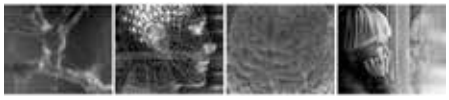
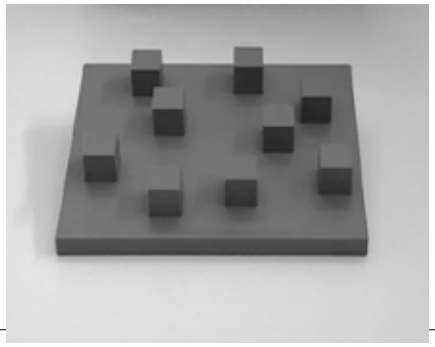


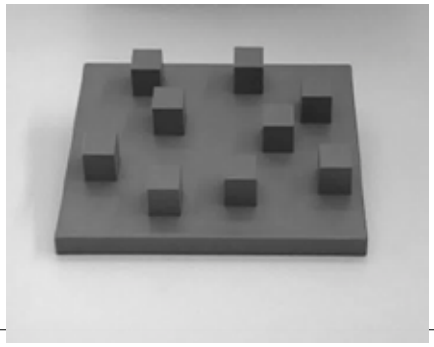
The neuroscience of WM capacity and training

Torkel Klingberg
Dept. Neuroscience
Karolinska Institutet

Overview

- Neural basis of working memory
- Working memory training
- Transfer to attention
- WM, mathematics and development



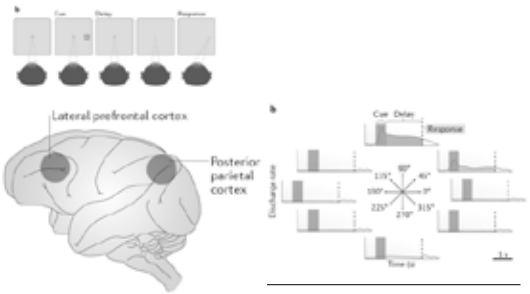


WM relevance

WM capacity correlates with:
- Attention
- Non-verbal reasoning ability
- Mathematics
- Reading

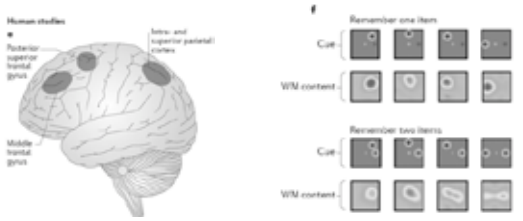
WM impairments
- ADHD
- Children born prematurely
- In children after cancer treatment
- Traumatic brain injury

WM in non-human primates

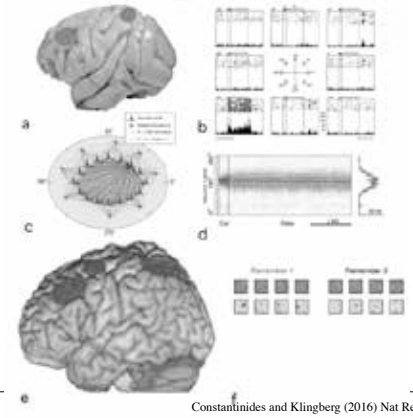


Fuster and Alexander, 1971; Kubota and Niki, 1971 Funahashi et al. 1989

Visuo-spatial WM

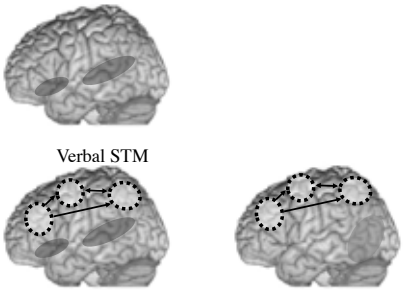


Adapted from Sprague et al. 2014



Constantinides and Klingberg (2016) Nat Rev Neurosci

Human WM



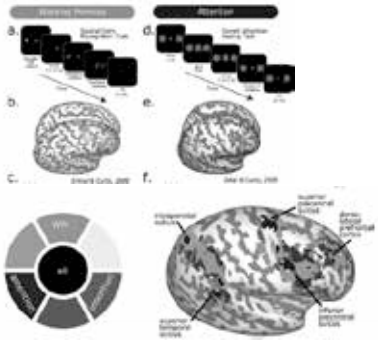
Verbal STM

Verbal WM

Visuospatial WM and STM

Klingberg et al. 1996; Wager and Smith 2003; Curtis D'Esposito 2003; Linden 2007

Attention and WM



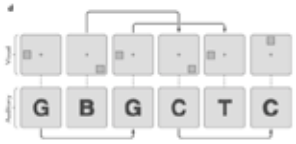
Ikkai and Curtis (2011)
Jerde et al. (2012)

Inattention in ADHD and WM

- Children with ADHD have impaired working memory
  - Kempton et al. 1999
  - Barnett et al. 2001
  - Westerberg et al. 2004
  - Willcut 2005
  - Martinussen et al. 2005
- WM deficits specifically linked to inattention
  - Lui and Tannock 2007
- Inattention deficits predict poor academic performance
  - Pingault et al. 2011
- WM deficits predict academic performance
  - Gathercole et al. e.g. 2003, 2004

Working memory training

• Klingberg et al. 2002, 2005	Cogmed. Visuo-spatial WM
• Jaeggi et al. 2008	Dual n-back
• Dahlin et al. 2008, Li et al. 2008	N-back lists
• Chein and Morrison, 2010	Complex WM tasks



Cogmed WM training
(Klingberg et al. 2002, 2005)

- Repeated performance with feedback (no strategy instruction)
- Adaptive difficulty close to capacity limit
- Mainly visuo-spatial WM tasks
- Intense and extensive
  - → 35 min per day
  - → 5 days/week
  - → 5 weeks
- TK has no associations with Cogmed or Pearson

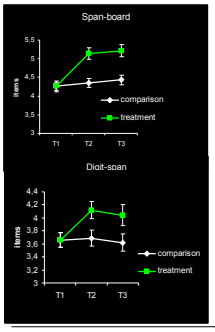
Computerized Training of Working Memory in Children With ADHD—A Randomized, Controlled Trial

TORKEL KLINGBERG, M.D., Ph.D., ELISABETH FERNELL, M.D., Ph.D., PERNILLE J. OLESEN, M.Sc., MATS JOHNSON, M.D., PER GUSTAFSSON, M.D., Ph.D., KERSTIN DAHLSTRÖM, M.D., CHRISTOPHER G. GILLBERG, M.D., Ph.D., HANS FORSSBERG, M.D., Ph.D., and HELENA WESTERBERG, L.P., PhD

Treatment
- Adaptation of difficulty level

Control
- Easy trials (level 2)

Klingberg et al. 2005



Span-board

Digit-span

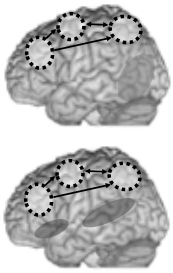
”2 8 4 7 2 9”

”9 2 7 4 8 2”

Klingberg et al. 2005

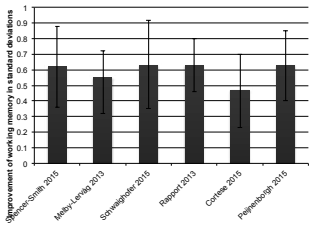
Cogmed WM training transfer

- Visuo-spatial WM tasks
  Klingberg et al. 2002; 2005; Thorell et al. 2008
- “Complex” WM tasks
  Holmes et al. 2009; Holmes et al. 2010; Bergman-Nutley et al. 2012
- Cross modal
  Thorell et al. 2009
- Instructions
  Holmes et al. 2009;
  Bergman-Nutley and Klingberg (2014)



Improvement of WM capacity after training
d = 0.6

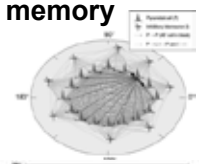
Meta-analyses of WM improvements after training

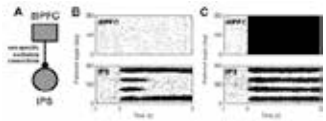


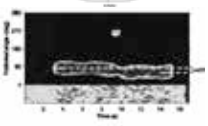
Dual aims of WM training

- Experimental tool to study brain plasticity associated with higher cognitive functions
- Potentially a useful intervention

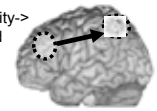
Computational models of persistent activity as working memory







Functional connectivity->
Higher firing rate and
Increased capacity



Compte et al. (2000)
Constantinidis, Wang (2004)

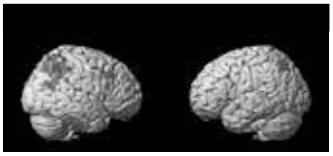
Edin et al. (2007) JOCN
Edin et al. (2009) PNAS

Neural correlates of WM training

Experiment 1

fMRI

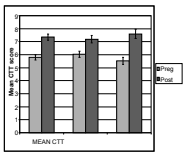
WM training



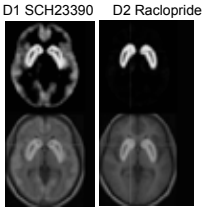
Olesen, Westerberg, Klingberg (2004) Nature Neurosci.

Dopamine and WM training

- 13 healthy, young adults
- 5 weeks of training (Klingberg et al., 2005)
- Measurement of verbal and visuospatial WM
- fMRI during performance of WM tasks
- PET of D1 and D2 binding, before and after



D1 SCH23390 D2 Raclopride

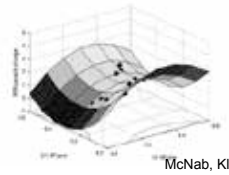


McNab, Klingberg et al. Science 2009

DA1 BP change vs WM change

Linear model:
$y_2 - y_1 = (a + \beta_1 x_2) - (a + \beta_1 x_1) = \beta_1 (x_2 - x_1)$ $r^2=0.42$; p=0.016

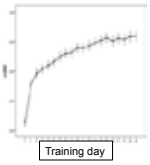
Quadratic model:
$y_2 - y_1 = (a + \beta_1 x_2 + \beta_2 (x_2)^2) - (a + \beta_1 x_1 + \beta_2 (x_1)^2)$ $r^2=0.75$; p=0.001
β_1 estimate p = 0.002
β_2 estimate p = 0.005



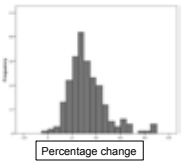
McNab, Klingberg et al. Science 2009

Genetics of cognitive plasticity

(Söderqvist et al. (2013) J Cog Neursci



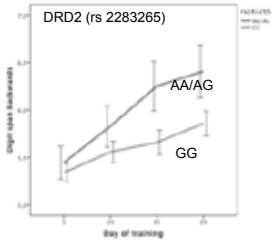
Training day



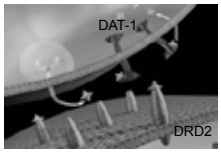
Percentage change

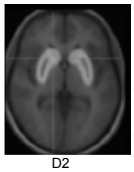
N = 251
Age = 6 – 16
Training 24.7 days

DRD2 (rs 2283265)



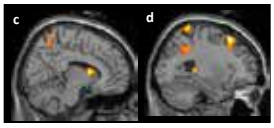
(Söderqvist et al. (2013) J Cog Neursci



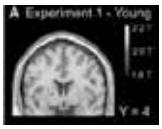


D2

DAT-1

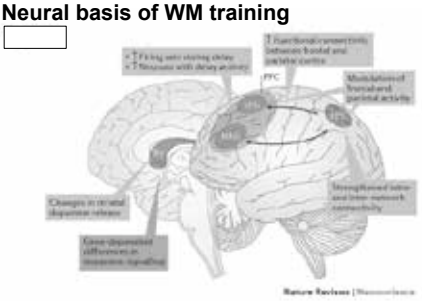


Olesen et al. 2004



Dahlin et al. 2008
Bäckman et al. 2011

Neural basis of WM training



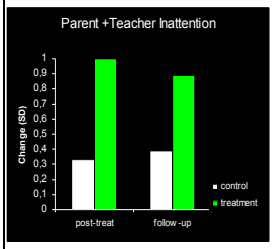
Constantinides and Klingberg (2016)

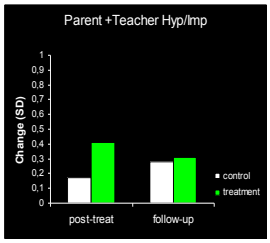
Dual aims with WM training

- Experimental tool to study brain plasticity associated with higher cognitive functions

- Potentially a useful intervention
  - Attention
  - IQ
  - Mathematics, reading, …

WM training in children with ADHD



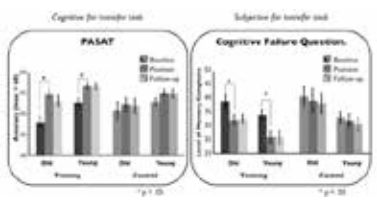


Effect size (Cohen's delta) inattention = 0.7

Klingberg et al. (2005)

WM training in old and young healthy adults

Young 20-30 years; n=50
Old 60-70 years; n=50
Randomized, blinded, controlled

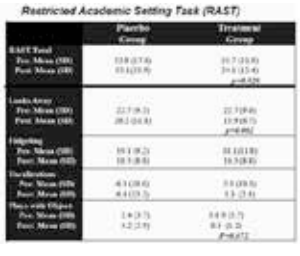


Brehmer et al. 2012

WM training in ADHD – RAST

Children with ADHD (N = 26)

Restricted Academic Setting Task



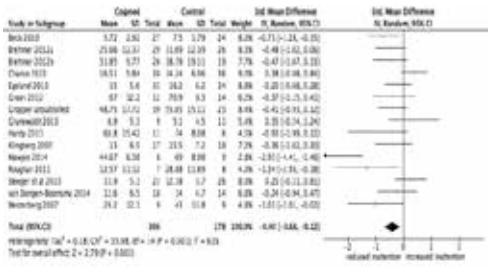
Green, Schweitzer et al. (2012)

Long-term far-transfer effects of working memory training in children with ADHD: a randomized controlled trial

Children with ADHD (N = 66)
Randomized
WM training
non-adaptive training
BRIEF

Computerized Cognitive Training for Amelioration of Cognitive Late Effects Among Childhood Cancer Survivors: A Randomized Controlled Trial

Effect of CWMT training on attention
d = 0.4



Spencer-Smith and Klingberg, 2015

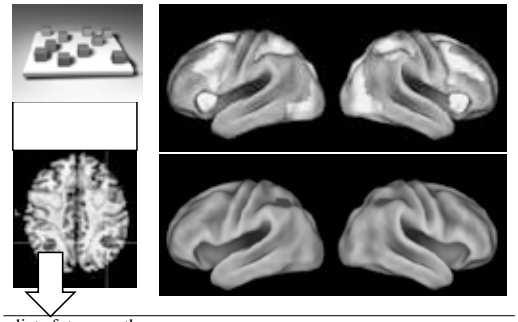
WM and mathematics

Working memory capacity is correlated with arithmetical performance both in children with and without known learning difficulties
HenryandMacLean2003;Kyttäläetal.2003;MayberyandDo2003; Alloway et al. 2005, 2009, Geary et al. 2009; Meyer et al. 2010

Working memory capacity predict future development of arithmetical ability
Jarvis and Gathercole 2003; Gersten et al. 2005; Bull et al. 2008; Dumontheil and Klingberg 2012

Working memory and reasoning ability contribute partly unique variance to predict arithmetics
Alloway and Alloway 2010, Dumontheil and Klingberg 2012

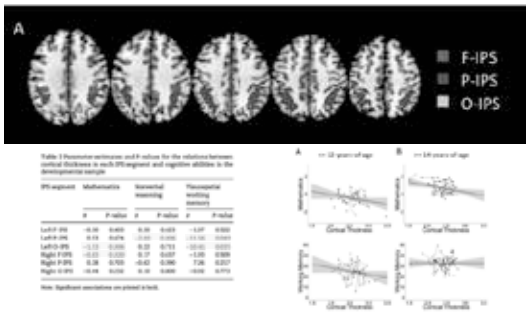
WM activity predicts mathematics



predicts future math scores

Dumontheil and Klingberg, 2011

Development of Math and WM



Schel and Klingberg (2016) Cerebral Cortex

Effect of WM training on mathematics

Author	Participants	N	Effect size (d)
Dahlin et al. 2013	Inattention	62	0.69 *
Holmes et al. 2013	Low achievers	75	0.60 *
Holmes et al. 2009	Low WM	22	0.11 ns
Dunnings et al. 2013	Low WM	60	0.30 ns
Bergman-Nutley 2014	Inattention	304	0.3 *
Roberts 2016	Low WM	452	0 ns

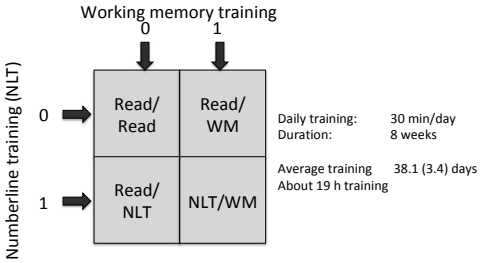
37

Combined WM and numberline training

Federico Nemmi, Elin Helander, Ola Helenius, Rita Almeida, Martin Hassler, Pekka Räsänen, Torkel Klingberg

Nemmi et al. (2016)

Combined WM and numberline training



Daily training: 30 min/day
Duration: 8 weeks

Average training 38.1 (3.4) days
About 19 h training

Age: 6-year olds (80.3 months, SD=3.5)
Group 1: Typically developing children (n = 210) Class-based training
Group 2: Children with low WM (n = 98) Individual training

Symbol
Place on numberline
Length (vector)
Counting of object

Pre- and post measures

Working memory
- Span-board forward
- Span-board backwards
- Grid task (visuo-spatial WM)

} Standardized and averaged to one composite WM measure

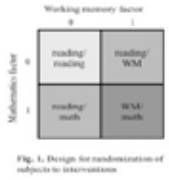
Mathematics
- WISC verbal arithmetics
- Addition (without numberline)
- Subtraction (without numberline)

} Standardized and averaged to one composite Math measure

Magnetic resonance imaging (n=58)
- functional MRI during WM performance
- structural MRI

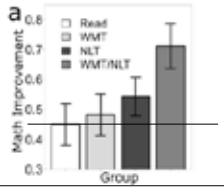
Results

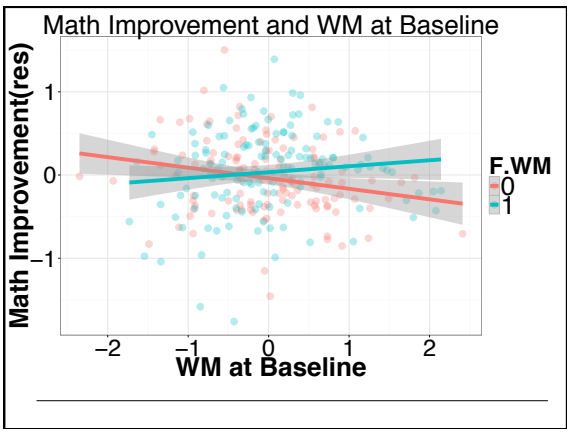
$$Math\ Performance\ post = \beta_0 + \beta_1 WMT + \beta_2 NLT + \beta_3 Math_{bl} + \beta_4 WM_{bl} + \beta_5 WMT\ x\ NLT + \beta_6 WMT\ x\ WM_{bl} + \beta_7 NLT\ x\ Math_{bl} + \beta_8 Cohort + \beta_9 Sex + \beta_{10} Population + \beta_{11} Age\ \varepsilon$$

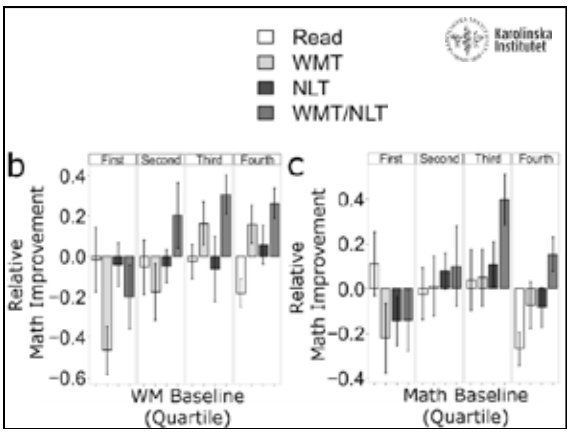


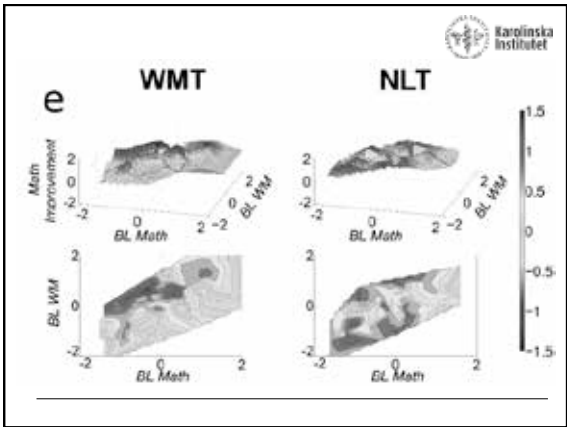
Results

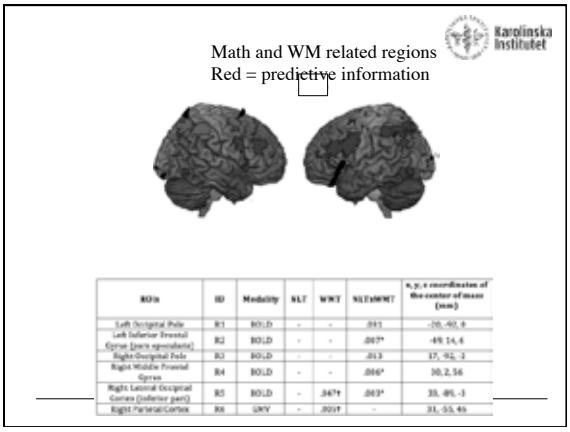
$$Math\ Performance\ post = \beta_0 + \beta_1 WMT + \beta_2 NLT + \beta_3 Math_{bl} + \beta_4 WM_{bl} + \beta_5 WMT\ x\ NLT + \beta_6 WMT\ x\ WM_{bl} + \beta_7 NLT\ x\ Math_{bl} + \beta_8 Cohort + \beta_9 Sex + \beta_{10} Population + \beta_{11} Age\ \varepsilon$$



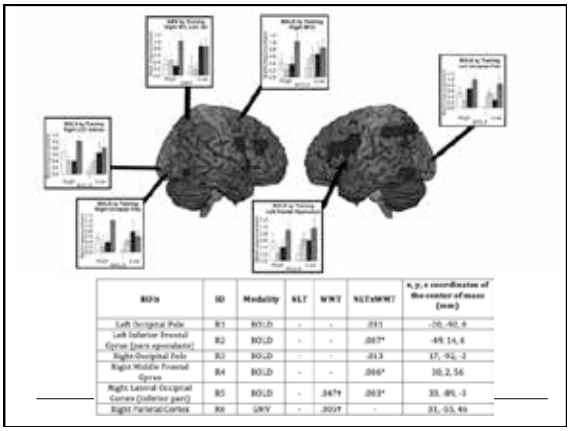


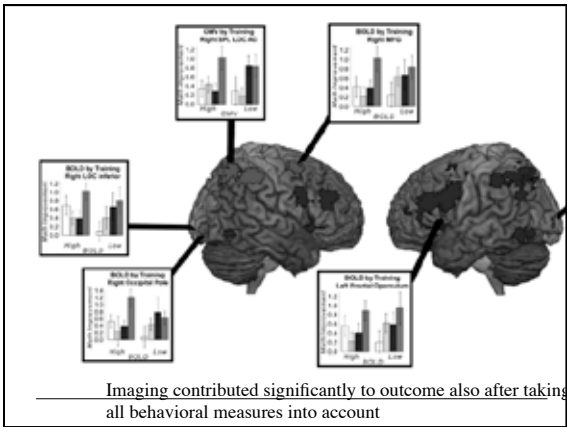


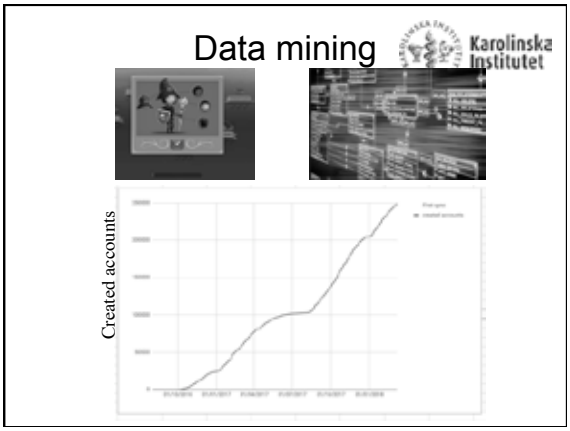




ROIs	ID	Modality	NLT	WMT	NLTxWMT	x, y, z coordinates of the center of mass (mm)
Left Occipital Pole	R1	BOLD	-	-	.011	-20, -92, 8
Left Inferior Frontal Gyrus (pars opercularis)	R2	BOLD	-	-	.007*	-49, 14, 4
Right Occipital Pole	R3	BOLD	-	-	.013	17, -92, -2
Right Middle Frontal Gyrus	R4	BOLD	-	-	.006*	30, 2, 56
Right Lateral Occipital Cortex (inferior part)	R5	BOLD	-	.047†	.003*	33, -89, -3
Right Parietal Cortex	R6	UNV	-	.001†	-	31, -53, 46







Conclusions

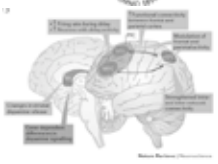
Working memory training

improves working memory, e.g. remembering instruction — d = 0.6 (0.5-0.7)

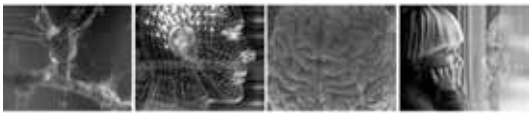
improve inattention in everyday life — d = 0.4 (0.3-0.5)

effect for other tasks, i.e. mathematics, IQ, reading, grades, are still inconclusive

Future directions



- Better measures of inattention
- Larger populations in training studies
- Combined training (WMT+ cog, TMS, drugs, physical,⋯)
- Individualized training
- Continued role of neuroscience



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Thanks!

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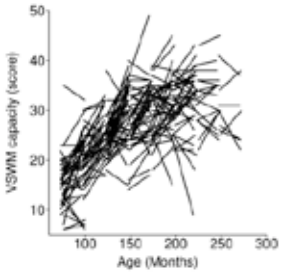
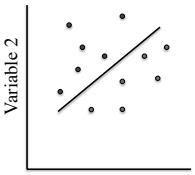
Predicting future WM



Support vector regressior



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Predicting WM two years later (T2)

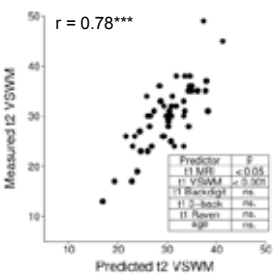
I.

Predictor	*r*	*p*
t1 BOLD	0.52	<0.001***
t1 FA	0.58	<0.001***
t1 GMD	0.29	<0.05*

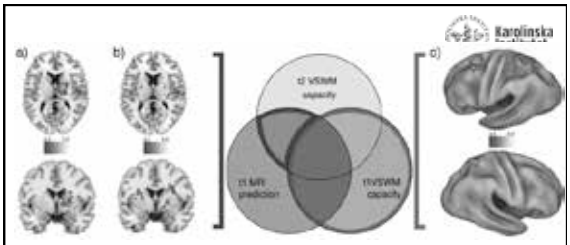
II. Combining MRI predictions in a multiple regression:

Predictor	*p*
t1 BOLD	<0.05*
t1 FA	<0.01**
t1 GMD	ns.

Model r = 0.64***

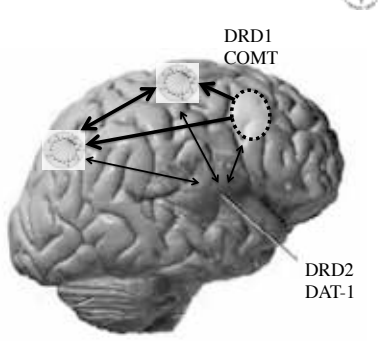


III. Combine MRI prediction with baseline (T1) behavior

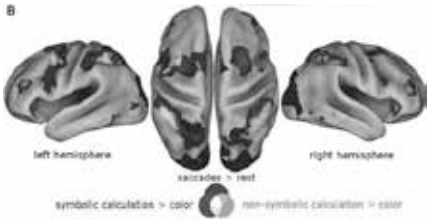


- Fronto-parietal activity correlates with current WM capacity
  - Klingberg et al. 2002
  - Kwong et al. 2002
  - Crone et al. 2004
- Basal ganglia-thalamus, and white matter structure predicts future WM capacity

Ullman, Almeida, Klingberg (2014) J Neurosci



Arithmetics and attention



Knops et al. 2009