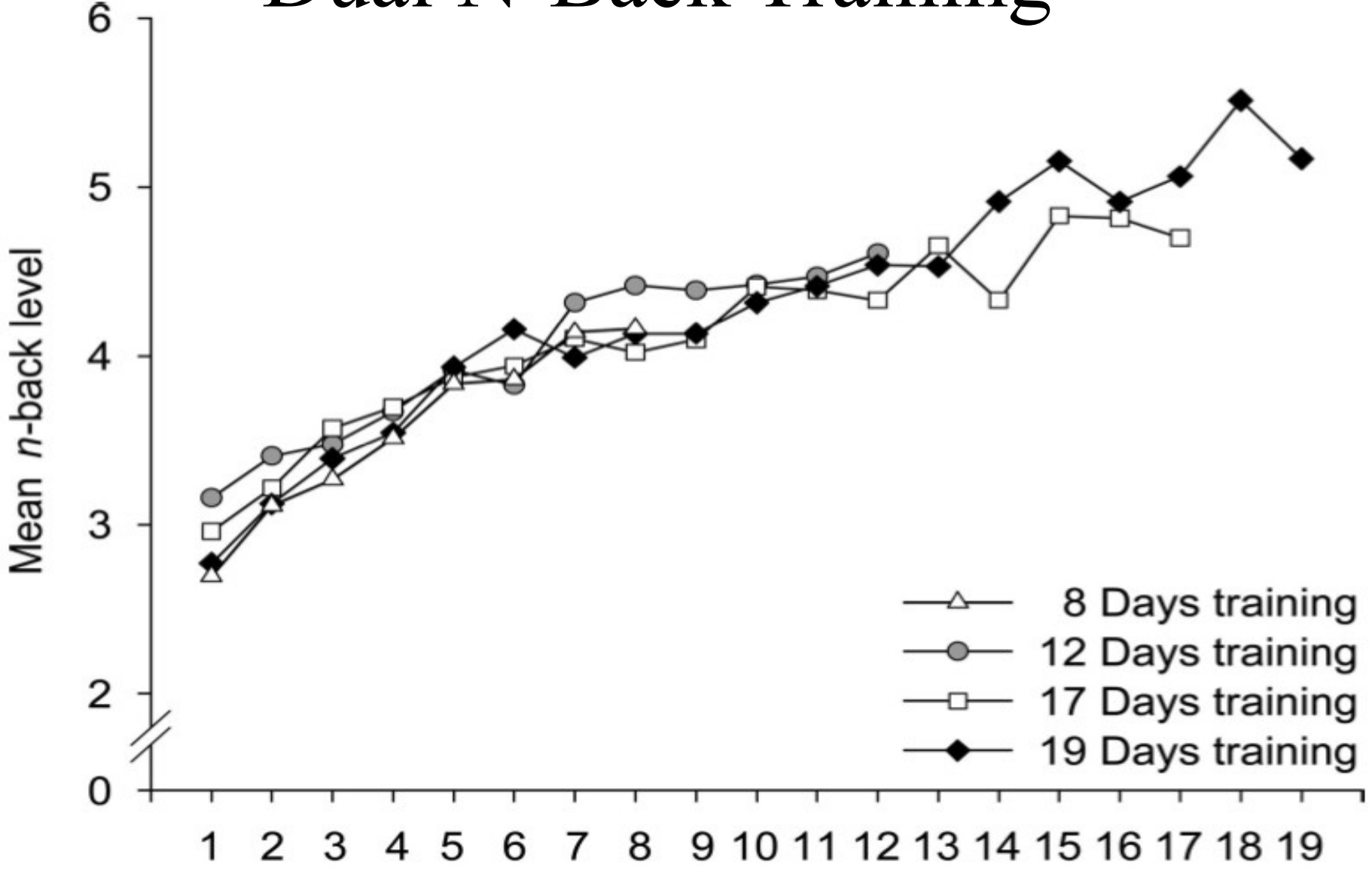
PSYCHOLOGY

Dual N-Back Task



Jaeggi et al., 2008

Dual N-Back Training



Jaeggi et al., 2008

Dual N-Back IQ Test Performance

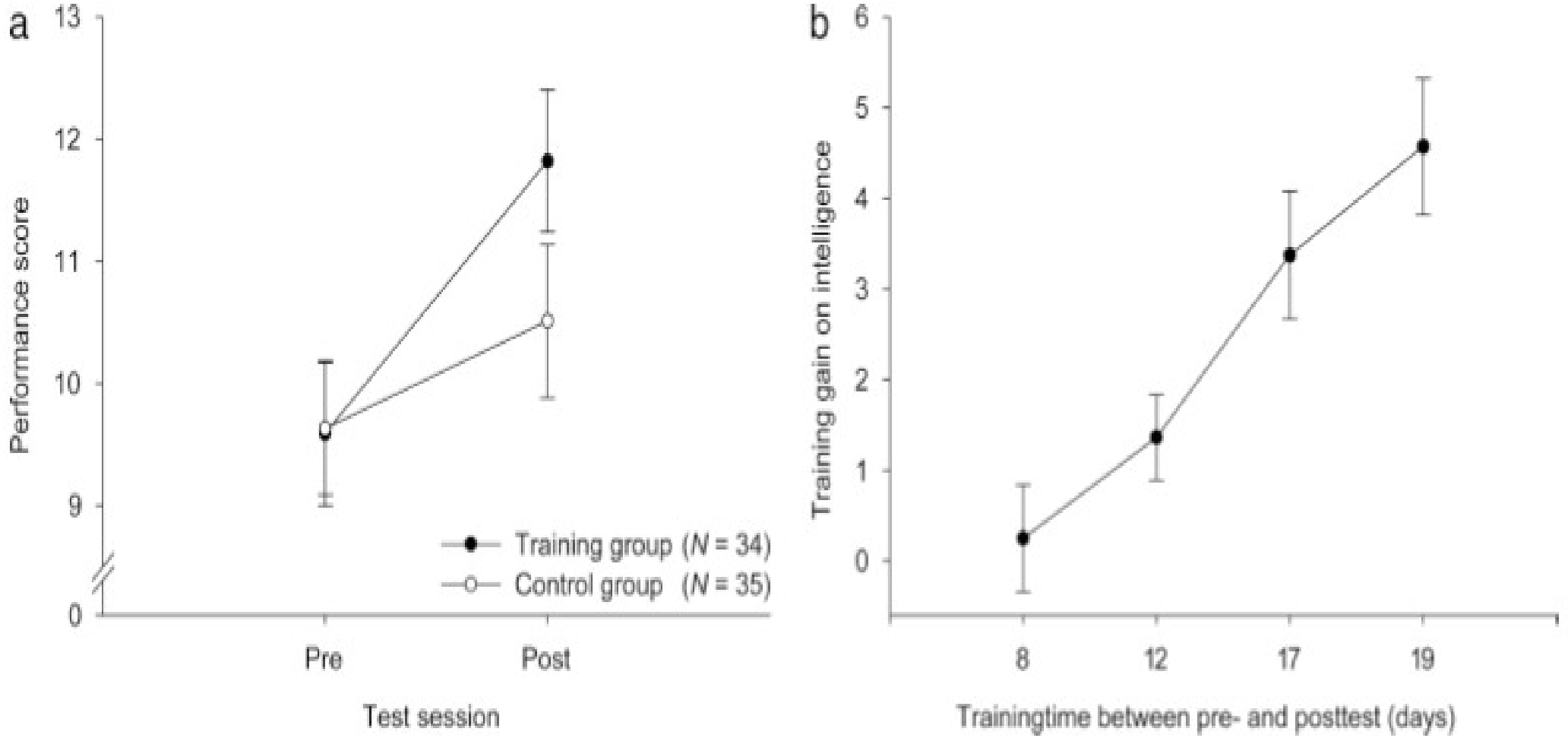


Fig. 3. Transfer effects. (*a*) Mean values and corresponding standard errors of the fluid intelligence test scores for the control and the trained groups, collapsed over training time. (*b*) The gain scores (posttest minus pretest scores) of the intelligence improvement plotted for training group as a function of training time. Error bars represent standard errors.

Brain Workshop - a Dual N-Back game

Download - **Tutorial** - **Details & Options**

Brain Workshop is a free open-source version of the Dual N-Back mental exercise.

What if a simple mental exercise could improve your memory and intelligence?

A recent study published in PNAS, an important scientific journal, shows that a particular memory task called Dual N-Back may actually improve **working memory** (short term memory) and **fluid intelligence**. This finding is important because fluid intelligence was previously thought to be unchangeable. The game involves remembering a sequence of spoken letters and a sequence of positions of a square at the same time.

Anecdotal evidence suggests that the dual n-back task also enhances focus and attention and may help improve the symptoms of ADHD/ADD.

In addition to its ability to closely replicate the conditions of the original study by Jaeggi et al. (2008), Brain Workshop includes optional extended game modes such as **Triple N-Back** and **Arithmetic N-Back**. It also includes features such as statistics tracking, graphs and easy configurability.

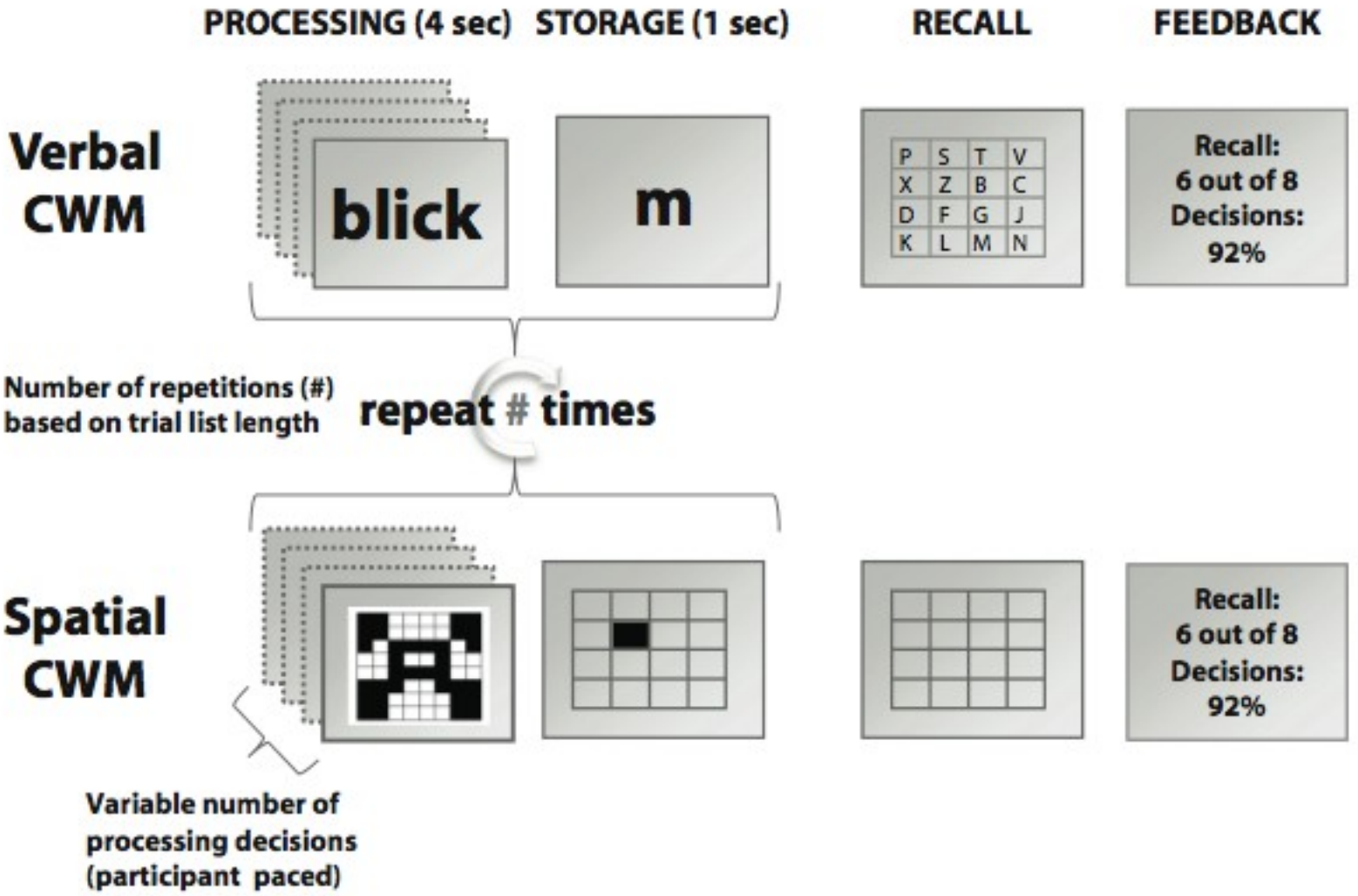
Brain Workshop works on Windows XP, Windows Vista, Mac OS X and Linux.

Since its initial release in August 2008, Brain Workshop has been downloaded over **40,000 times!**

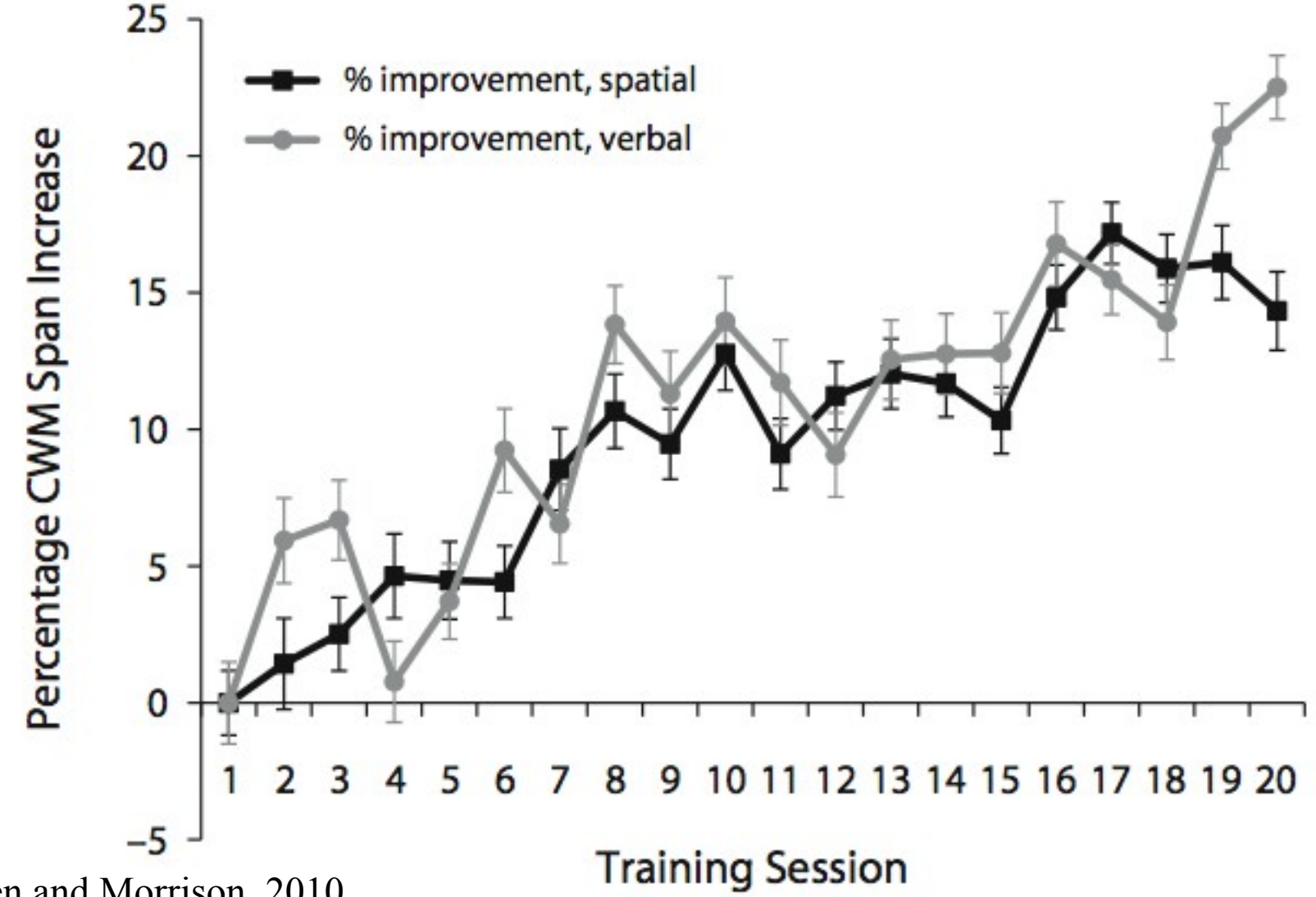
New to the Dual N-Back phenomenon?

- See this Wired article for an introduction to the Dual

Training Working Memory – Chien and Morrison 2009

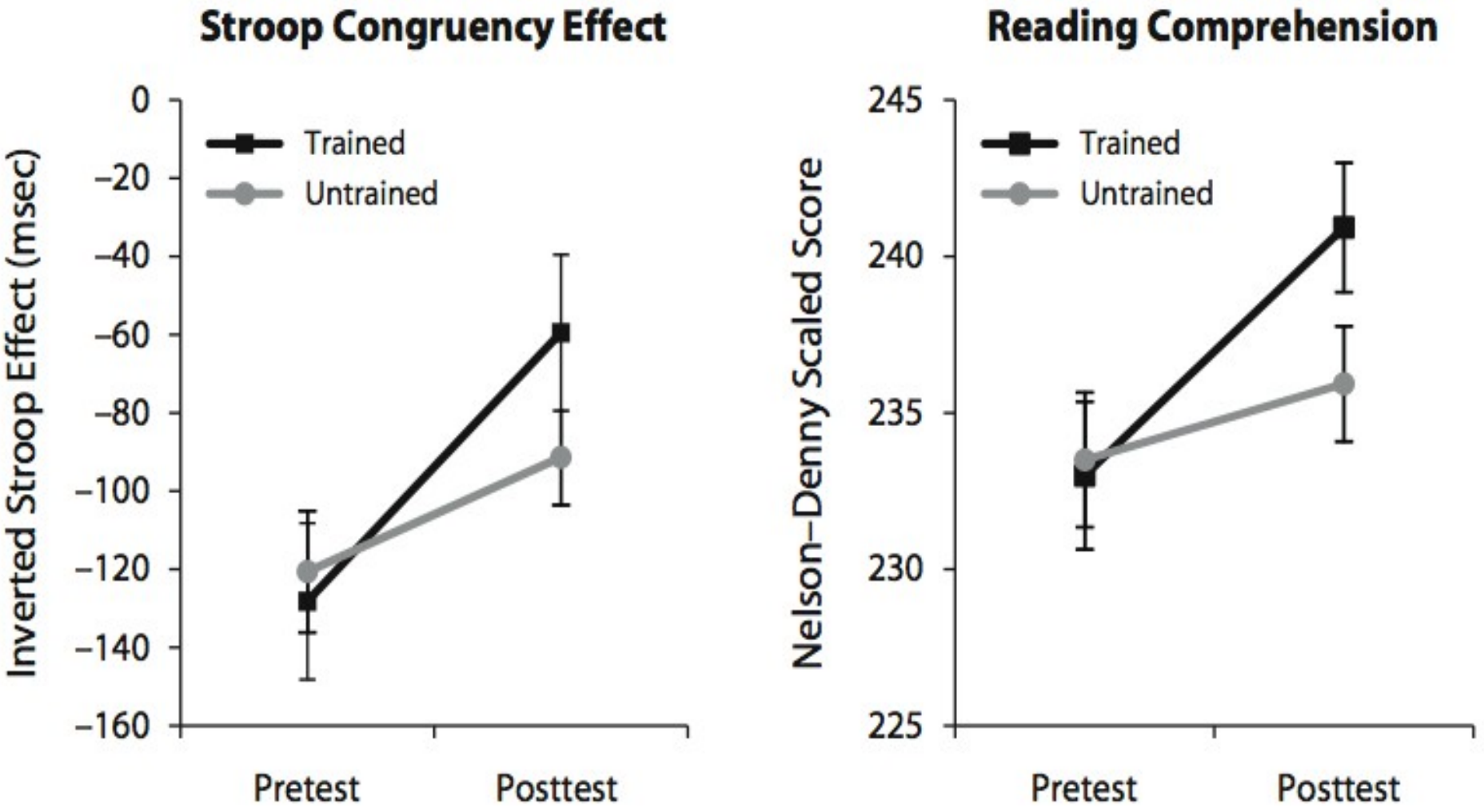


Training Working Memory



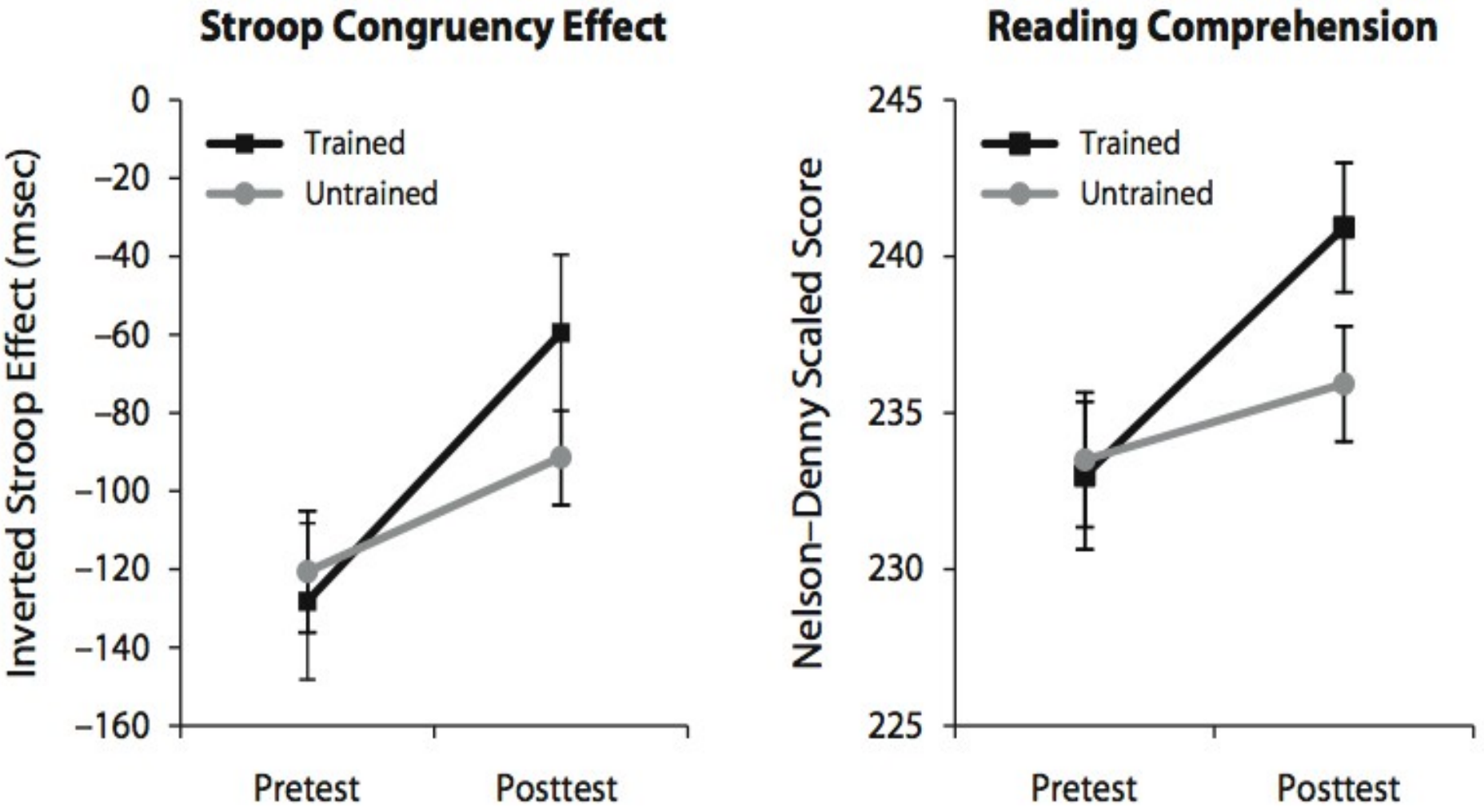
Chien and Morrison, 2010

Training Working Memory



Chien and Morrison, 2010

Training Working Memory



Chien and Morrison, 2010

Neurotechnology

- Odor cues during sleep (Rasch et al., 2007)
- Personal-genomics guided drug therapy
- Neurofeedback
- Audio-visual entrainment
- Trans-cranial electrical (!) stimulation during sleep (Marshall et al., 2006)