Brain Injury
MedTech Co-operative

NHS
National Institute for Health Research

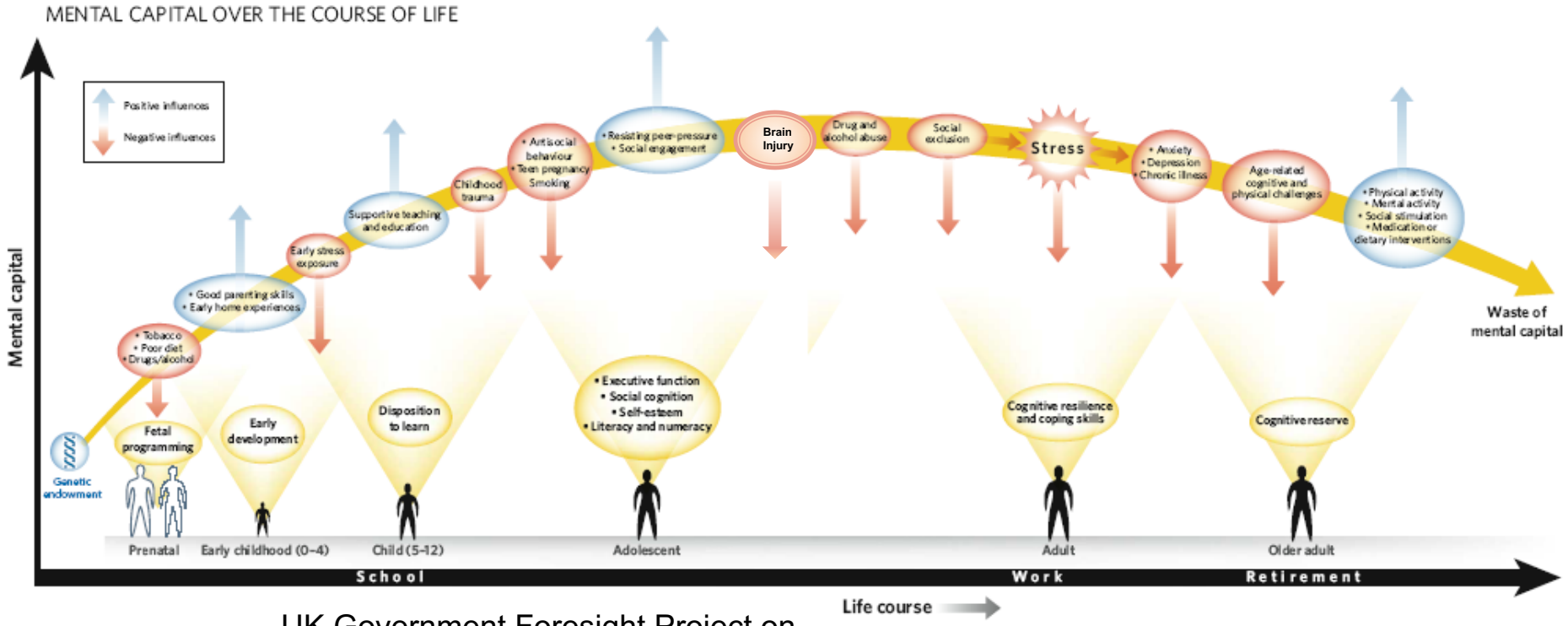
Cognition & Mental Health

MIC Theme 10

Professor Barbara Sahakian

Factors that promote good brain health and wellbeing (blue) and factors that detract from good brain health and wellbeing (red) across the lifespan

Mental capital encompasses both cognitive and emotional resources, and resilience in the face of stress



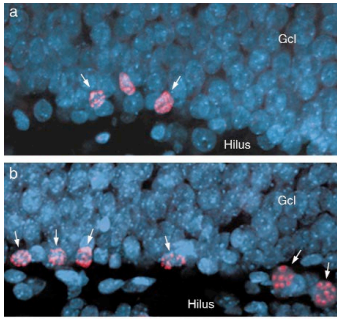
UK Government Foresight Project on Mental Capital and Wellbeing

Beddington, Cooper, Field, Goswami, Huppert, Jenkins, Jones, Kirkwood, Sahakian & Thomas "The mental wealth of nations" (2008) Nature

Some Possible Methods of Boosting Your Brain Power

- **Pharmacological (Smart Drugs)**
- Neuroprosthetics for cognition
- **Education**
- **Brain training/cognitive training**
- **Physical exercise**

Learning helps to generate new brain cells



New brain cells in control

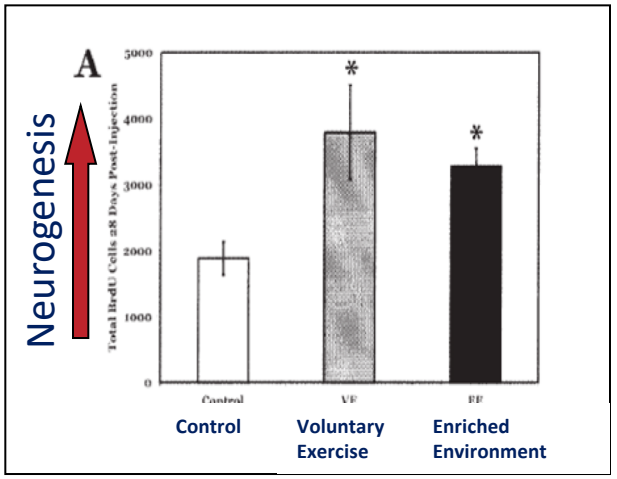
'New' brain cells after spatial learning

Gould et al (2000) Nature Neurosci

Beddington, Cooper, Field, Goswami, Huppert, Jenkins, Jones, Kirkwood, Sahakian & Thomas (2008) 'The mental wealth of nations' Nature, 455

Voluntary exercise leads to an increase in overall neurogenesis

In rats, after 2-3 weeks of access to an exercise wheel, the number of BrdU positive cells (a DNA precursor) has almost doubled after 28 days



Olson et al (2006) Hippocampus
Eadie et al (2005) J Comp Neurol

Personalised treatments in traumatic brain injury: cognitive, emotional and motivational targets

National Institute for Health Research

Peak

1. **Cognitive assessment using tablet-based technology**

2. **Using CANTAB to predict functional status**

3. **Cognitive enhancement using drugs**

4. **Efficacy of cognitive training**

5. **Non-invasive brain stimulation (tDCS, TMS)**

6. **Collaboration**

CANTAB PAL

Savulich, Menon, Stamatakis, Pickard, & Sahakian, Psychological Medicine (2018)

Background

Cognition & Mental Health

National Institute for Health Research

Problems of cognition and motivation impair functionality and wellbeing in patients with traumatic brain injury

- **Cognitive dysfunction** is a devastating consequence of brain injury and has been shown to impair quality of life, interpersonal relationships and activities of daily life and to promote antisocial behaviour. *Newcombe, Outtrim, Chatfield, Manktelow, Hutchinson, Coles, Williams, Sahakian & Menon (2011) Brain; Fortin et al. (2003) Cortex*
- **Apathy** is regarded as a major complication of traumatic brain injury (TBI) as it has a negative impact on rehabilitation. *Starkstein & Pahissa (2014) Psychiatric Clinics of North America*
- **Depressive symptoms** (BDI) are associated with functional outcome (Functional Status Examination) in patients with traumatic brain injury. *Hudak et al. (2012) The Journal of Head Trauma Rehabilitation*
- Increased psychiatric symptoms and illness such as depression are seen in over half of patients hospitalised for TBI Bombardier et al. (2010); Savulich, Menon, Stamatakis, Pickard, & Sahakian (2018)

Using Innovative Technology to Assess Cognition, including Attention, Learning and Memory

Invention

- CANTAB was co-invented by Trevor Robbins and Barbara Sahakian
- CANTAB computerised tests which use a touch-sensitive screen.
- Used in over 800 universities, research institutes and hospitals in over 80 countries
- Validated by over 1,200 peer-reviewed publications
- FDA and EMA approved

"I see it in the extraordinary work of UK life sciences companies, like Ixico, Cambridge Cognition, Psychology Online and Proteome Sciences, working with others to develop new tests for Alzheimer's Disease."

-- Former Prime Minister David Cameron's G8 Speech, 11 December 2013

UNIVERSITY OF CAMBRIDGE enterprise

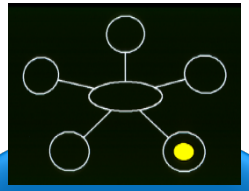
CAMBRIDGE COGNITION

www.cantab.com www.cantabmobile.com www.camcog.com

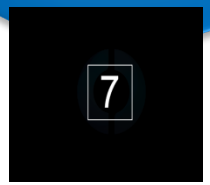
Objective Methods for Measuring Components of Cognition

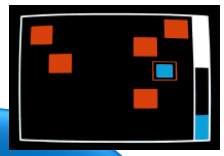
National Institute for Health Research

Attention/Concentration



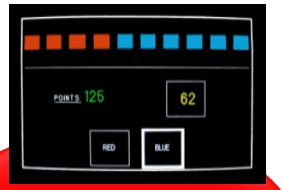
Attention



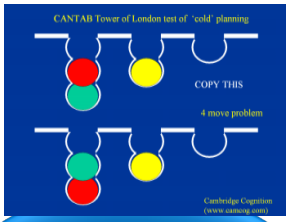


Working memory

Executive Function including cognitive control



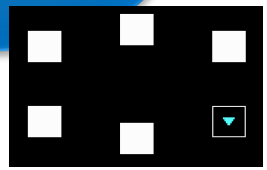
Risky Decision-making

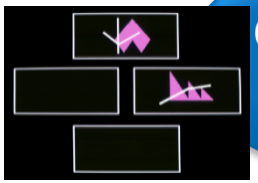


Planning

Learning and Memory

Episodic memory





Cognitive Flexibility

Impulsivity

BEEP!

Impairments in sustained attention, learning and memory following traumatic brain injury: involvement of the basal forebrain and associated structures

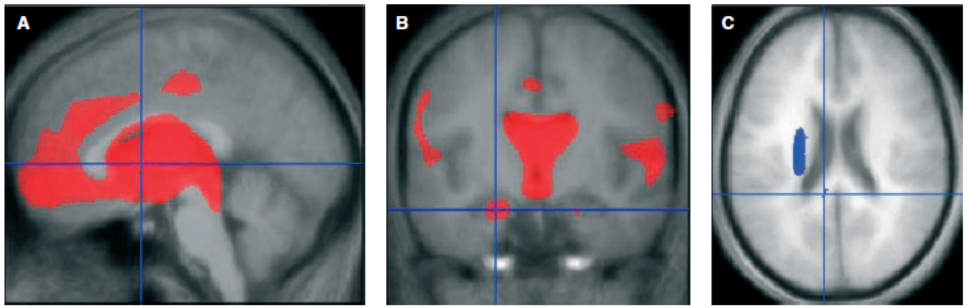


Fig. 2 Representative results from VBM analysis. Red indicates areas of decreased grey matter density. Blue indicates areas of decreased white matter density. Images thresholded at FDR $P < 0.01$ (grey matter) and FDR $P < 0.05$ (white matter) (A) septal nuclei, diagonal band of Broca, nucleus basalis of Meynert (−2 4 2), (B) bilateral hippocampal formation (−21 −11 −22) and (C) medial pathway (−8 −41 21) (lateral capsular pathway abnormality also visible).

Attention/Concentration

- **Simple reaction time**
- **Sustained attention (RVP)**

Learning and Memory

- **Paired associate learning**
- **Pattern recognition**

Executive Function was relatively unaffected

Conclusions:

- The patients showed deficits in reaction time, sustained attention and paired associate learning but were relatively preserved on the executive function tests.
- Voxel-based morphometry revealed reduced grey matter density in the head injured group, in the basal forebrain, the hippocampal formation and regions of neocortex.

These findings suggested that cholinergic enhancers may be an effective treatment for some of the cognitive deficits post injury.

Salmond, Chatfield, Menon, Pickard & Sahakian (2005) Brain

Cognitive reserve (education, IQ, etc) as a resilience factor against depression after moderate/severe traumatic brain injury

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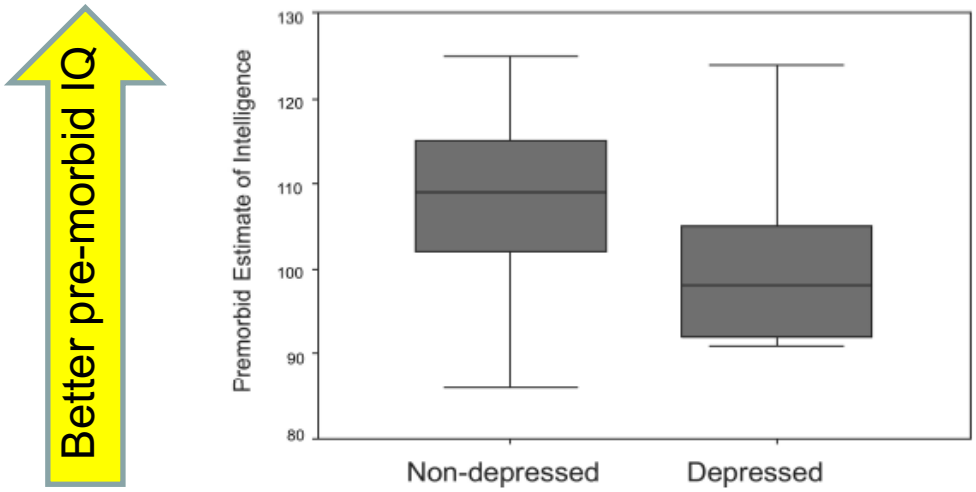
- **Cognitive reserve, which is a resilience factor, protects individuals against the worst impacts of neurodegeneration (e.g. Alzheimer's disease), head injury and the normal ageing process, both in terms of functionality and in terms of psychiatric sequelae e.g. depression.**
- Depression, a frequent and distressing complaint following head injury.
- It exacerbates impairments, complicates recovery and impedes rehabilitation.



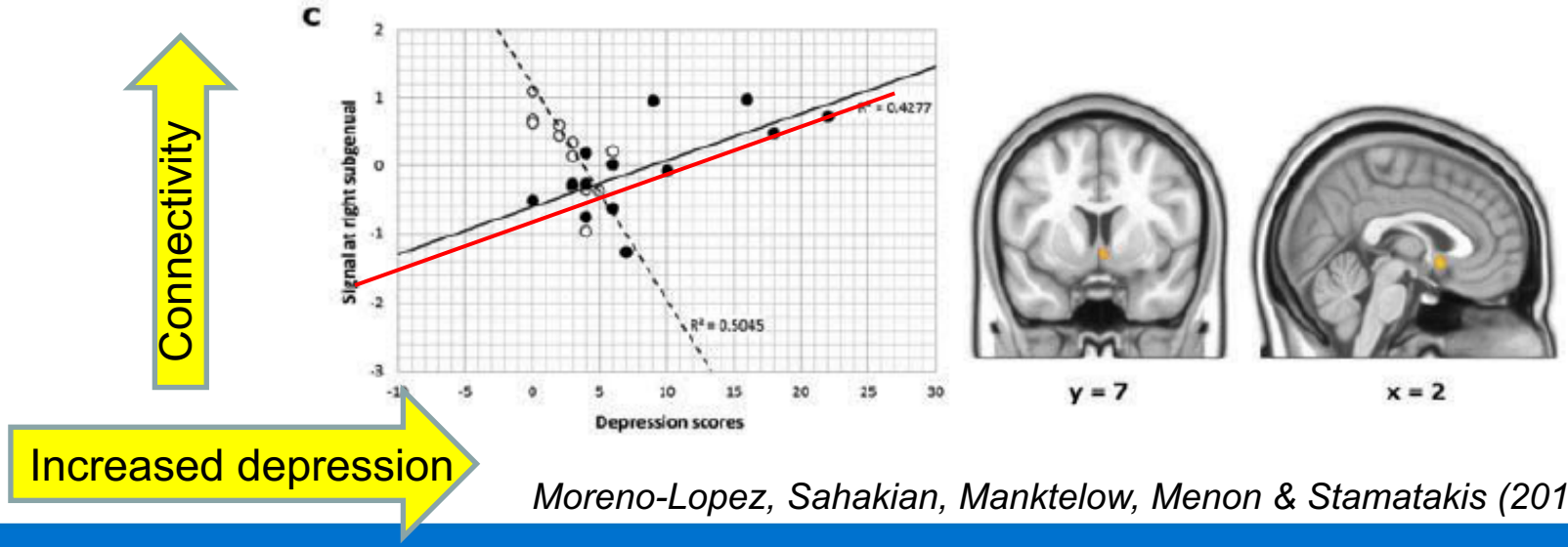
In people with TBI, cognitive reserve was a protective factor against depression.

Salmond, Menon, Chatfield Pickard & Sahakian (2006) Journal of Neurotrauma; Barnett, Salmond, Jones & Sahakian (2006) Psychological Medicine

TBI-induced depression may result from altered functional connectivity of a set of networks associated with emotional regulation, including the subgenual cingulate

National Institute for Health Research

- Mayberg has shown abnormal elevation of baseline subgenual activity in depressed patients. The subgenual cingulate is the site for deep brain stimulation for treatment-resistant patients
- In this study, we have shown the correlation of connectivity with depression scores was positive in patients with TBI for the right subgenual anterior cingulate cortex.

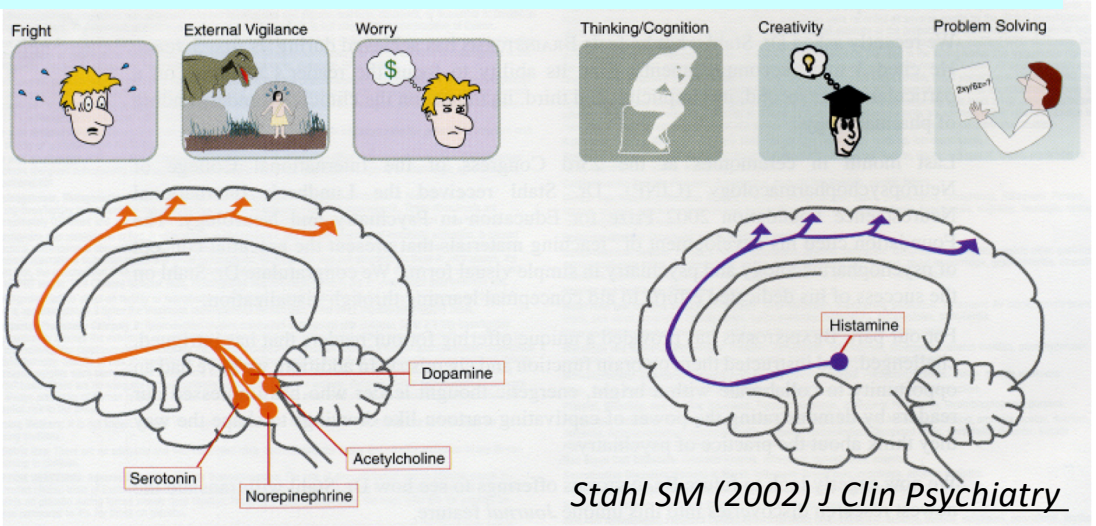


Moreno-Lopez, Sahakian, Manktelow, Menon & Stamatakis (2016) Brain Injury

Drugs for cognitive enhancement.
Action of Methylphenidate, Modafinil, and Atomoxetine

Methylphenidate (Ritalin) increases synaptic concentration of **dopamine and noradrenaline by blocking their reuptake.**

Atomoxetine (Strattera) is a relatively selective **noradrenaline reuptake inhibitor** (SNRI).



Stahl SM (2002) J Clin Psychiatry

Modafinil (Provigil) action is unclear; Possibilities include: indirect mediation of ACh and/or Adrenergic alpha –1 receptor activity. Appears to effect hypothalamic orexin and histamine, and has a small effect on dopamine transporter activity. **Recent evidence suggests NA** (Minzenberg et al 2008), **DA** (Volkow et al 2009) **and glutamatergic mechanisms** (Scoriels, Jones, Sahakian 2013).

Neuroscience-based nomenclature (Zohar et al, 2014) classifies modafinil as a dopamine reuptake inhibitor.

http://www.ecnp.eu/~/media/Files/ecnp/Projects%20and%20initiatives/Nomenclature/Review%20articleNEUPSY_10717v2%20pdf.pdf

Methylphenidate (Ritalin) improves working memory & increases 'efficiency' of dorsolateral prefrontal cortical network in healthy volunteers

NHS
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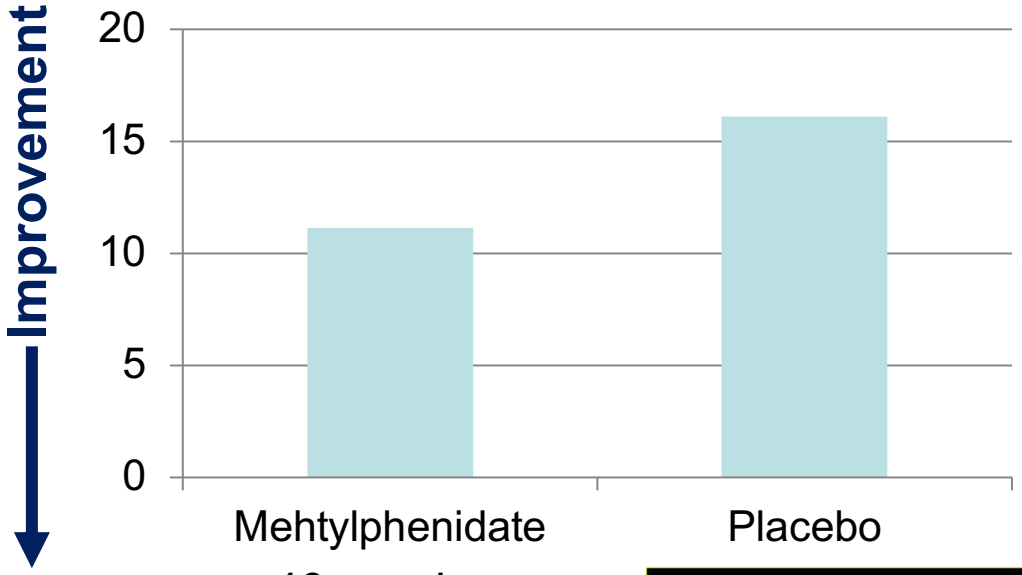
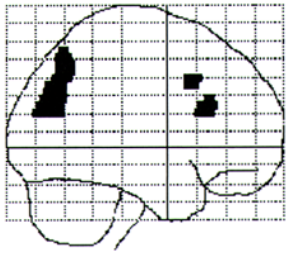
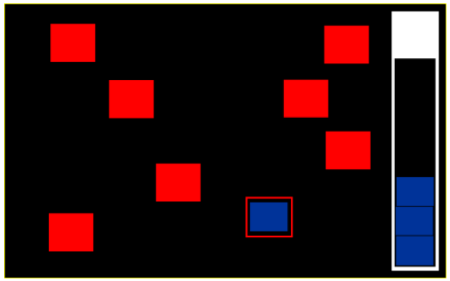
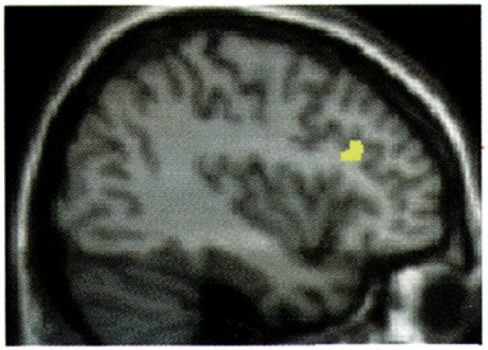


(a)

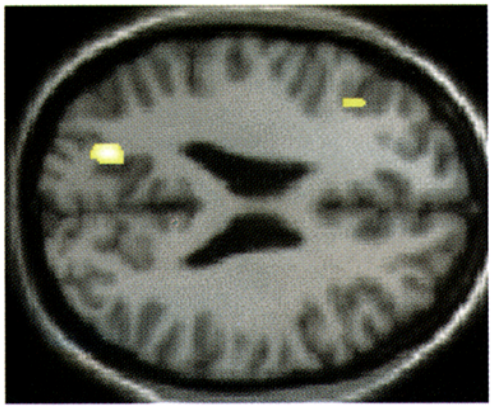




(b) sagittal



(c) transverse



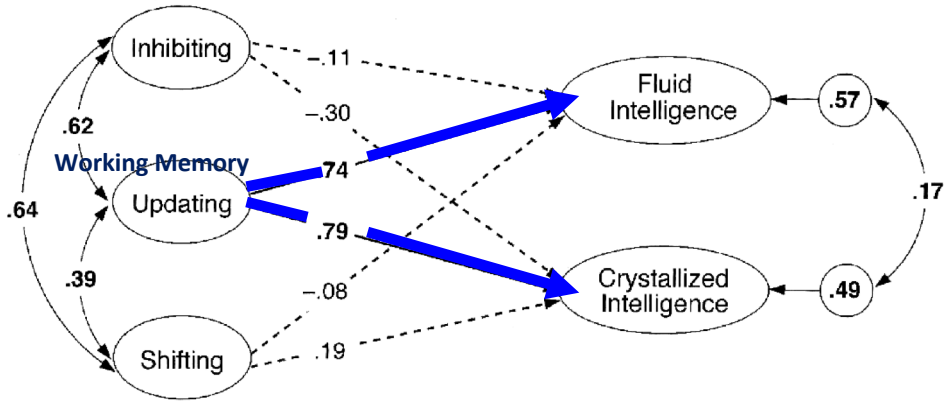
Mehta, Owen, Sahakian, Mavadatt, Pickard & Robbins (2000) J Neuroscience

Working memory: An important domain (Research Domain Criteria (RDoC))

Insel (2014), American Journal of Psychiatry

- Working Memory is related to fluid and crystallized intelligence

Friedman, Miyake et al (2006) Psychological Science



- **Working memory is a key process for most executive function tasks, such as planning and problem solving**

- Correlational studies supported a close relationship between WM and measures of fluid intelligence and science achievement

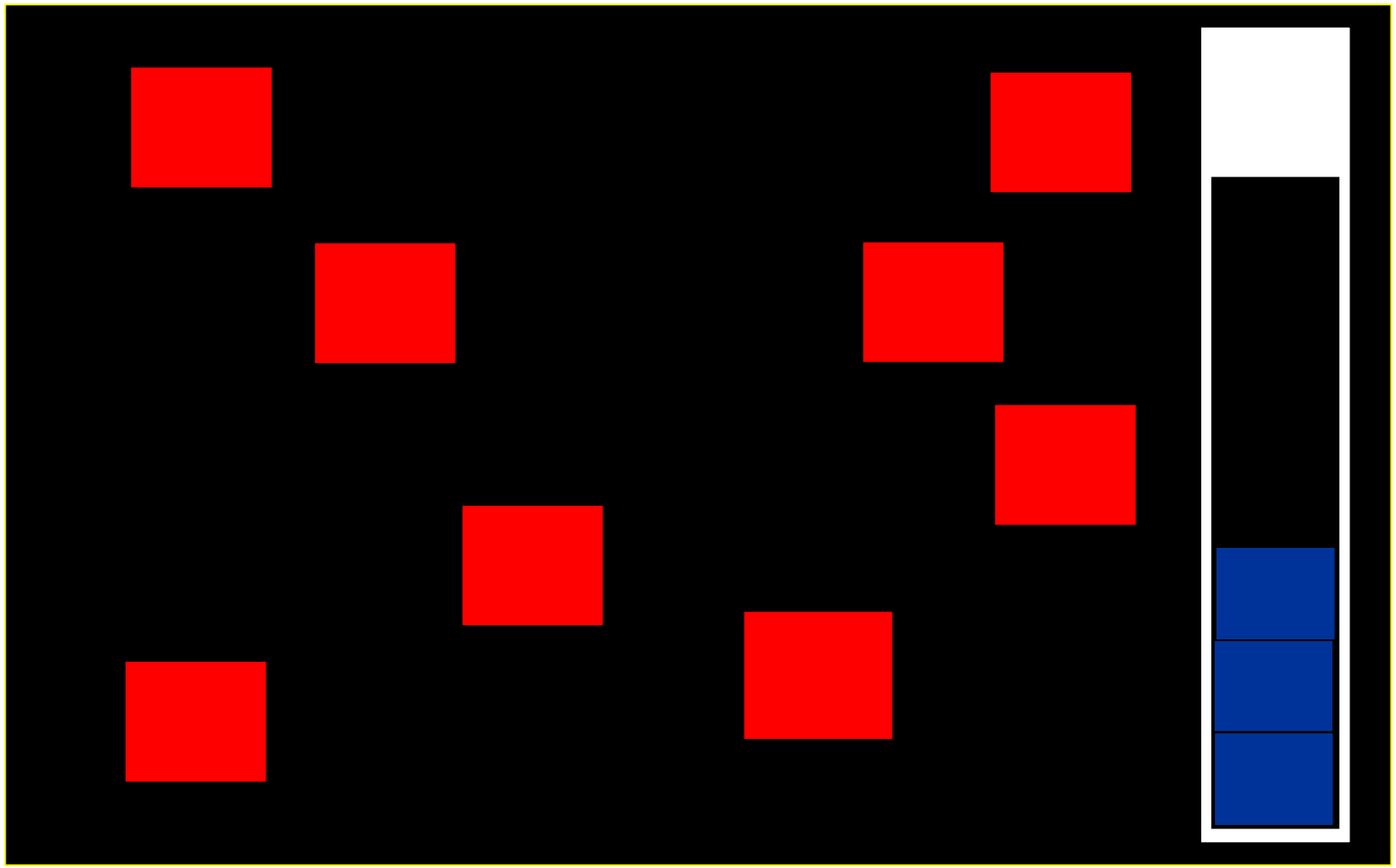
Yuan et al (2002) Educational Research Review

- Working memory at the start of formal education is a more powerful predictor of subsequent academic success than IQ

Alloway and Alloway (2010) J Exp Child Psychol

Working memory is impaired in traumatic brain injury
Manktelow, Menon, Sahakian, Stamakatis (2017)

CANTAB Spatial Working Memory (SWM)



Look for a blue token hidden in one of the boxes, without returning to a box where a token has previously been found.

Cambridge Cognition (www.cambridgecognition.com)

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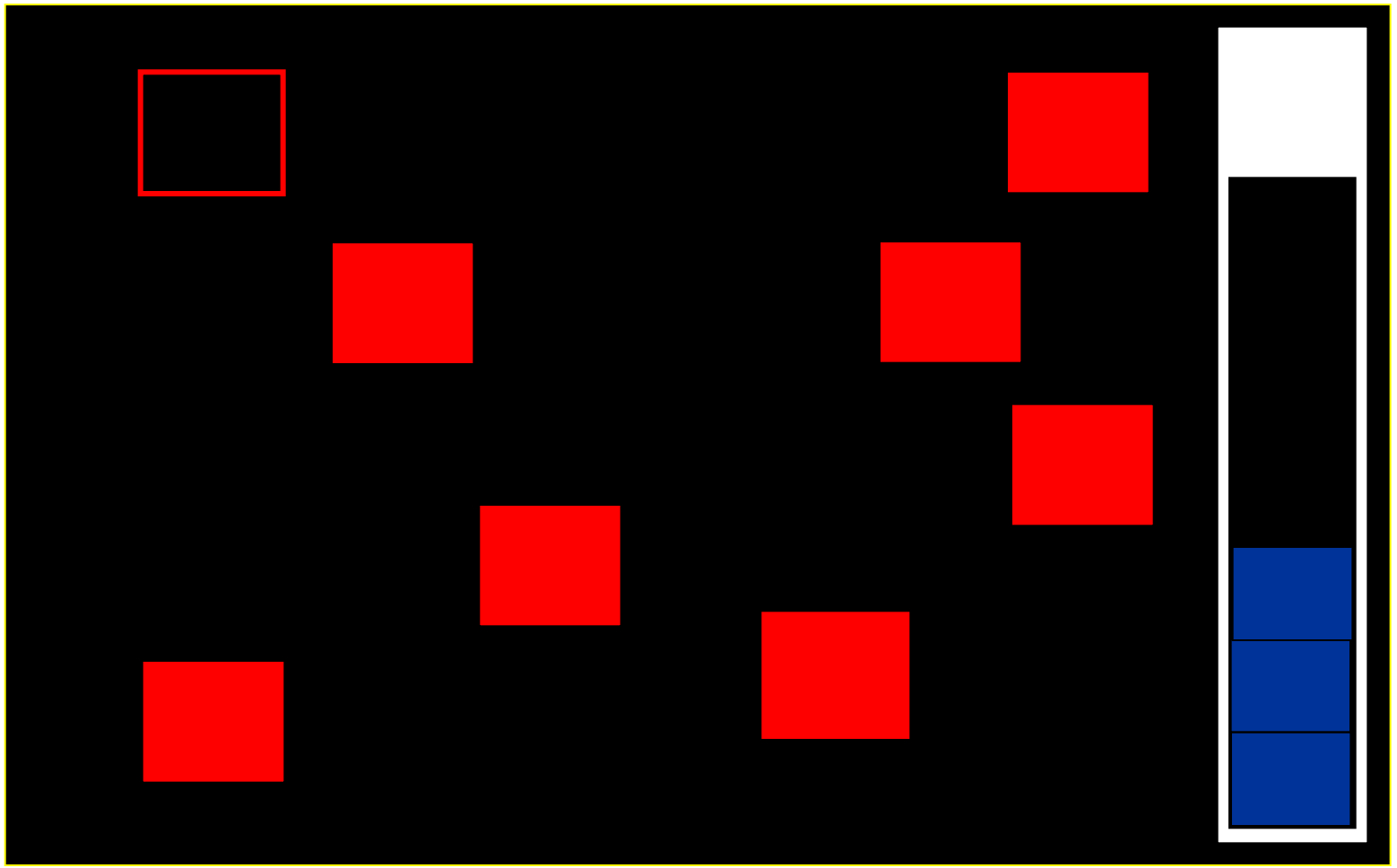

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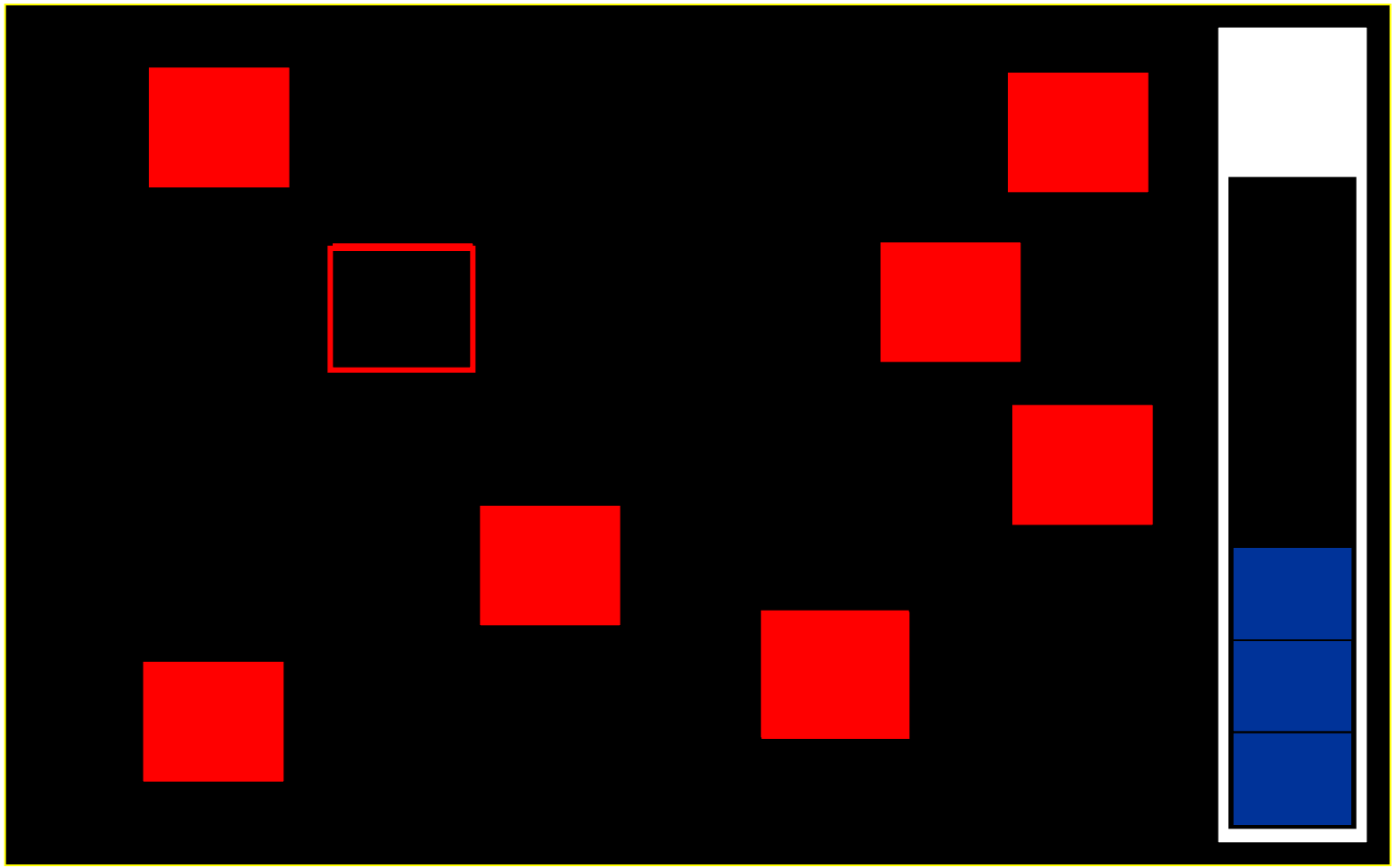

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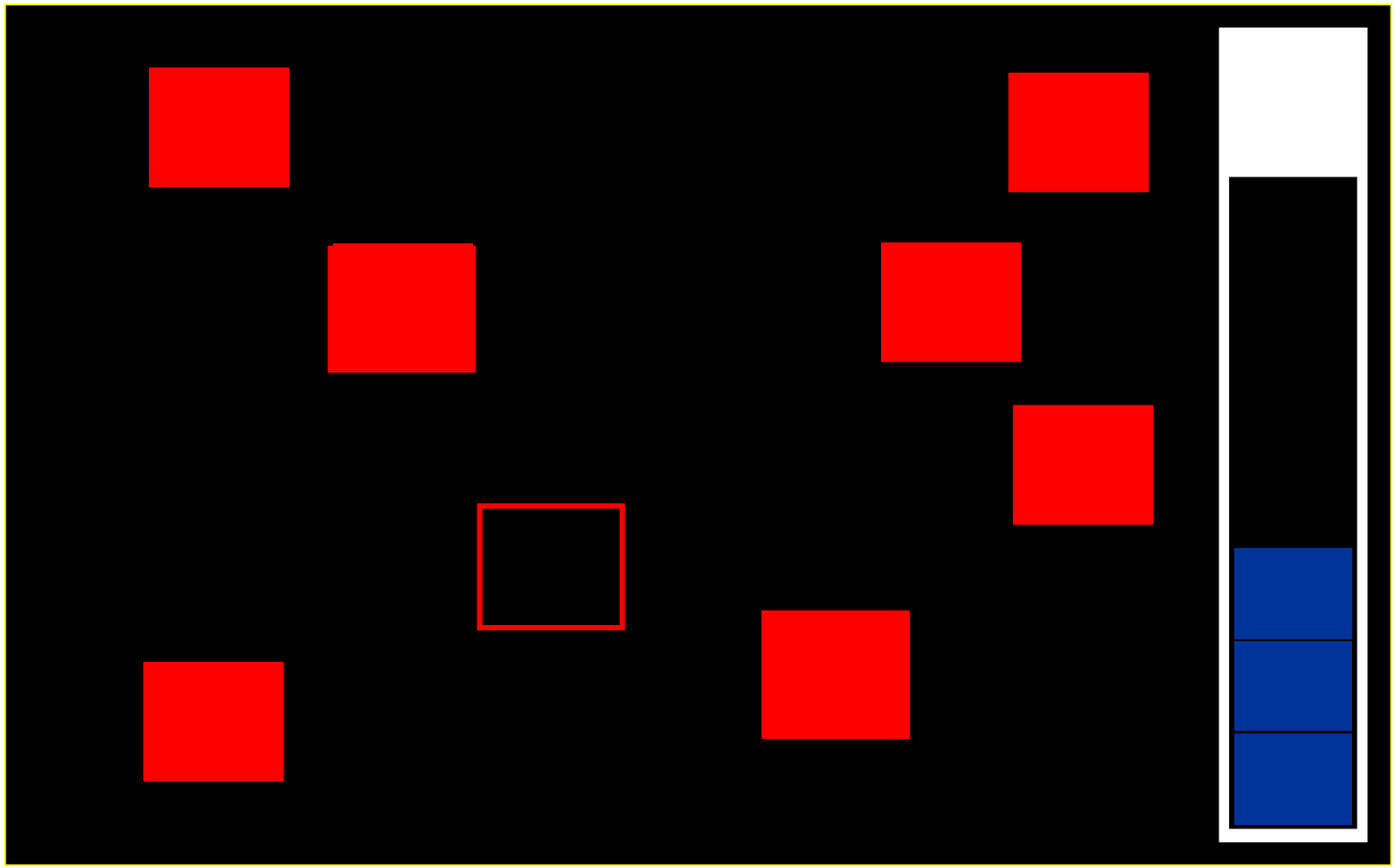

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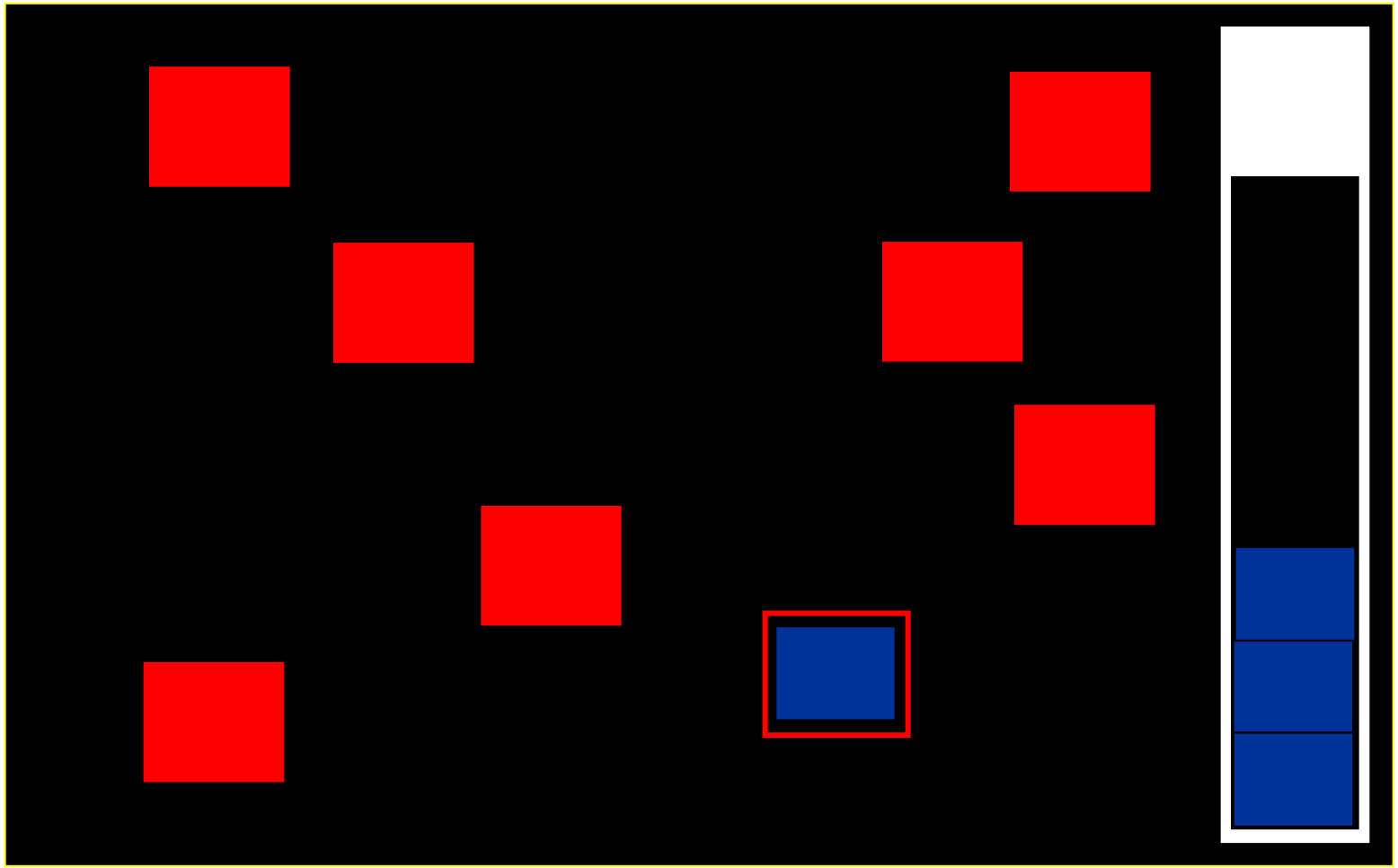

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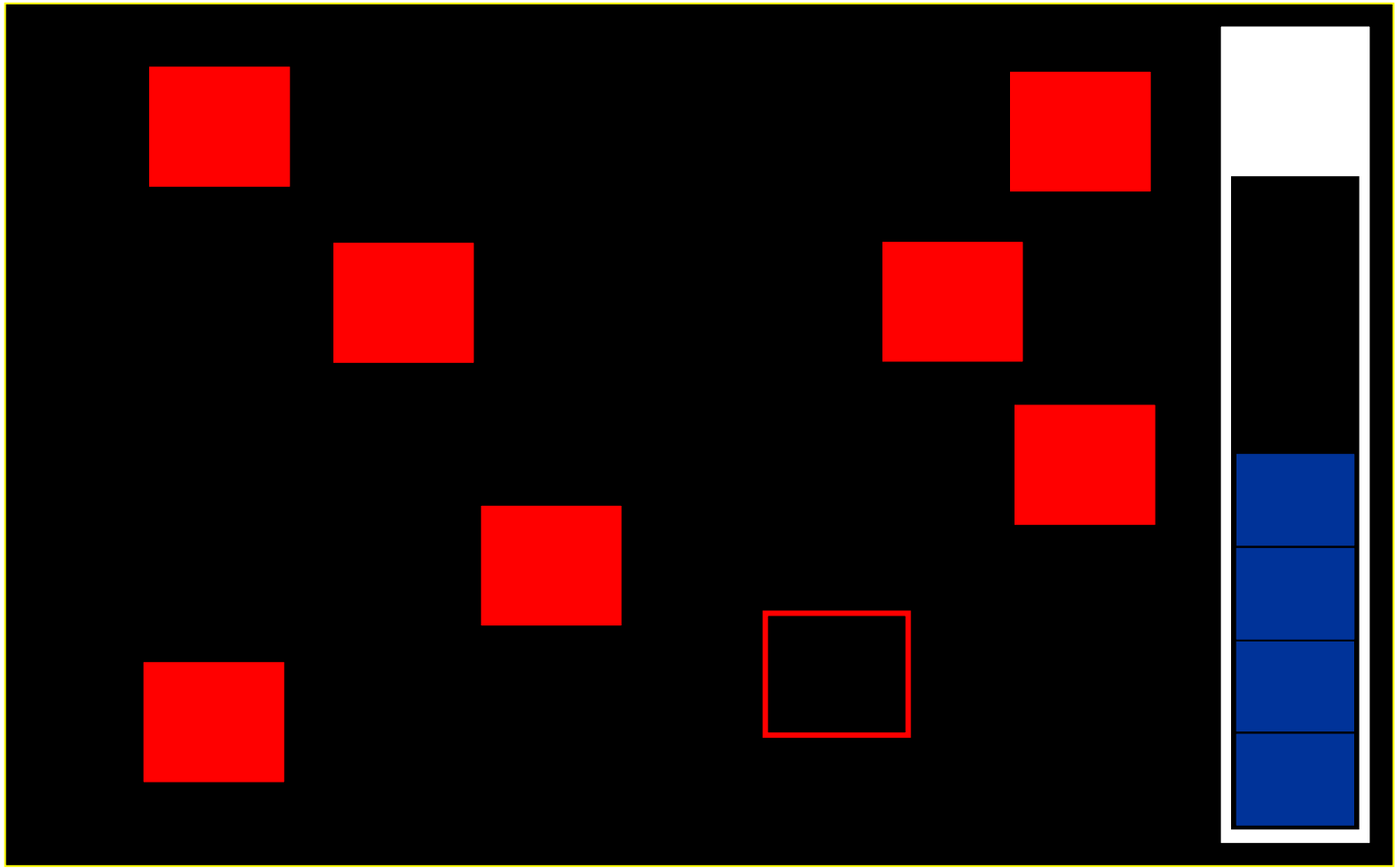

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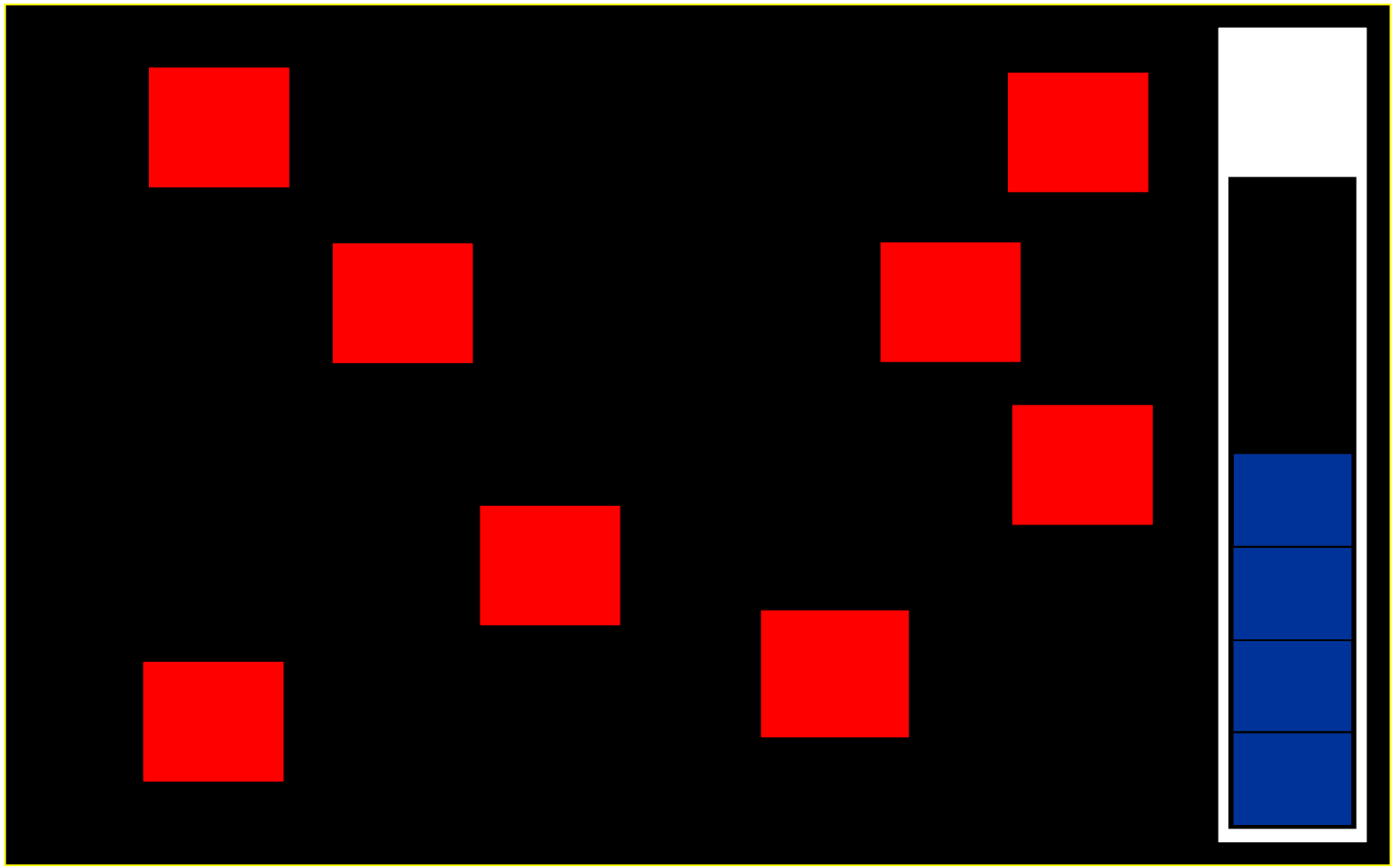

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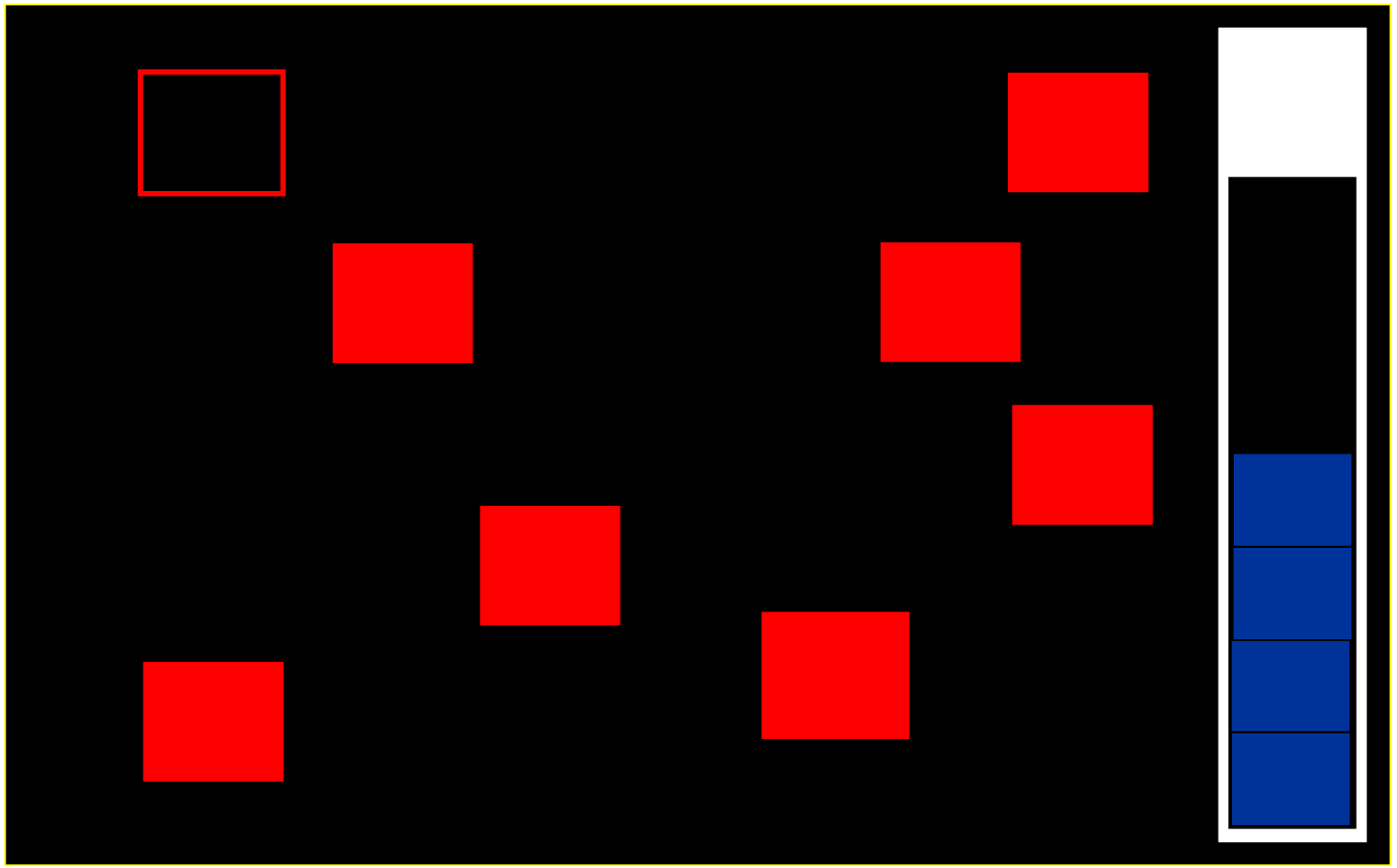

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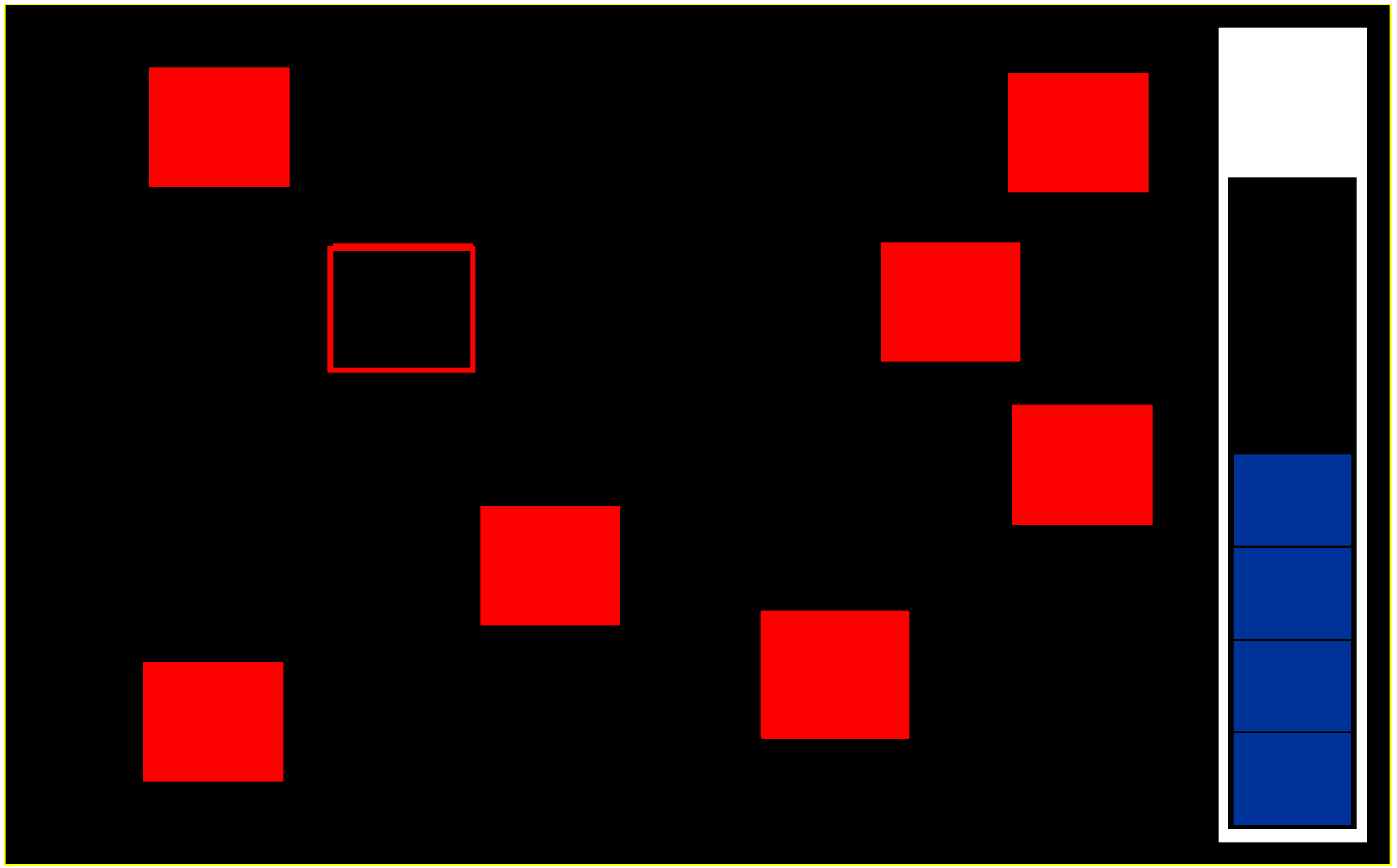

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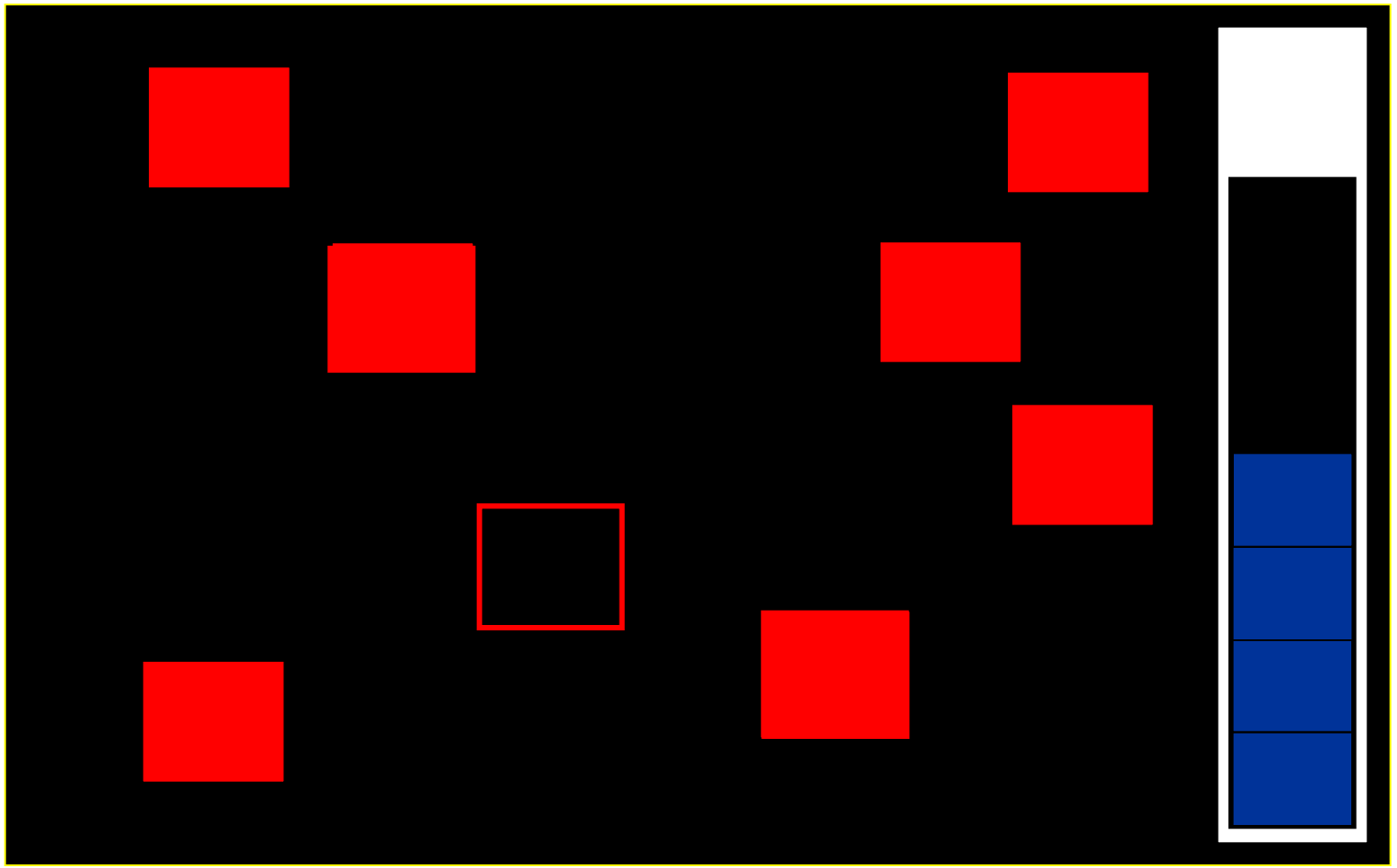

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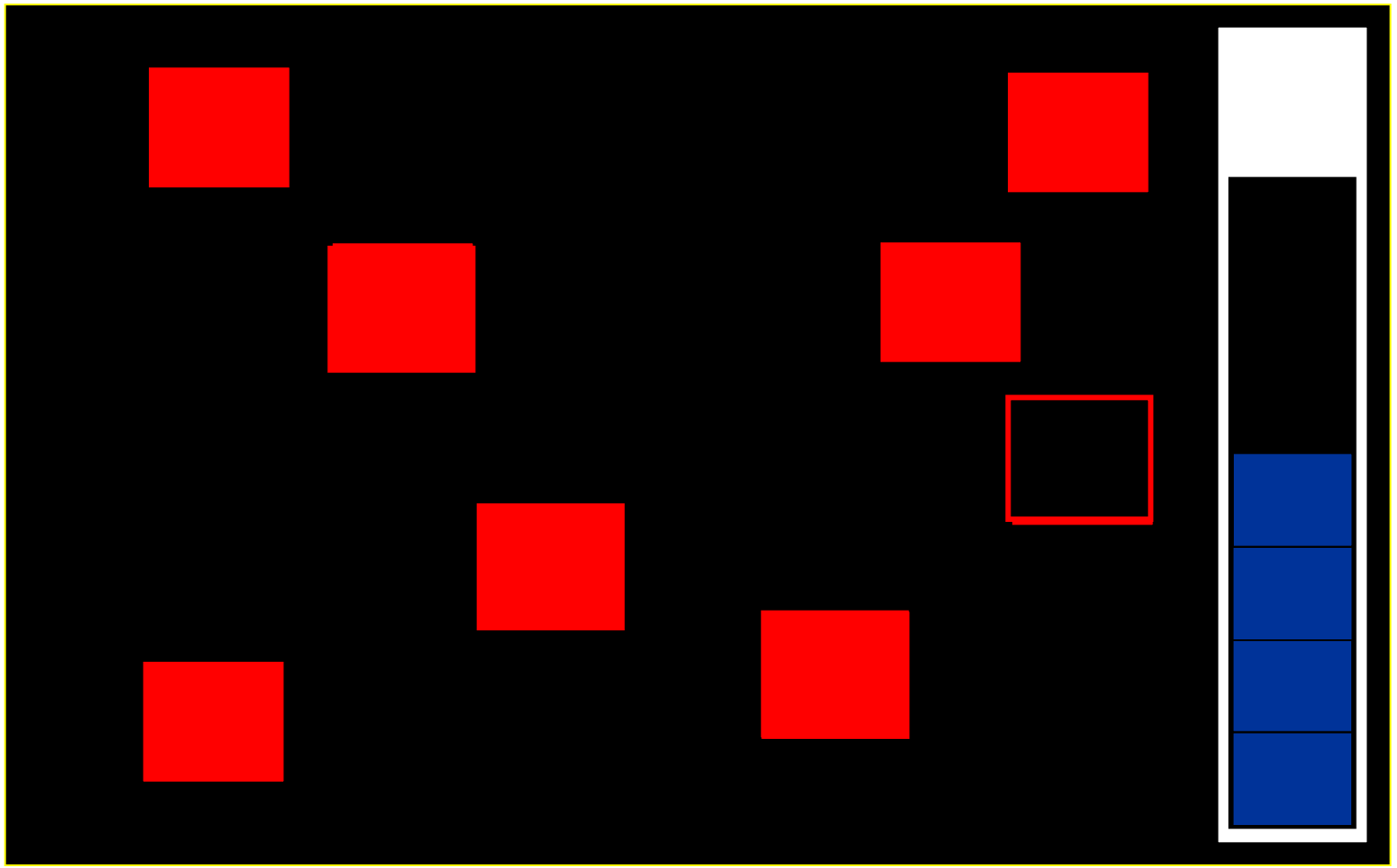

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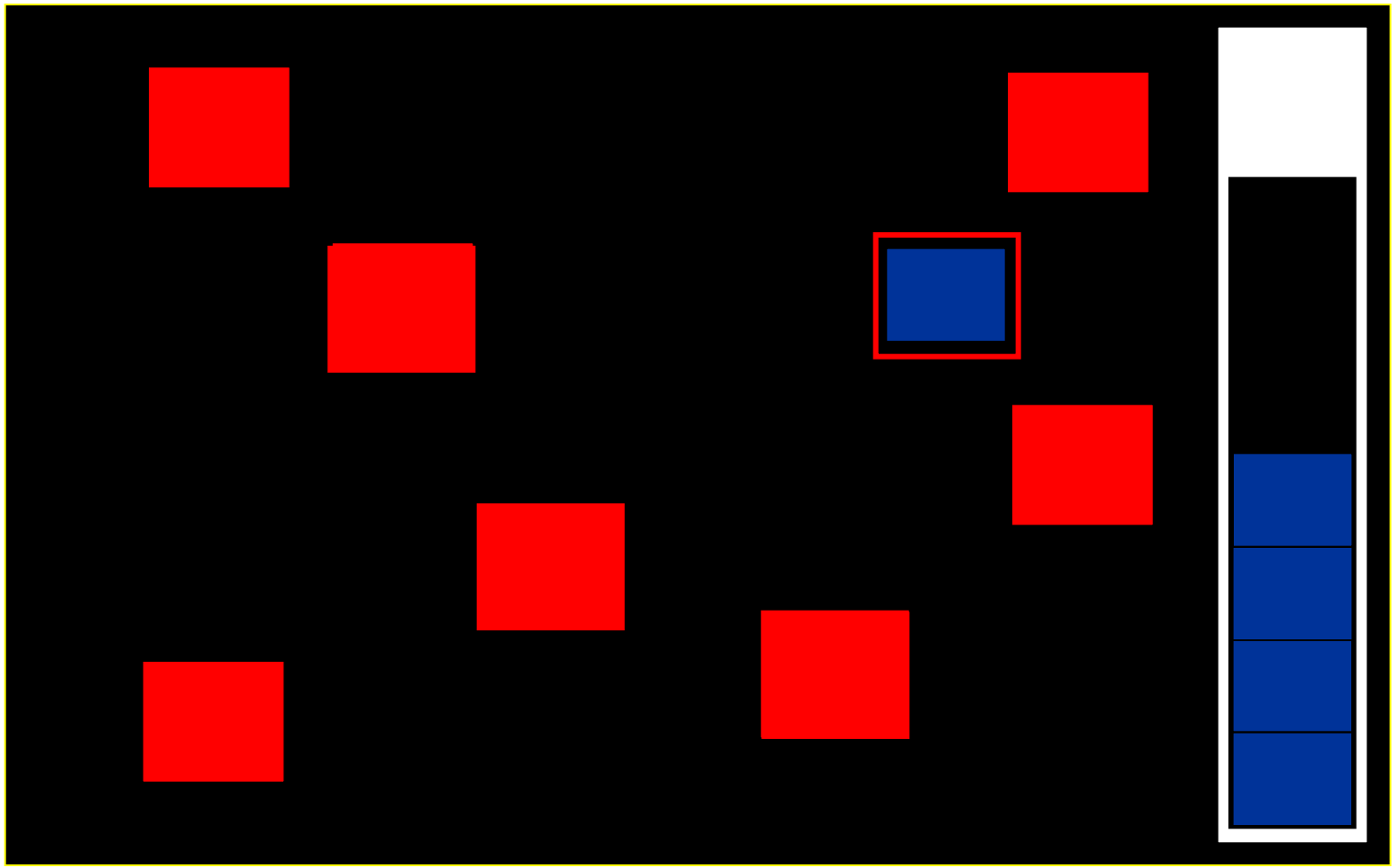

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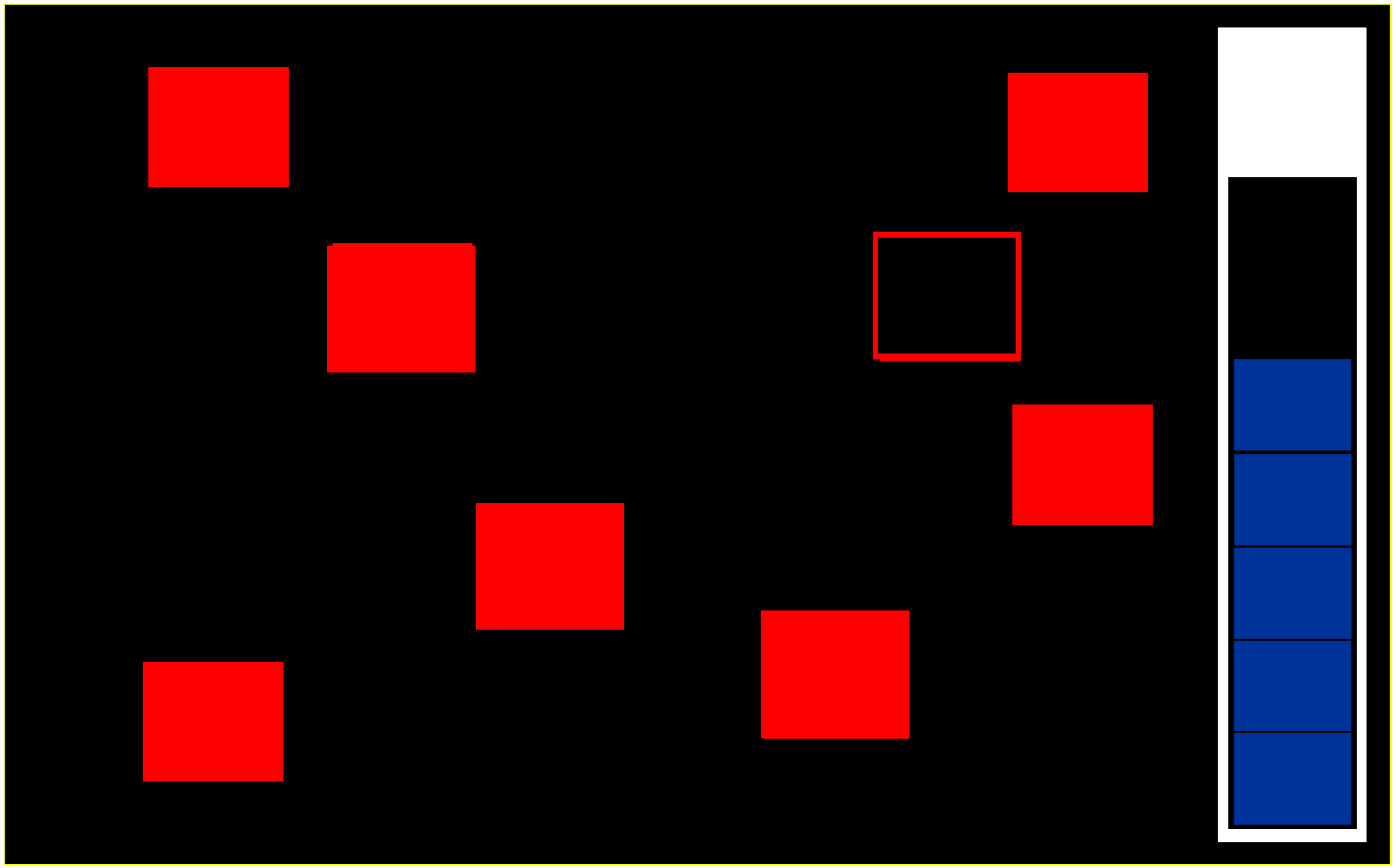

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Cambridge Cognition (www.cambridgecognition.com)

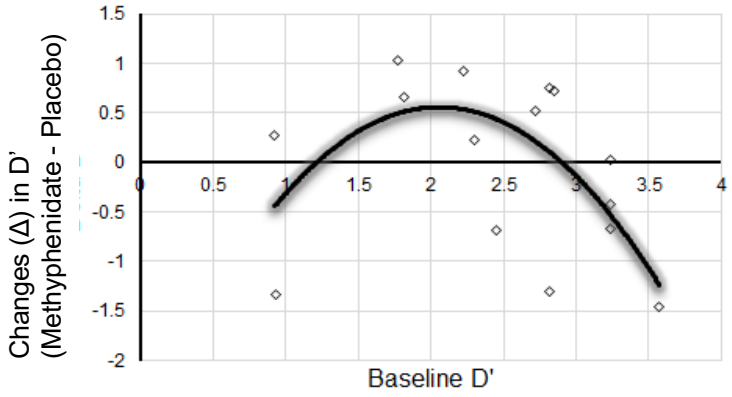
Working memory performance and functional connectivity is improved by methylphenidate (30 mg) in patients with traumatic brain injury

Statistical comparisons for D' scores

Methylphenidate

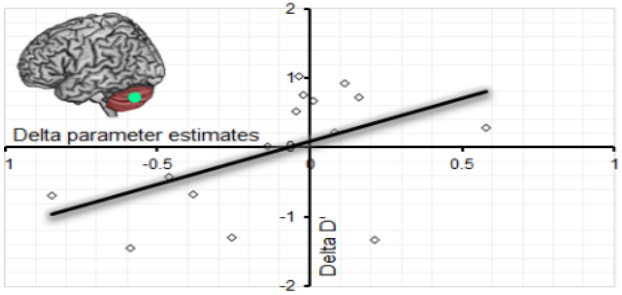
HC — Not significant
F(1,28)=3.665, p=0.66

Placebo — Significantly different
F(1,28)=4.426, p<0.05



Greatest behavioural benefit in patients with baseline performance within the middle range of D' scores

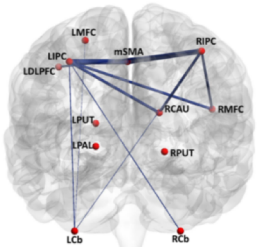
Significant positive correlation between change in patient activation (Methylphenidate - Placebo) in Left Cerebellum with change in performance (D') (R^2=0.259)



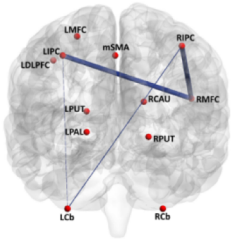
PPI Connectivity

Controls > **Placebo**

Controls > **Methylphenidate**



Lines show significantly greater connectivity for HC than for TBI patients between areas implicated in working memory. Thicker lines signify greater differences.



Connectivity improves with Methylphenidate
Fewer differences between HC and patients on Methylphenidate

Manktelow, Menon, Sahakian, Stamatakis (2017)

NIHR Brain Injury MedTech Co-operative

Use it or lose it!

Increased brain activity after training of working memory

Martin Orrell & Barbara Sahakian


BMJ

LONDON, SATURDAY 15 APRIL 1995

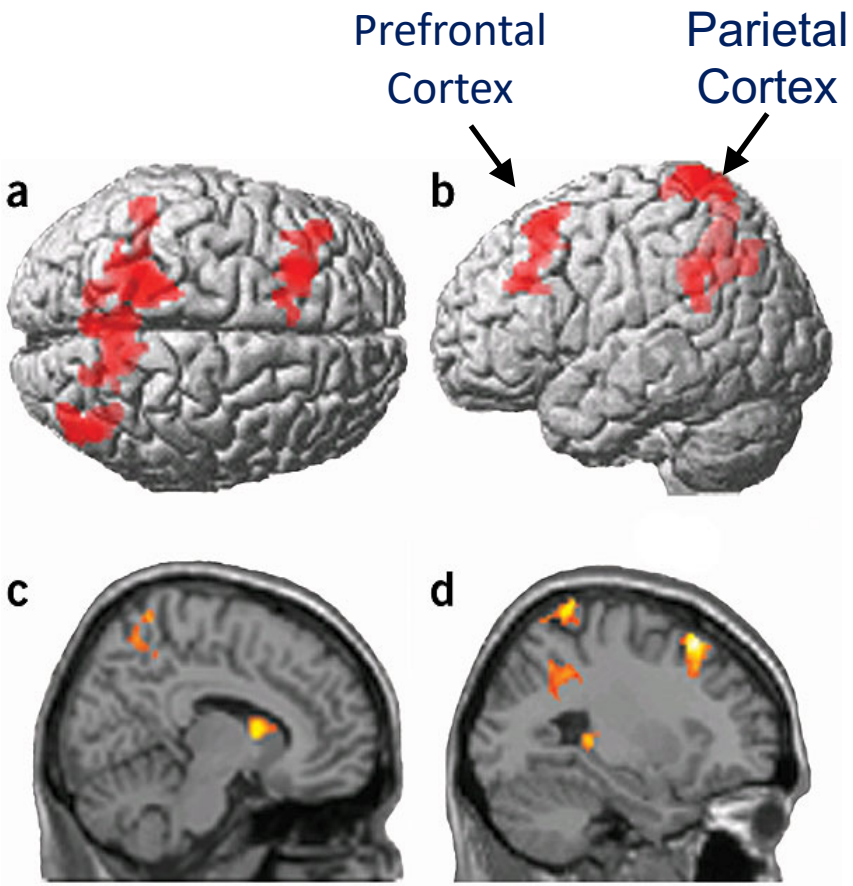
Education and dementia

Research evidence supports the concept "use it or lose it"

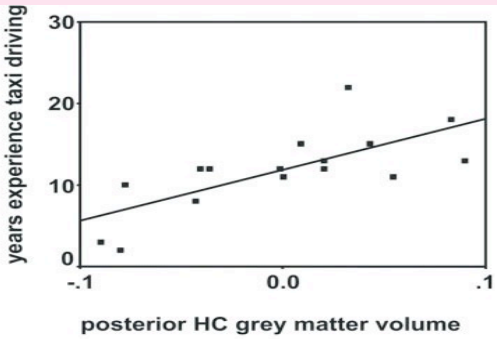
As long ago as the 2nd century BC poets and philosophers considered that an active mental life might forestall or delay the enfeeblement of old age.[1] In "De Senecute" Cicero suggested that old men preserved their intellects if they preserved their interests—"the use it or lose it" hypothesis.[1] In this week's journal a population based study reports that in elderly people a low level of education was associated with a higher prevalence of dementia, particularly Alzheimer's disease (p 970).[2] In addition, several recent studies have indicated that education may protect against dementia.[3-5] Bonaiuto *et al* found that the prevalence of Alzheimer's disease was 7·2% among illiterate people, 2·8% among those whose education had ceased at the fifth grade, and 0·5% Alzheimer's disease, and seems to be influenced by environmental change.[6] Those links might partly explain the actions of education and continued mental activity in delaying the onset of Alzheimer's disease.[7-10]

The evidence in support of the neuronal networking mechanism has been reviewed by Katzman, who noted that cognitive change in Alzheimer's disease is largely predicted by the density of neocortical synapses.[11] He suggested that education could increase brain reserve by increasing the density of neocortical synapses, so delaying the onset of symptoms in Alzheimer's disease by up to five years. That delay would halve the prevalence of dementia in the better educated people. Katzman also argued that research on rats

14 hours of training over 5 weeks was associated with increased brain activity on a working memory task and also changes in dopamine receptor D1 binding potential in the same areas.



Increased hippocampus volume after learning

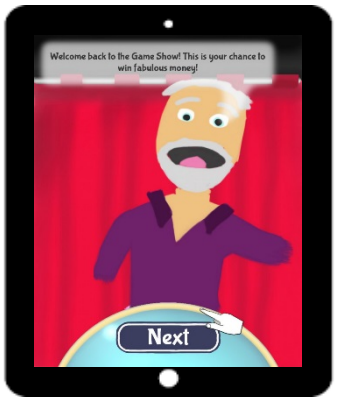


The size of the posterior hippocampus increases with time spent as a taxi driver (spatial learning)

Maguire et al. (2006) Hippocampus
McNab et al. (2009) Science;
Olesen et al. (2004) Nature Neuroscience

Games Development: a Neurobiological Approach to Improving Episodic Memory and Sustained Attention

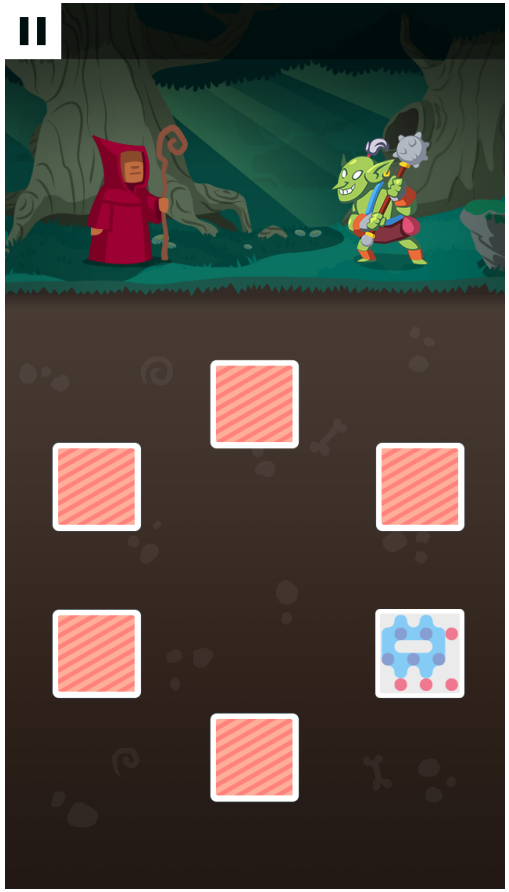
- Gamification of **cognitive training**
- Games for **episodic memory and sustained attention** were developed based on neuropsychological and neuroimaging evidence .
- Collaboration over 9 months between psychologists, neuroscientists, a professional games-developer and service-users
- Focus groups of patients were invited to play the games, and modifications were made until they were rated as:
  - Fun
  - Attention-grabbing
  - Motivating
  - Easy to understand

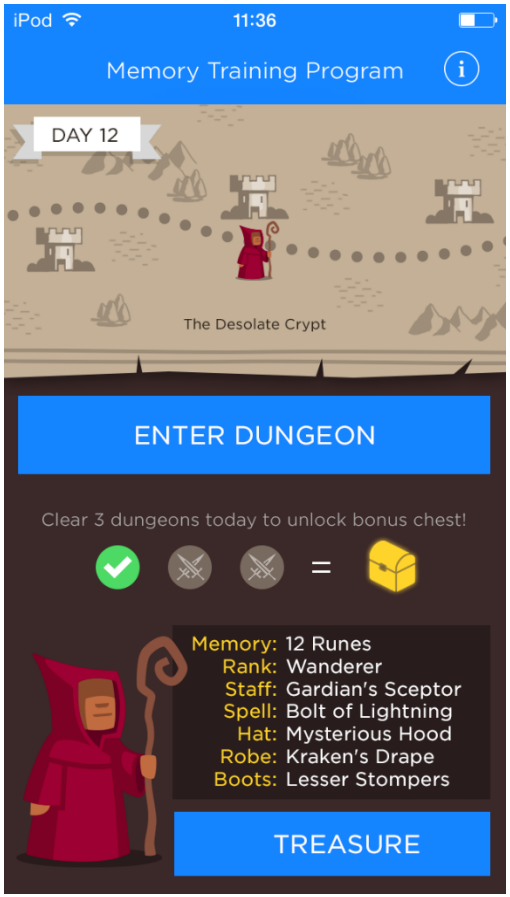


Technology Transfer – Partnership with games company PEAK

University of Cambridge and PEAK Advanced Training Programme

- In April 2015, the Sahakian Laboratory teamed up with the games company PEAK to produce scientifically-tested brain training apps www.peak.net
- Allows the Wizard memory game to become widely available, inexpensively on mobile phones.
- PEAK (science@peak.net) was recently selected as a "Future Fifty" company by TechNation and won awards from Apple and Google
- 2018: PEAK Wizard Apprentice now available





Liron Jacobson at PEAK:
liron@peak.net

GET IT ON Google Play

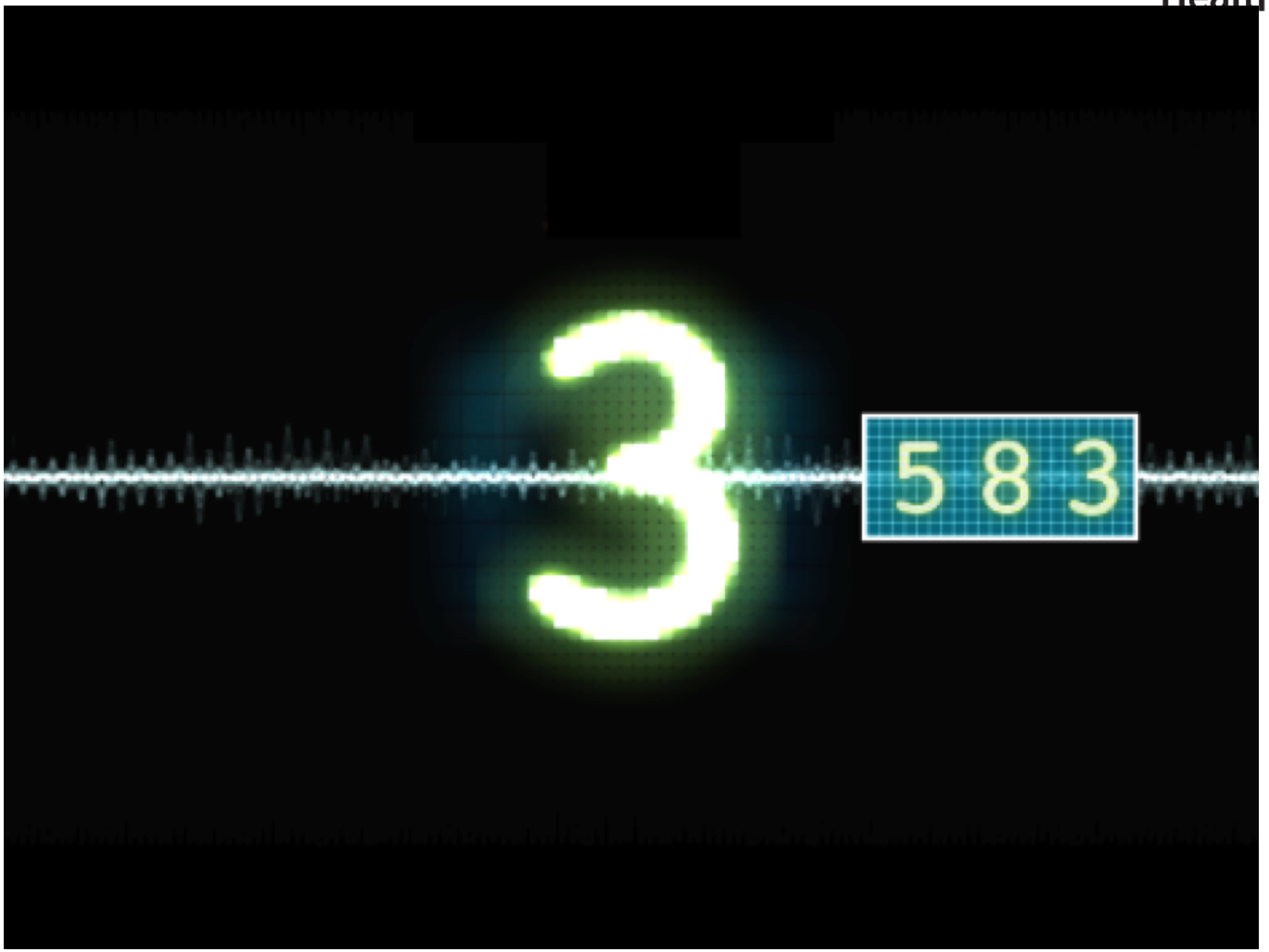
UNIVERSITY OF CAMBRIDGE enterprise

Download on the App Store

https://itunes.apple.com/gb/app/peak-brain-training/id806223188?mt=8

New Development From the Sahakian Laboratory: Attention and Concentration Game – now on your phones!

National Institute for Health Research



Barbara J. Sahakian, George Savulich,
Thomas Piercy, Katie Peterson & John Pickard

NIHR Brain Injury MedTech Co-operative

Future studies - Measuring real world outcomes: Future project will include wearable tech in TBI

National Institute for Health Research

Cognition Kit (www.cambridgecognition.com) is a custom-designed digital health platform delivering wearable and smartphone apps for high frequency data collection to demonstrate the real world value of treatments.

Cognitive Assessment

Mood Assessment

Cognition Kit apps provide engaging digital health solutions to improve patient engagement, demonstrate treatment efficacy and increase the understanding of brain injury and a patient's response to medication

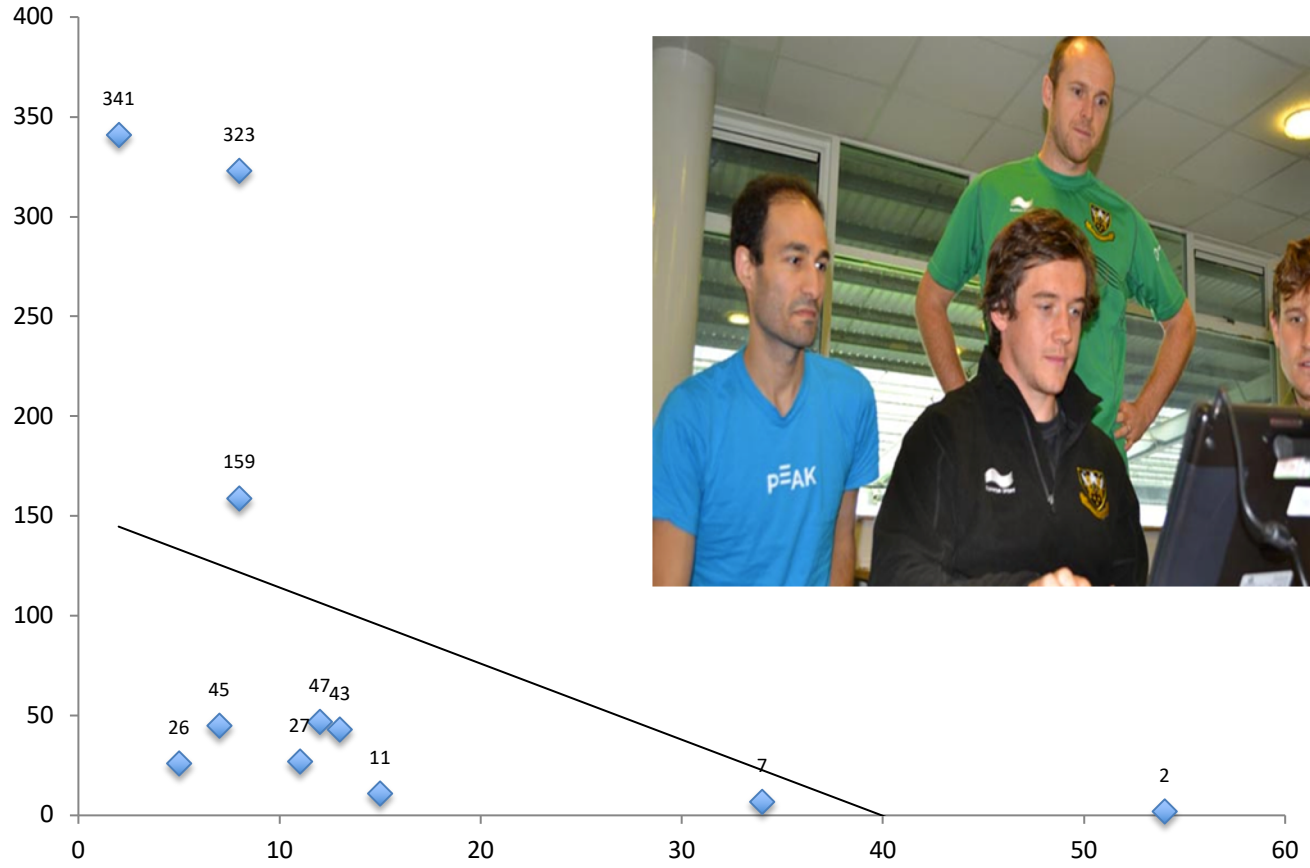
Future studies – Effects of concussion (brain injury) in rugby players

- Rugby has one of the highest rates of concussion of all contact sports – 4.73 concussions for every 1,000 match hours.
- Protective equipment was not found to reduce concussive injury.
- Published data is limited!

(Gardner et al., 2014, *Sports Medicine*; 2017, *British Journal of Sports Medicine*)

The more rugby players played the game, the better their learning and memory

More game play (minutes)



Number of PAL Errors at Outcome

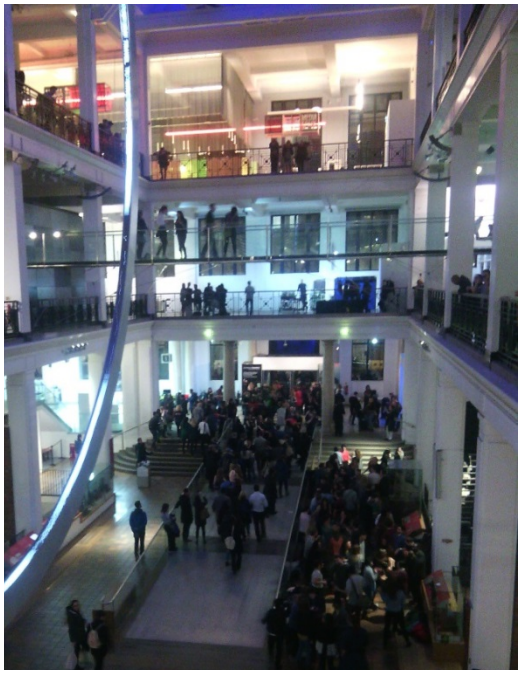
Better performance

Association between minutes of gameplay by the rugby players and the total error score on the CANTAB PAL at outcome (second test). Spearman's rho = -0.72, p = 0.013

Sahakian, d'Angelo & Savulich, in press

You Have Been Upgraded: A Festival of Human Enhancement at the Science Museum in London

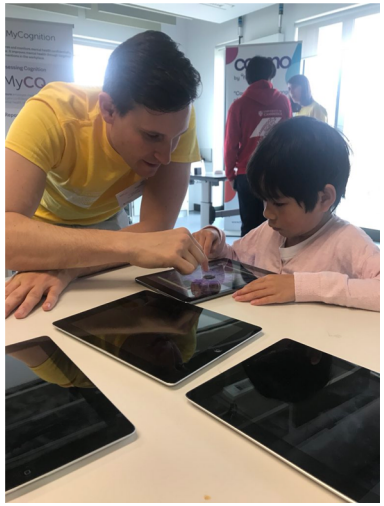
"From brain training to brain gaming: Peak and the University of Cambridge's Sahakian Labs present games to keep your brain in peak performance."



Over **3,500** members of the public attended over the 4 days (25-29 March 2015)

University of Cambridge 2018 Science Festival

National Institute for Health Research



High tech gizmos and apps for a healthy brain (25th March 2018)

Dr George Savulich assisting with Decoder and Wizard games for improving attention/concentration and learning and memory

Five Ways to Mental Wellbeing

Exercise – Be Active!
Exercising improves your mood, physical health and your cognition

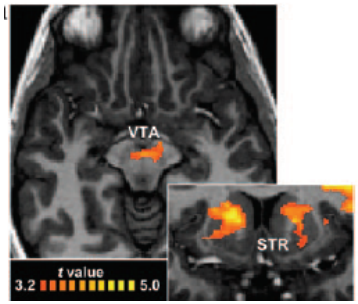
Mindfulness – Take Notice

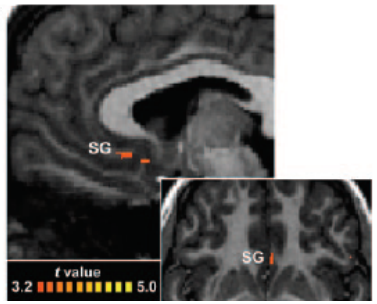
Be aware of the world around you and what you are feeling. Reflecting on your experiences will help you appreciate what matters to you.

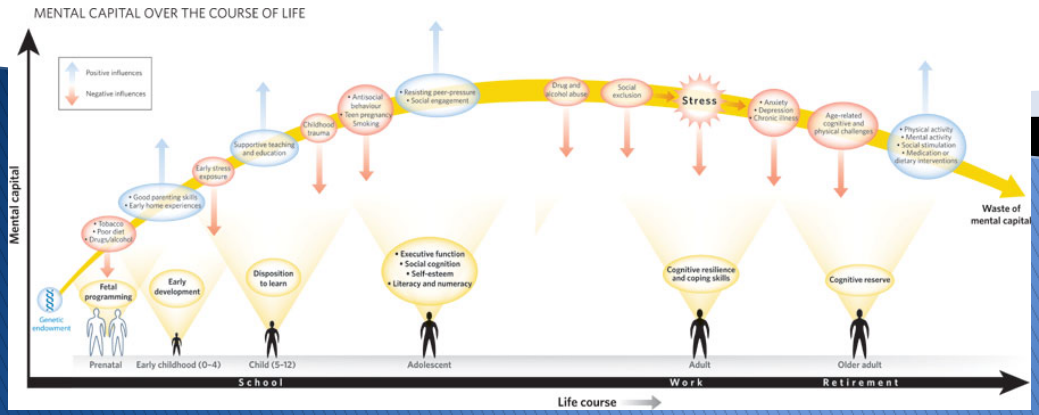
Keep Learning!

Connect

With the people around you. With family, friends, colleagues and neighbours. At home, work, school or in your local community. This helps build social support and resilience.







Give – It's Rewarding!

Donating to societal causes recruited the VTA-ventral striatum network (also involved in monetary rewards) and the subgenual area involved in social attachment and affiliative reward mechanisms.

Strategy

Cognition & Mental Health

National Institute for Health Research

Year 1 **Short-term**	**Improve network interaction and continue public engagement activities** **Complete study of game-based attentional training ('Decoder') in patients with TBI** **Explore the therapeutic potential of neuromodulation of emotional dysregulation in adults with developmental or acquired brain damage using transcutaneous vagal stimulation.**
Year 2-3 **Medium - term**	**Work with subgroups of the Cognition theme and apply for funding of studies on cognition and TBI** **Technology-transfer Decoder (attention app) to make it available to the public** **Develop wrist-worn activity measurements as a potential real-world biomarker for people with memory problems and TBI**
Year 4-5 **Long-term**	**Establish a catapult in Cambridge in the area of technology, mental health, brain injury and wellbeing** **Collaborate with industry in the development and evaluation of cognitive enhancing drugs.** **Secure funding for the development of other apps to address cognitive training in patients with TBI, stroke and tumours (e.g. apps for improving working memory, cognitive control, response inhibition)**

Team

Cognition & Mental Health

National Institute for Health Research

- Barbara J Sahakian, Psychiatry
- John D Pickard, Clinical Neurosciences
- Jenny Barnett, Cambridge Cognition
- Edward T Bullmore, Psychiatry
- Isabel Clare, NIHR CLAHRC East of England
- Charlotte Housden, Cambridge Cognition
- Peter Hutchinson, Clinical Neurosciences
- Peter B Jones, Psychiatry
- David K Menon, Division of Anaesthesia
- Liron Jacobson, Peak
- John T O'Brien, Psychiatry
- Trevor W Robbins, Psychology
- **George Savulich, Psychiatry**
- Emmanuel A Stamatakis, Division of Anaesthesia