Brain Plasticity: Implications for Early Intervention

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Michael E. Tennenbaum Family Professor of Psychiatry & Biobehavioral Sciences, and
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David Geffen School of Medicine at UCLA
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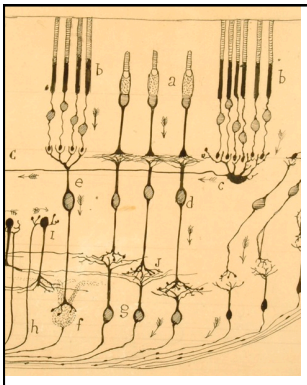
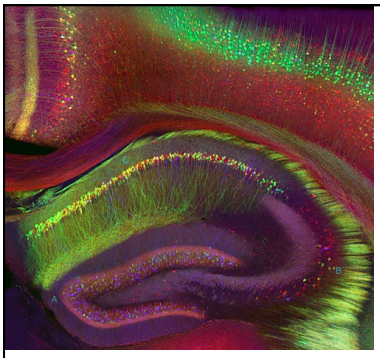


- Classical view
  - Neurogenesis restricted to prenatal period
  - Patterns of connectivity generally immutable after critical periods in development

from Portraits of the Mind:Visualizing the Brain from Antiquity to the 21st Century by Carl Schoonover

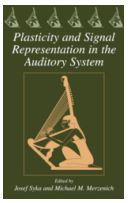


- New view
  - Neuro-genesis even in adulthood
  - Patterns of connectivity can show dramatic activity-dependent plasticity

from Portraits of the Mind:Visualizing the Brain from Antiquity to the 21st Century by Carl Schoonover

The neuroplasticity revolution

Paula Tallal



Michael Merzenich

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Implications for Intervention?

- Methods to improve neurogenesis?
- Methods to improve connectivity?
- Methods to improve cellular function?

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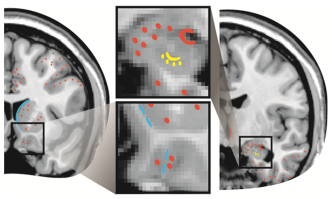
The Journal Of Neuropsychiatry and Clinical Neurosciences
psychiatryonline

From: The Dynamic Brain: Neuroplasticity and Mental Health

J Neuropsychiatry Clin Neurosci. 2012;24(2):118-124. doi:10.1176/appi.neuropsych.12050109



It is now generally accepted that adult neurogenesis occurs in two locations in all mammals, including humans.[1–5] Neurons born in the subventricular zone adjacent to the caudate (solid blue area) migrate ventrally, then rostrally (blue dashes), to be incorporated into the olfactory bulb. Neurons born in the subgranular zone of the dentate gyrus (solid yellow area) are incorporated into the dentate gyrus (yellow dots). Although controversial, there is evidence in adult primates for generation of new neurons in other ventricular regions (solid orange areas) and incorporation of new neurons into other cortical and subcortical areas (orange dots).[2,6–10]

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Ways to Promote Neurogenesis

- environmental enrichment
- exercise
- learning
- electroconvulsive shock
- chronic administration of antidepressants and other psychotropic medications
- Metformin (glucophage)

Ways to Suppress Neurogenesis

- Chronic stress
- Depression
- Illness

Differential environmental regulation of neurogenesis along the septo-temporal axis of the hippocampus

Arnaud Tanti [a,b,*], Quentin Rainer [a,b], Frederic Minier [a,b], Alexandre Surget [a,b,c], Catherine Belzung [a,b]

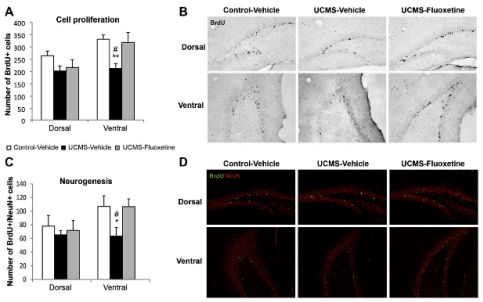
TABLE 1.

Summary of the Effects Induced by EE, 4 Weeks Fluoxetine Treatment (20 mg/kg, ip) and UCMS on Different Steps of Neurogenesis

	Ki67 (cell proliferation)		BrdU (cell survival)		DCX+/Prox1+/CR-(neuronal progenitors)		DCX+/Prox1+/CR+ (early post-mitotic immature neurons)		DCX-/Prox1+/CR+ (late post-mitotic immature neurons)	
	Septal = Temporal		Septal = Temporal		Septal = Temporal		Septal > Temporal		Septal < Temporal	
EE	↗↗	0	↗↗	0	0	0	↗	0	0	0
Fluoxetine	0	↗	0	↗	0	0	0	0	0	0
UCMS - Fluoxetine	↘↘-R	↘↘-R	↘	↘↘-R	0	↘-R	↘-R	↘-R	0	0

Arrows indicate a significant decrease (↘) or increase (↗) in the density of the respective population assessed. The number of arrows corresponds to the number of septal or temporal divisions in which changes were observed. R indicates that the UCMS-induced effects were reversed by fluoxetine treatment. (=), (>) or (<) indicate respectively similar densities in the septal and temporal divisions, higher or lower densities in the septal hippocampus.

Neuropharmacology, Volume 63, Issue 3, September 2012, Pages 374–384



Tanti et al., Neuropharmacology;Volume 63, Issue 3, September 2012, Pages 374–384

Mesenchymal Stem Cell (MSC) therapy for Autism Spectrum Disorders?

- Current treatments (behavioral, pharmacological, nutritional) at best partially effective
- MSC's in theory can both promote plasticity and reduce inflammatory states
- Shenzhen Beike Bio-Technology Co (China) completed clinical trial; no results posted (since 2011)
  - See Siniscalco et al., 2012

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 287, NO. 14, pp. 42488–42600, December 31, 2012
Published in the U.S.A.

Resveratrol Inhibits the Proliferation of Neural Progenitor Cells and Hippocampal Neurogenesis*

Received for publication, August 2, 2012, and in revised form, October 25, 2012 Published, JBC Papers in Press, October 26, 2012, DOI 10.1074/jbc.M112.406413

Hee Ra Park[1], **Kyoung Hye Kong**[1], **Byung Pal Yu**[2], **Mark P. Mattson**[3], **and Jaewon Lee**[1]

From the [1]*Department of Pharmacy, College of Pharmacy, and Molecular Inflammation Research Center for Aging Intervention, Pusan National University, Geumjeong-gu, Busan 609-735, Republic of Korea, the* [2]*Department of Physiology, The University of Texas Health Science Center at San Antonio, San Antonio, Texas 78229-3900, and the* [3]*Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, National Institutes of Health, Baltimore, Maryland 21224*

Background: Resveratrol has been suggested to have protective effects against many diseases, but its biological actions on brain in healthy subjects are unclear.
Results: Resveratrol impaired hippocampal neurogenesis and memory acquisition by AMPK activation and suppression of pCREB and BDNF.
Conclusion: Resveratrol impairs hippocampal neurogenesis and cognitive function.
Significance: Unlike DR and exercise, resveratrol can adversely affect neurogenesis and cognition.

Neuroplasticity is mostly NOT about growing new neurons!

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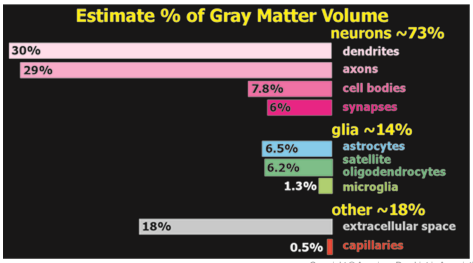
The Journal Of Neuropsychiatry and Clinical Neurosciences
psychiatryonline

From: The Dynamic Brain: Neuroplasticity and Mental Health

J Neuropsychiatry Clin Neurosci. 2012;24(2):118-124. doi:10.1176/appi.neuropsych.12050109



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The Journal Of Neuropsychiatry and Clinical Neurosciences
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From: The Dynamic Brain: Neuroplasticity and Mental Health

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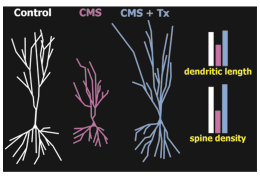

Exposure of rats to 6 weeks of unpredictable chronic mild stress (CMS; pink) induces depressive-like behaviors (e.g., anhedonia, learned helplessness) and multiple detrimental effects in the hippocampus and medial prefrontal cortex (mPFC), including decreases in neurogenesis, dendritic length, and synaptic density, as compared with control conditions (white). Both behavioral and structural deficits can be reversed by administration of antidepressants (Tx) during the final 2 weeks of CMS (CMS + Tx; blue).[1] Schematic representations of mPFC neurons under the three conditions illustrate average dendritic changes. The authors of this study noted that these results were independent of neurogenesis, suggesting that restoration of normal dendritic length and synaptic density underlie behavioral recovery.

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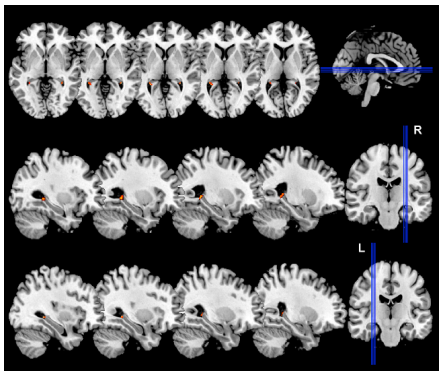

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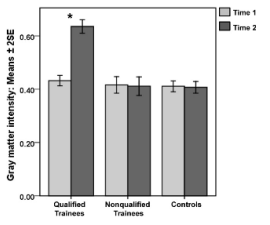
Current Biology 21, 2109–2114, December 20, 2011 ©2011 Elsevier Ltd All rights reserved DOI 10.1016/j.cub.2011.11.018

Acquiring "the Knowledge" of London's Layout Drives Structural Brain Changes



Total training time (months)	38.84 ± 7.02	35.80 ± 10.32
Training time per week (hours)[a]	34.56 ± 12.40	16.70 ± 8.21
Number of appearances[a]	15.64 ± 3.66	2.60 ± 3.45

The groups also differed on the delayed recall of the Taylor complex figure [F(2,87) = 4.38; p = 0.015], with qualified trainees being significantly **worse** at recalling the complex Figure after 30 min delay than the control participants (p=0.01).

Katherine Woollett[1] and Eleanor A. Maguire[1,*]
[1]Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, 12 Queen Square, London WC1N 3BG, UK

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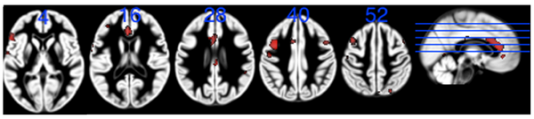
Figure 2. Reductions in GM volumes in stressed subjects.



Blix E, Perski A, Berglund H, Savic I (2013) Long-Term Occupational Stress Is Associated with Regional Reductions in Brain Tissue Volumes. PLoS ONE 8(6): e64065. doi:10.1371/journal.pone.0064065
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0064065

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PLOS | ONE

Attention Regulation and Monitoring in Meditation

- Focused attention (FA) versus open monitoring (OM) practices

Table 1. Schematic descriptions of FA and OM meditations

FA meditation	Directing and sustaining attention on a selected object (e.g. breath sensation)
	Detecting mind wandering and distractors (e.g. thoughts)
	Disengagement of attention from distractors and shifting of attention back to the selected object
	Cognitive reappraisal of distractor (e.g. 'just a thought', 'it is okay to be distracted')
OM meditation	No explicit focus on objects
	Nonreactive meta-cognitive monitoring (e.g. for novices, labeling of experience)
	Nonreactive awareness of automatic cognitive and emotional interpretations of sensory, perceptual and endogenous stimuli

– Lutz et al 2008

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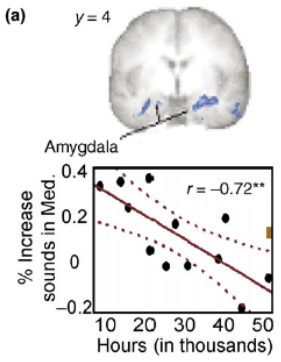
Decreased amygdala response to negative distractor sounds with greater experience in FA meditation



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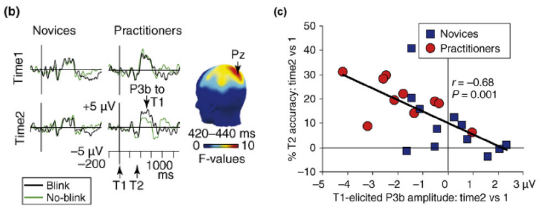
OM meditation reduces "elaborative processing" response to initial distracting material (at T1) and improves detection of targets at T2



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Neuroplasticity-Based Early Interventions

- Motor training
  - Constraint-induced movement therapy (Taub) [Sterling et al 2013 Pediatrics]
- Motivational interventions
  - Not yet proven [Tatla et al 2013 AACPDM Rev]
- Attention training in reading disability
  - Promising, EEG markers [Stevens et al 2013]
- Mindfulness training

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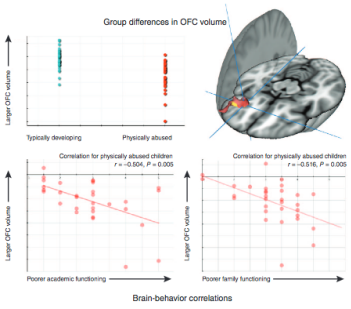
Davidson & McEwen 2012



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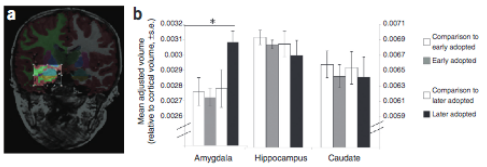
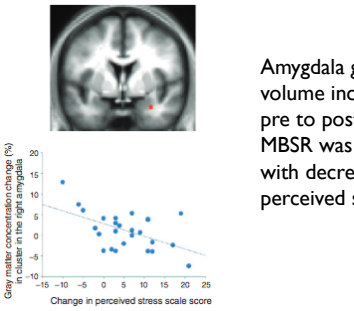
Davidson & McEwen 2012



- Amygdala volume increases associated with:
  - Maternal depression
  - Internalizing behavior
  - Anxiety

NATURE NEUROSCIENCE VOLUME 15 | NUMBER 5 | MAY 2012

Davidson & McEwen 2012



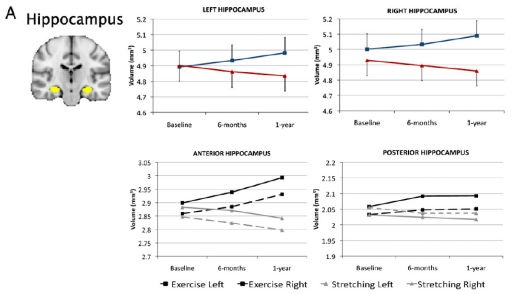
Amygdala gray matter volume increases from pre to post 8 weeks of MBSR was associated with decreases in perceived stress.

NATURE NEUROSCIENCE VOLUME 15 | NUMBER 5 | MAY 2012

Exercise training increases size of hippocampus and improves memory

PNAS | February 15, 2011 | vol. 108 | no. 7 | 3017–3022

Kirk I. Erickson[a], Michelle W. Voss[b,c], Ruchika Shaurya Prakash[d], Chandramallika Basak[e], Amanda Szabo[f], Laura Chaddock[b,c], Jennifer S. Kim[b], Susie Heo[b,c], Heloisa Alves[b,c], Siobhan M. White[g], Thomas R. Wojcicki[f], Emily Mailey[f], Victoria J. Vieira[f], Stephen A. Martin[f], Brandt D. Pence[f], Jeffrey A. Woods[f], Edward McAuley[b,f], and Arthur F. Kramer[b,c,1]



Health Psychology
2011, Vol. 30, No. 1, 91–98

0278-6133/11/$12.00 DOI: 10.1037/a0021766

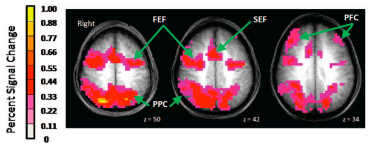
Exercise Improves Executive Function and Achievement and Alters Brain Activation in Overweight Children: A Randomized, Controlled Trial

Catherine L. Davis
Medical College of Georgia

Phillip D. Tomporowski, Jennifer E. McDowell, Benjamin P. Austin, and Patricia H. Miller
University of Georgia

Nathan E. Yanasak and Jerry D. Allison
Medical College of Georgia

Jack A. Naglieri
George Mason University



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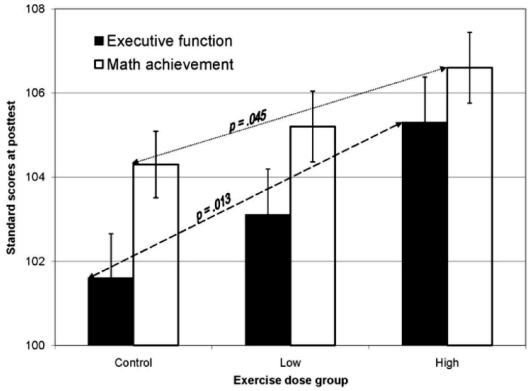
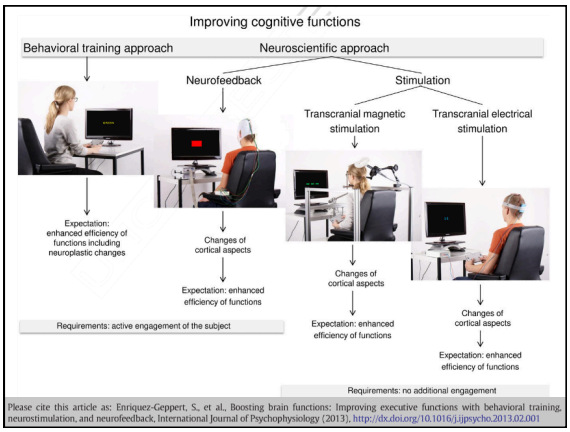
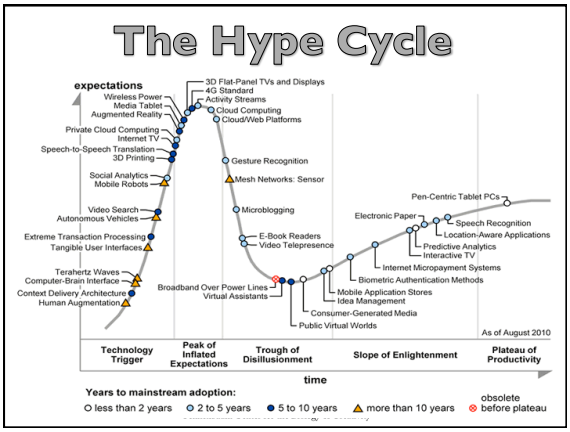
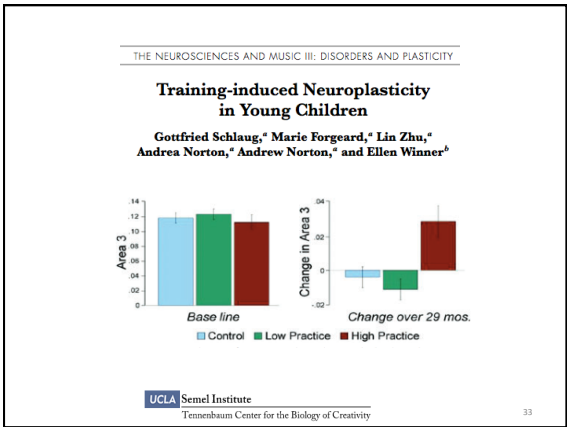
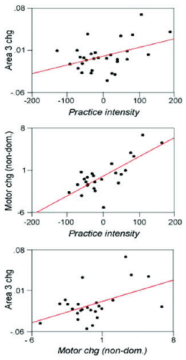




Please cite this article as: Enriquez-Geppert, S., et al., Boosting brain functions: Improving executive functions with behavioral training, neurostimulation, and neurofeedback, International Journal of Psychophysiology (2013), http://dx.doi.org/10.1016/j.ijpsycho.2013.02.001







- Prior to age 7
- Note: area 3 connects motor, premotor cortices
- Practice Groups: Hi (2-5 hrs/wk) and Low (1-2 hrs/wk)

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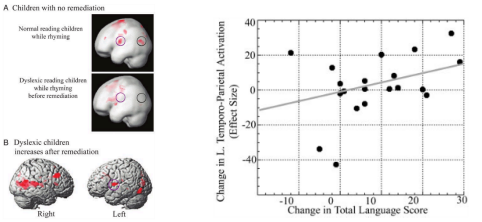
Neural deficits in children with dyslexia ameliorated by behavioral remediation: Evidence from functional MRI

Elise Temple[†‡], Gayle K. Deutsch[§], Russell A. Poldrack[¶], Steven L. Miller[‖], Paula Tallal[†††], Michael M. Merzenich[‡‡], and John D. E. Gabrieli[†§]



2860–2865 | PNAS | March 4, 2003 | vol. 100 | no. 5

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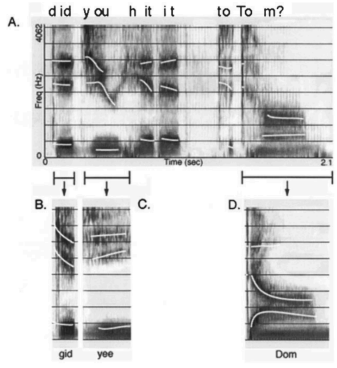

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Meta-Analysis of Fast Forword

THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY
ACAMH
Journal of Child Psychology and Psychiatry 52:3 (2011), pp 224–235 doi:10.1111/j.1469-7610.2010.02329.x

A systematic meta-analytic review of evidence for the effectiveness of the 'Fast ForWord' language intervention program

Gemma K. Strong,[1] Carole J. Torgerson,[2] David Torgerson,[1] and Charles Hulme[1]
[1]University of York, UK; [2]University of Birmingham, UK

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Strong et al 2011 Findings

- Only 6 studies satisfied criteria to be included in the meta-analysis
- Results: No significant effect of Fast ForWord on any outcome measure relative to active or untreated control groups
- Conclusions: There is no evidence from the analysis carried out that Fast ForWord is effective as a treatment for children's oral language or reading difficulties

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Scientific Learning replies

- Strong et al were overly selective, picking only 6 out of almost 200 studies
- Other studies (dissertations, not RCT's, or where groups were not equal at baseline) may be important
- Implementations were suboptimal in the 6 studies selected
- Selected studies did not include newer (post-2005) innovations in the programs

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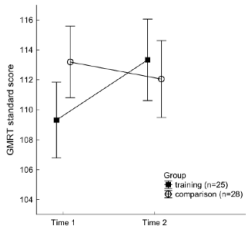
frontiers in PSYCHOLOGY
ORIGINAL RESEARCH ARTICLE
published: 25 March 2013
doi: 10.3389/fpsyg.2013.00137

Neuroplasticity-based cognitive and linguistic skills training improves reading and writing skills in college students

*Beth A. Rogowsky, Pericles Papamichalis, Laura Villa, Sabine Heim and Paula Tallal **



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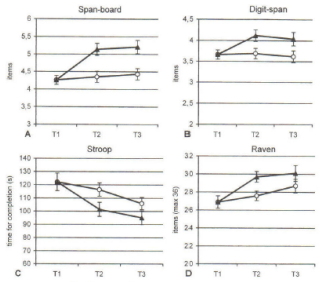
Attention and Working Memory Training

Klingberg et al



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nature neuroscience

Increased prefrontal and parietal activity after training of working memory

Pernille J Olesen, Helena Westerberg & Torkel Klingberg

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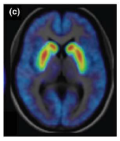
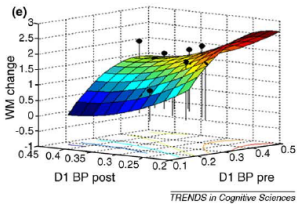
WM Training Effect on D1 Dopamine Receptor Binding





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Developmental Psychology

0012-1649/12/$12.00 DOI: 10.1037/a0028228

Is Working Memory Training Effective? A Meta-Analytic Review

Monica Melby-Lervåg
University of Oslo

Charles Hulme
University College London and University of Oslo

- reliable, short-term improvements - verbal and nonverbal tasks
- verbal WM: short-term near-transfer effects not sustained ~9 months
- visuospatial WM: modest training effects maybe 5 months
- No evidence for generalization to verbal ability, word decoding, or arithmetic, even immediately after training.
- Non-verbal reasoning: small but reliable improvement immediately after training
- Attention (Stroop): small to moderate effect immediately after training, zero at follow-up

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Memory Training
Engvig et al., 2010

- Method of Loci
  - Visualize a series of mental landmarks (locations on a route)
  - Improves serial recall in older adults
  - 25 minutes of training, 5 days per week, for 8 weeks
  - Yielded significant improvement in source memory (was word from 1st, 2nd, or 3rd segment of 15 word list)

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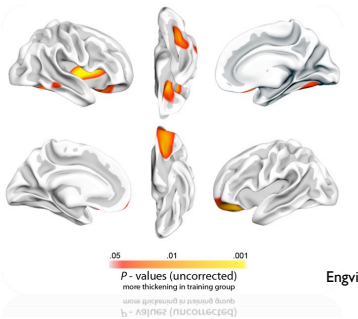
Brain Training Increases Cortical Thickness



Engvig et al 2010

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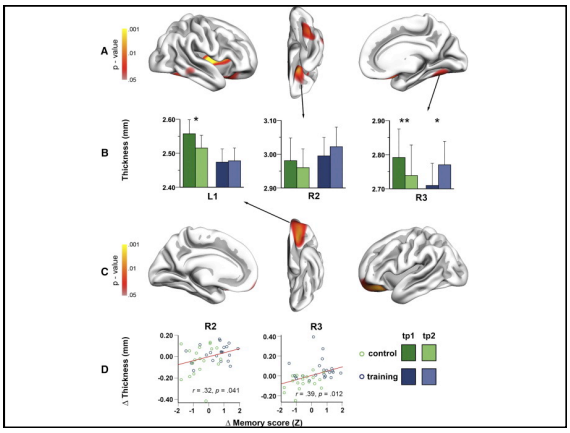
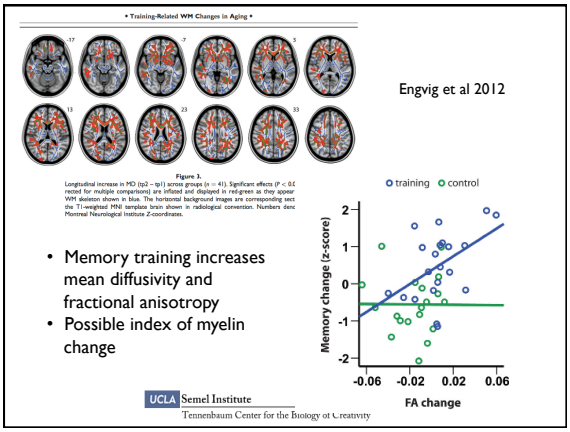

A
P - value
001
01
05
B
Thickness (mm)
2.60
2.50
2.40
L1
3.10
3.00
2.90
R2
2.90
2.80
2.70
R3
C
P - value
D
Δ Thickness (mm)
R2
R3
r = .32, p = .041
r = .39, p = .012
tp1 tp2
control
training
Δ Memory score (Z)


• Training-Related WM Changes in Aging •
Engvig et al 2012
training
control
Memory change (z-score)
FA change
-0.06
-0.02
0.02
0.06
• Memory training increases mean diffusivity and fractional anisotropy
• Possible index of myelin change
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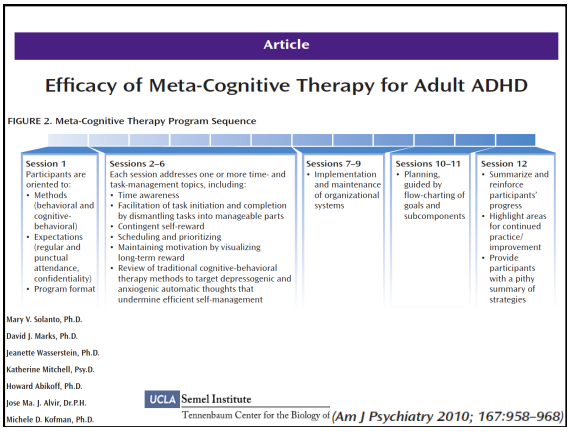
Article
Efficacy of Meta-Cognitive Therapy for Adult ADHD
FIGURE 2. Meta-Cognitive Therapy Program Sequence
Session 1
Participants are oriented to:
• Methods (behavioral and cognitive-behavioral)
• Expectations (regular and punctual attendance, confidentiality)
• Program format
Sessions 2–6
Each session addresses one or more time- and task-management topics, including:
• Time awareness
• Facilitation of task initiation and completion by dismantling tasks into manageable parts
• Contingent self-reward
• Scheduling and prioritizing
• Maintaining motivation by visualizing long-term reward
• Review of traditional cognitive-behavioral therapy methods to target depressogenic and anxiogenic automatic thoughts that undermine efficient self-management
Sessions 7–9
• Implementation and maintenance of organizational systems
Sessions 10–11
• Planning, guided by flow-charting of goals and subcomponents
Session 12
• Summarize and reinforce participants' progress
• Highlight areas for continued practice/improvement
• Provide participants with a pithy summary of strategies
Mary V. Solanto, Ph.D.
David J. Marks, Ph.D.
Jeanette Wasserstein, Ph.D.
Katherine Mitchell, Psy.D.
Howard Abikoff, Ph.D.
Jose Ma. J. Alvir, Dr.P.H.
Michele D. Kofman, Ph.D.
UCLA Semel Institute
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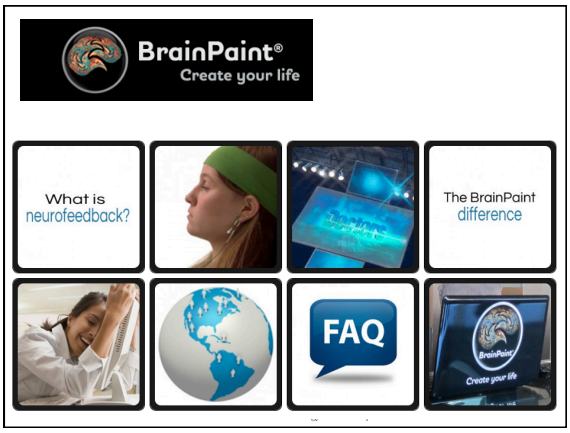
(Am J Psychiatry 2010; 167:958–968)



Neurofeedback applications

- Attention Deficit/Hyperactivity Disorder (ADHD)
- Epilepsy
- Autism spectrum disorders
- Headaches
- Insomnia
- Anxiety
- Substance abuse
- Traumatic Brain Injury (TBI)

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Some NF Targets

- Sensory Motor Rhythm (SMR)
  - Low beta range (12-15 Hz)
  - High amplitude at rest (immobility)
  - Low amplitude during motor activity
  - Reflects "brakes on" (good for ADHD?)
- Theta/Beta Ratio (TBR)
- Slow Cortical Potentials (SCPs)
  - Contingent negative variation (CNV) reflects preparedness to respond

Recent reviews of Neurofeedback for ADHD

- Arns et al., 2009
  - ES for controlled trials: inattention (d=.81); hyperactivity (d=.40); impulsivity (d=.69)
  - Conclusion: efficacious and specific (Level 5)
- Lofthouse et al., 2012
  - 14 studies, 1994-2010
  - Most used theta/beta NF
  - Effect size d=.69
  - Conclusion: probably efficacious
- Loo & Makeig, 2012
  - Theta/beta ratio markedly heterogeneous
  - Neurofeedback trials lacking adequate placebo controls

Neurofeedback for autism spectrum disorders?

Table 2 ASD neurofeedback case studies

Author	QEEG pattern	NF protocol	Improvements
Cowan and Markham (1994)	High alpha and theta	Suppress 4–10, enhance 16–20	Attention, motor behaviors, impulsivity, socialization, TOVA
Sichel et al. (1995)	High theta, low Beta	Suppress theta, enhance SMR	Socialization, self-stim behaviors, speech
Thompson and Thompson (1995)	High theta, low SMR	Suppress theta, enhance SMR P4-T4	Behaviors, social, academic
Ibric and Hudspeth (2003)	High beta, hypocoherence	QEEG based	Behavior, sleep, movements
Thompson and Thompson (2003a)	High theta, low beta/SMR	QEEG based; suppress theta, enhance 13–15 C4	EEG patterns, IQ, social interactions, alertness
Limsila et al. (2004)	Not measured	HEG frontally	Grades
Linden (2004)	High beta, high delta, low voltage, abnormal EEG, hypocoherence	QEEG based	Attention, impulsivity, hyperactivity, EEG patterns, communication, socialization
Scolnick (2005)	Abnormal patterns	EEG based	Behaviors

+5 controlled group studies; N = 180 total; level 2 "possibly efficacious"?

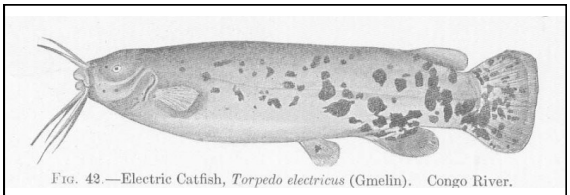

FIG. 42.—Electric Catfish, *Torpedo electricus* (Gmelin). Congo River.

- Scribonius Largus (the physician of the Roman Emperor Claudius), [used] a live torpedo fish over the scalp to deliver a strong electric current [to] relieve a headache.
- In the 11th century, Ibn-Sidah, a Muslim physician, suggested using a live electric catfish for the treatment of epilepsy.

From Brunoni et al., Brain Stimulation 2012

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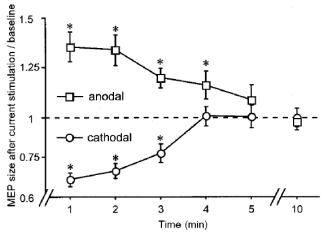
Journal of Physiology (2000), **527.3**, *pp.*633–639

Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation

M. A. Nitsche and W. Paulus



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Exp Brain Res (2005) 166: 23–30
DOI 10.1007/s00221-005-2334-6

RESEARCH ARTICLE

Felipe Fregni · Paulo S. Boggio · Michael Nitsche
Felix Bermpohl · Andrea Antal · Eva Feredoes
Marco A. Marcolin · Sergio P. Rigonatti
Maria T.A. Silva · Walter Paulus
Alvaro Pascual-Leone

Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory

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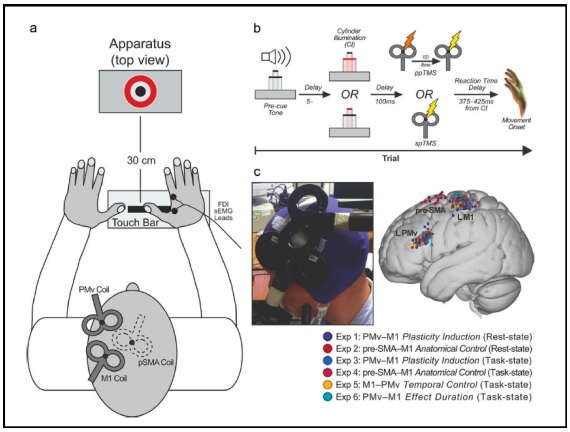

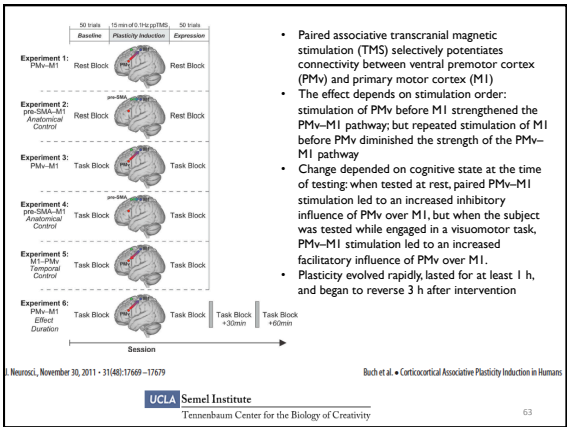

- Paired associative transcranial magnetic stimulation (TMS) selectively potentiates connectivity between ventral premotor cortex (PMv) and primary motor cortex (M1)
- The effect depends on stimulation order: stimulation of PMv before M1 strengthened the PMv–M1 pathway; but repeated stimulation of M1 before PMv diminished the strength of the PMv–M1 pathway
- Change depended on cognitive state at the time of testing: when tested at rest, paired PMv–M1 stimulation led to an increased inhibitory influence of PMv over M1, but when the subject was tested while engaged in a visuomotor task, PMv–M1 stimulation led to an increased facilitatory influence of PMv over M1.
- Plasticity evolved rapidly, lasted for at least 1 h, and began to reverse 3 h after intervention

J. Neurosci., November 30, 2011 • 31(48):17669–17679 Buch et al. • Corticocortical Associative Plasticity Induction in Humans

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63

- Prediction is difficult, especially when it comes to the future…
  - Attributed (falsely?) to Yogi Berra

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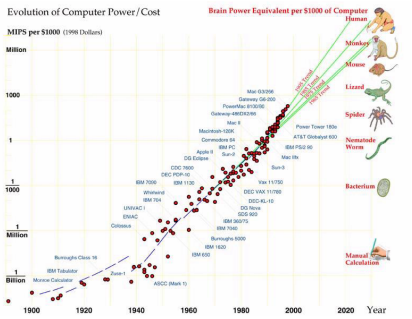
Is the singularity near?



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www.cscexecutiveexchange.com/Ray_Kurzweil.pdf

Nanobots & Neurodust

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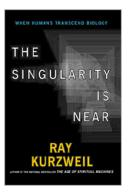

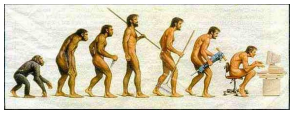

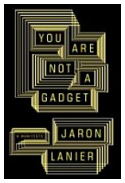

The Singularity…will enable us to transcend our biological limitations and amplify our creativity.

Your experience is ultimately up to you, not the tools.

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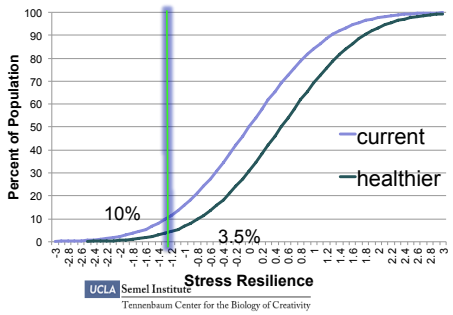
The 90% Solution



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Healthy.ucla.edu

MIND WELL

Promoting wellness of mind, brain and spirit, fostering creativity, and enhancing social connectedness throughout the UCLA community.

I

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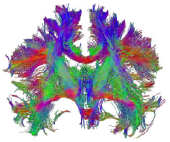
UCLA Healthy Campus Initiative's MIND WELL program presents:



UCLA Brain Gym:

flex your neurons.

Given recent discoveries showing marked neuroplasticity and research evidence suggesting that training may change both brain structure and function, our new facility aims to provide UCLA students, staff and faculty access to emerging cognitive training methods:

brain training
- LUMOSITY
- POSIT SCIENCE
- COGMED
- HAPPY NEURON
- ANTI-AGING GAMES
- NEUROBIC

neurofeedback, EEG, sleep staging
- ZEO
- EMOTIV
- MYNDPLAY

personal brain management resources
- SHARP BRAINS
- SUPERMEMO

- learn about state-of-the-art brain training methods and tools
- gain hands-on experience with brain-training software and hardware
- interact with knowledgeable "brain trainers" to address individual goals & optimal use of brain training systems.

To schedule an apt, email BrainGymUCLA@gmail.com
with: your name, email, and UCLA status (student/staff/faculty)

+ check our Google Calendar
to see our hours of operation for a drop-in session!

Brain image from Martinos Center for Biomedical Imaging, Randy Buckner, PhD and the Laboratory of Neuro Imaging, "The Human Connectome Project"

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co-sponsored by the UCLA Visual and Performing Arts Education (VAPAE) and the Max H. Gluck Foundation

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the biology of creativity • neurophysiology of flow/dissociation
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in art, music, drama, dance/movement, poetry therapy

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FREE for UCLA students, faculty, staff, and the public
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---

brain-mind-wellness

personal brain management

mindfulness practice & theory

integrative East-West medicine

UCLA Summer Institute – 2013

U-Reviews

- Academic reviews of well-being apps
- University-based, student-faculty partnership
- Health/Psych professors provide oversight and didactic input on science & design issues (reliability, validity, etc.)
- SRP program – students join teams dedicated to specific app domains
- Develop narrative summary and review criteria, including "snake oil factor"
- Examples:
  - Brain-Training
  - Sleep
  - Heart Rate Variability
  - Meditation

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Many thanks!

rbilder@mednet.ucla.edu

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