

Cognitive Dysfunction in Depression: The Need for Discovery, Development, and Translation in this Domain

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Declaration of Interests: Barbara Sahakian consults for Cambridge Cognition, Lundbeck, Otsuka and Servier. She holds a grant from Janssen/J&J.

Aims

- The importance of early detection and early effective treatment of depression
- Cognitive problems in depression
 - Implications for prognosis
 - Impact on patients
 - The concepts of hot and cold cognition
- Cognitive problems in remitted depressed patients
- Treatment of cognitive impairment in depression
- Fast-acting antidepressants
- Holistic treatment (eg pharmacological, psychological, cognitive, workplace, social)

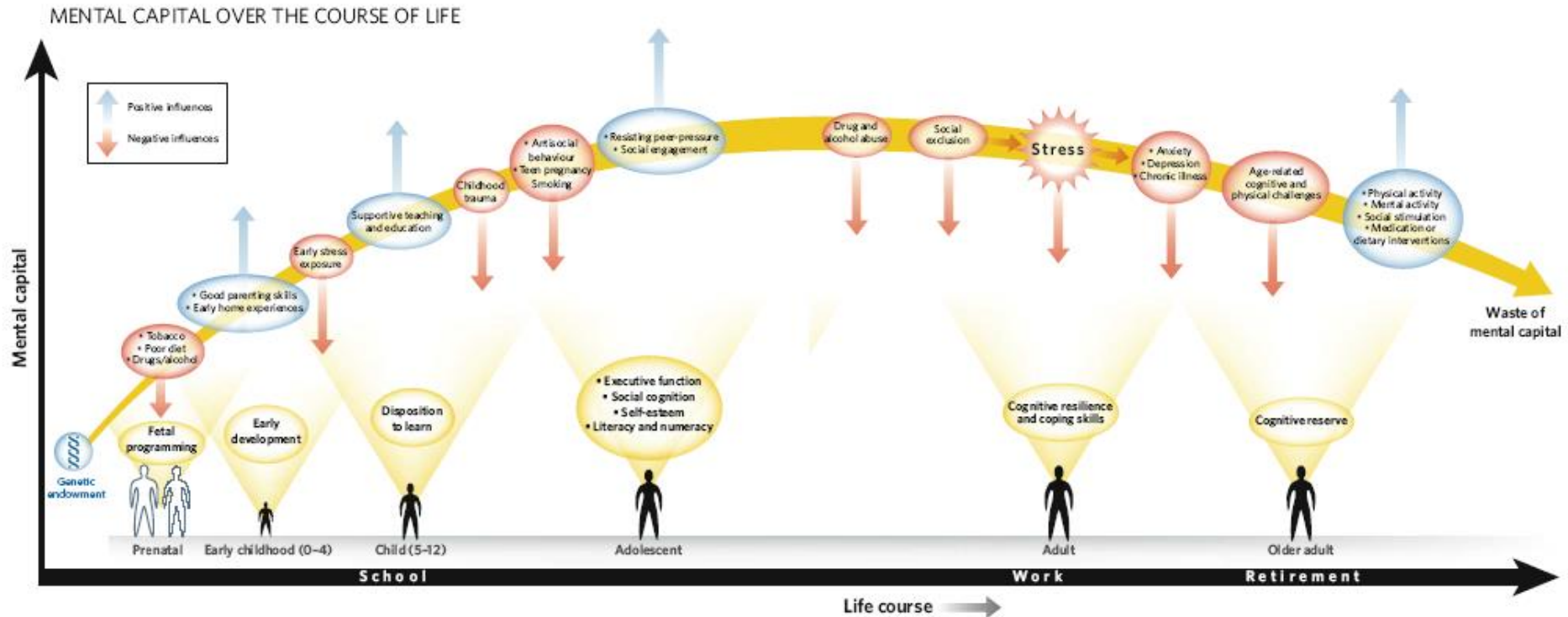
Early Detection and Early Treatment of Depression is Beneficial

If depression is left untreated, it leads to:

- Poorer response to antidepressant treatment
- Lower rate of remission
- Higher risk of chronicity
- Higher number of recurrences

Biomarkers for prevention, early detection and early effective treatment

- Biomarkers include cognitive, genetic, neuroimaging and blood based measures
- 25% of mood disorders start by 18 years of age



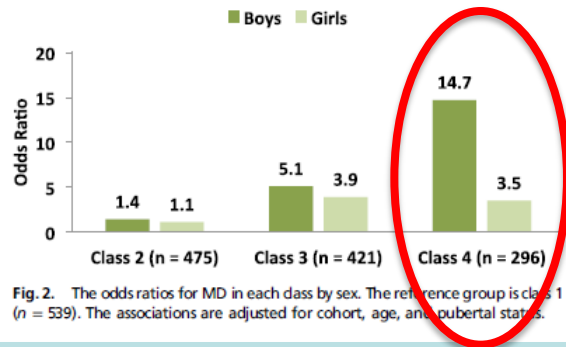
Mental capital encompasses both cognitive and emotional resources, and resilience in the face of stress.

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

Insel, Voon, Nye, Brown, Altevogt, Bullmore, Goodwin, Howard, Kupfer, Malloch, Marston, Nutt, Robbins, Stahl, Tricklebank, Williams, Sahakian, (2013) Innovative solutions to novel drug development in mental health. *Neuroscience & Biobehavioral Reviews*, 37 (10), 2438-2444.

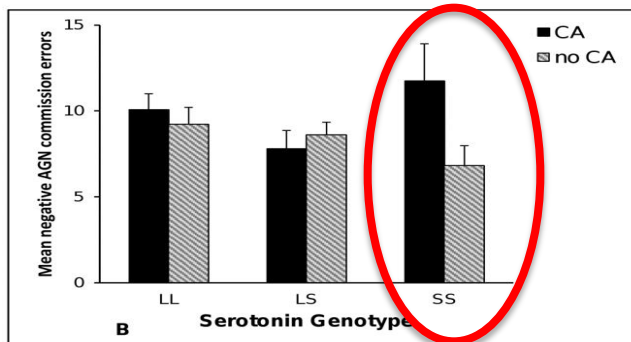
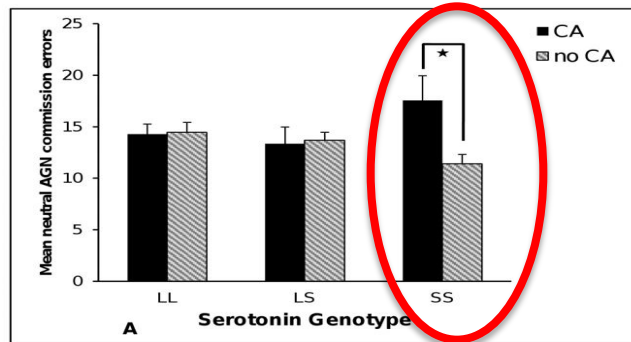
Jones (2013) Adult mental health disorders and their age of onset. *BJPsych*, 202, s5-s10

Biomarkers for Early Detection eg. Genetic, Cortisol, Cognition

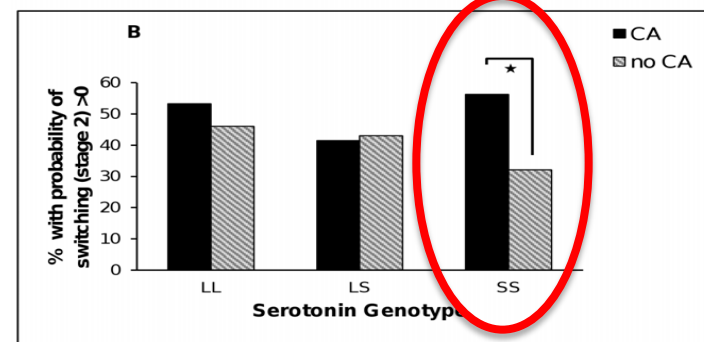
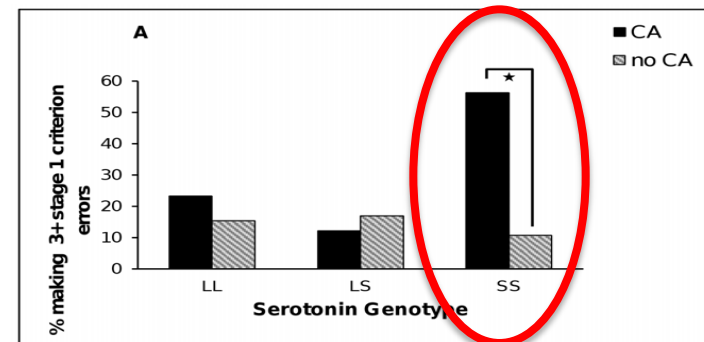


Elevated morning cortisol is a stratified population level biomarker for major depression in boys only with high depressive symptoms
Matthew Owens, Joe Herbert, Peter B. Jones, Barbara J. Sahakian, Paul O. Wilkinson, Valerie J. Dunn, Timothy J. Croudace, and Ian M. Goodyer, PNAS, 2014

Negative attentional bias



Over-sensitivity to negative feedback



Owens M, Goodyer IM, Wilkinson P, Bhardwaj A, Abbott R, Croudace T, Dunn V, Jones PB, Walsh ND, Ban M, Sahakian BJ (2012). 5-HTTLPR and Early Childhood Adversities Moderate Cognitive and Emotional Processing in Adolescence. PLOS ONE.

Cognitive Dysfunction is Core to Depression

Depression Affects both **Cold** and **Hot** Cognition

- Whereas **cold** cognition is non-emotional, **hot** cognition involves emotion
 - **Hot** cognitive function may involve a conflict between risk and reward
 - **Hot** decision making is frequently time-limited
- **Hot** cognition includes negative attentional biases, response to negative feedback and problems of risky decision-making
- **DSM 5:** Diminished ability to think or concentrate, or indecisiveness
- **Research Domain Criteria (RDoC):** Broad domains of function (eg negative emotionality, cognition)
 - Roiser & Sahakian (2013) CNS Spectrums
 - Roiser, Elliott, Sahakian (2012) Neuropsychopharmacology Reviews
 - Insel, Cuthbert, Garvey, Heinssen, Pine, Quinn, Sanislow, Wang (2010) American Journal of Psychiatry

Cognitive dysfunction in depression impacts on functionality

Cognitive deficits are associated with:

- Higher relapse rate
- Poorer functional outcome

Information processing, memory and verbal fluency are predictive of poor academic, occupational and daily functioning in major depressive disorder (MDD)

Workplace functionality (absenteeism and presenteeism)

<u>Disorder</u>	<u>Estimated number of subjects affected</u>	<u>Total costs - Estimated in Millions of Euros (2010)</u>			
		<u>Direct health care costs</u>	<u>Direct non-medical costs</u>	<u>Indirect costs</u>	<u>Total</u>
Major depression	30.3 million	24,156	13,762	53,996	91,914

- Direct health care costs include medical costs
- Non-medical costs include the cost of nursing homes etc.
- **Indirect costs** include the cost of **absenteeism from work**, pensions etc.

- Jaeger, J., Berns, S., Uzelac, S. & Davis-Conway, S. (2006). *Psychiatry Res* 145:39-48
- The economic case appendix, No health without mental health, Department of Health.
- Fineberg, Haddad, Carpenter, Gannon, Sharpe, Young, Joyce, Rowe, Wellsted, Nutt & Sahakian (2013). The size, burden and cost of disorders of the brain in the UK. *Journal of Psychopharmacology*.
- Sahakian (2013) Burdens of brain disorders ignored by government. *The Conversation*. Available at: <http://theconversation.com/burden-of-brain-disorders-ignored-by-government-16641>
- Olsen et al (2012) The economic cost of brain disorders in Europe. *European Journal of Neurology*

What is cognitive dysfunction in depression and how does it affect the lives of the patients?

“Depression is the curse of my generation. When did this epidemic begin?”

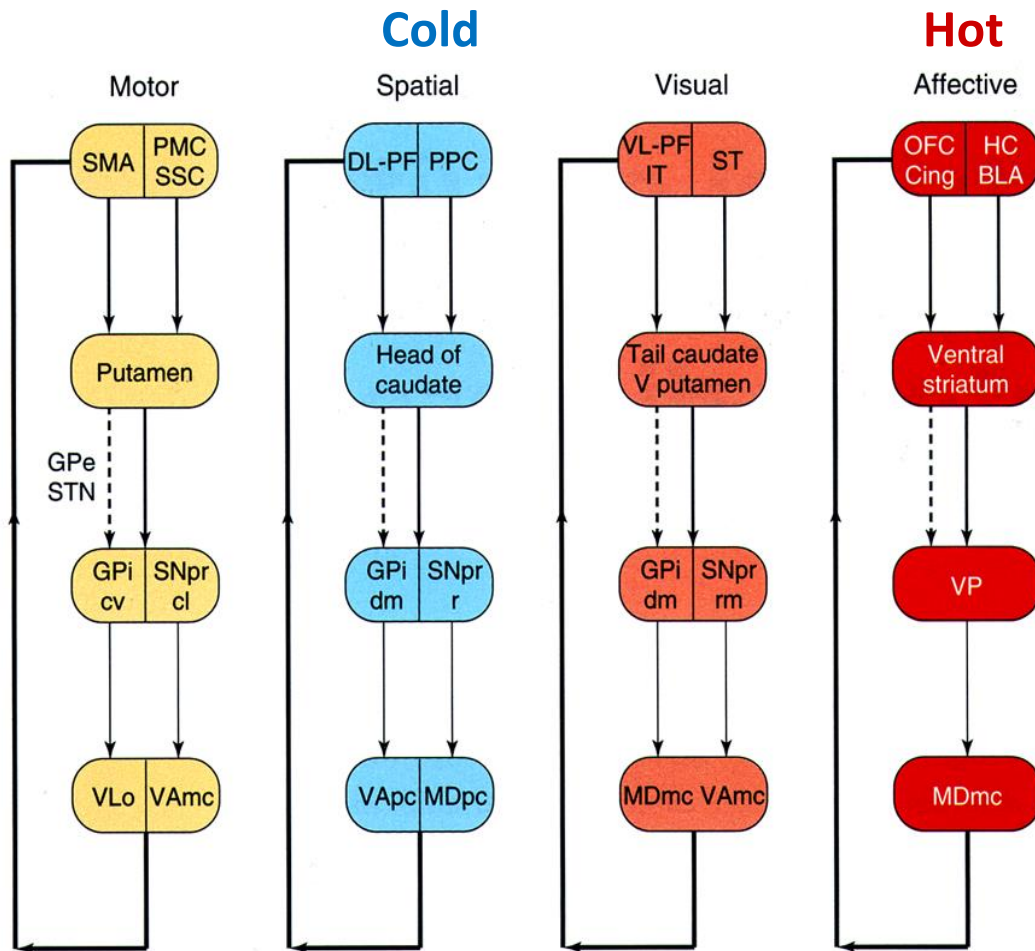
“When my depression was at its worst I was very forgetful; my short-term memory, which is usually good, was non-existent. My therapist pointed out that I wasn’t focusing well enough to even lay down a memory in the first place.

Being unable to remember simple things added to the feeling of being out of control. The antidepressants have helped with that. I am able to concentrate much better.”

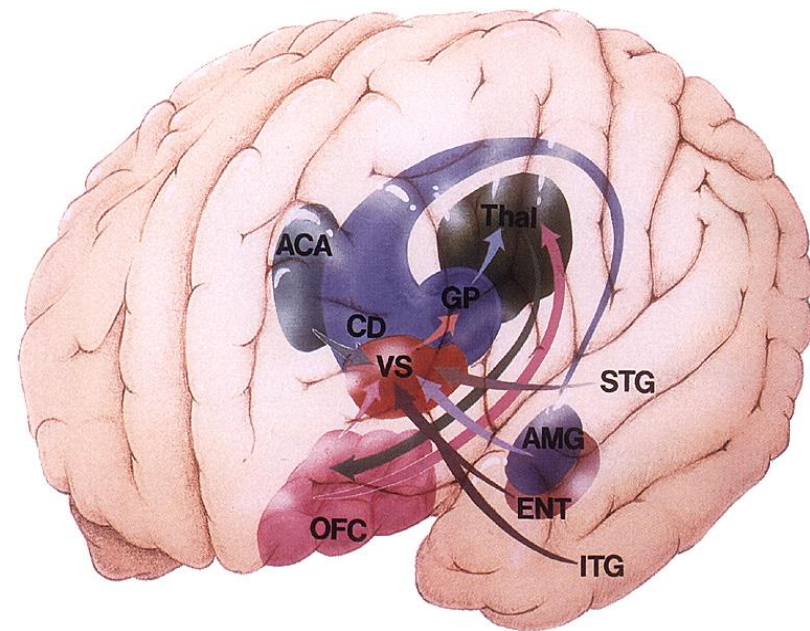
Allison Pearson (Newspaper Columnist and Novelist, Author of “I don’t know how she does it”)

Cold and Hot cognition

Affective cortico-striatal circuits in the human brain



- Emotional processing
- Motivation



-Alexander, G.E., DeLong, M.R. & Strick, P.L. (1986) *Annu Rev Neurosci.* 9:357-81.

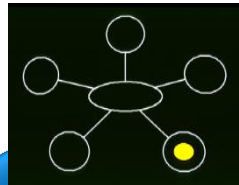
-Salloway, S., Malloy, P. & Cummings, J.L. (1997) *The Neuropsychiatry of Limbic and Subcortical Disorders*

See also: Roiser, J.P. & Sahakian, B.J. (2013) *CNS Spectrums*

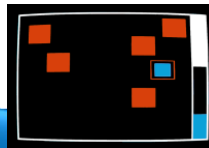
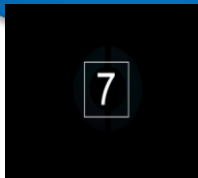
DA, NA, 5-HT

Objective Methods for Measuring Components of Cognition

Attention/Concentration



Attention



Working
memory

Learning and Memory

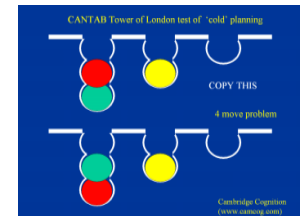
Episodic
memory



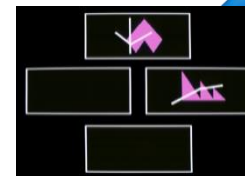
Executive Function including cognitive control



Risky Decision-
making



Planning



Cognitive
Flexibility

Impulsivity

BEEP!

Using Innovative Technology in Mental Health



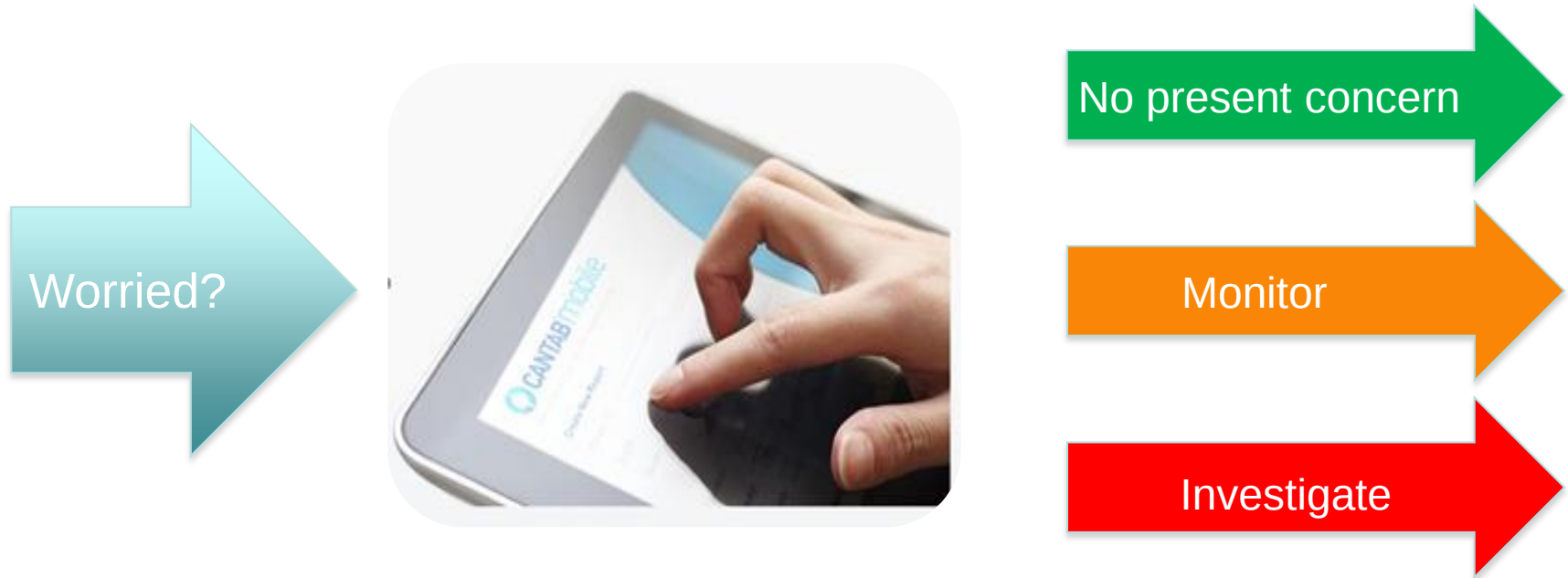
Cantab Mobile



CE Approved Class II European Medical Device

CAMBRIDGE
COGNITION

A general medical practitioner (GP) decision-making tool



- Improving access to cognitive assessment

In-depth assessment of cognition in depression and frequent monitoring of changes in severity



Deep “in clinic” profiling

- Measures of cold cognition
- Measures of hot cognition



Home based sampling

- Frequent
- Interval sampling



Ubiquitous computing

- Continual behaviour monitoring

Patients with major depressive disorder

Preclinical/Asymptomatic

Deep Phenotyping

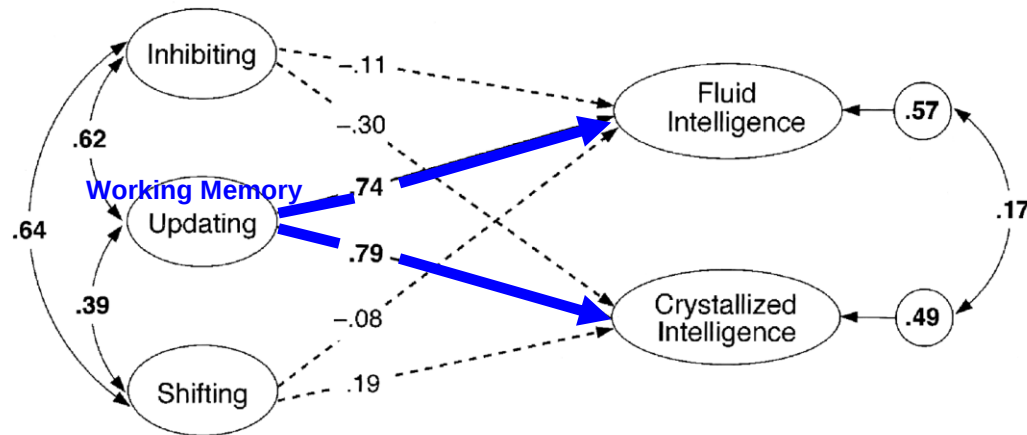
Frequent Phenotyping



Working memory is a core component of executive function tasks and is important for educational success

- Working Memory is related to fluid and crystallized intelligence

Friedman, N. P., Miyake, A., Corley, R. P., Young, S. E., DeFries, J. C. & Hewitt, J. K. (2006) Psychological Science



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

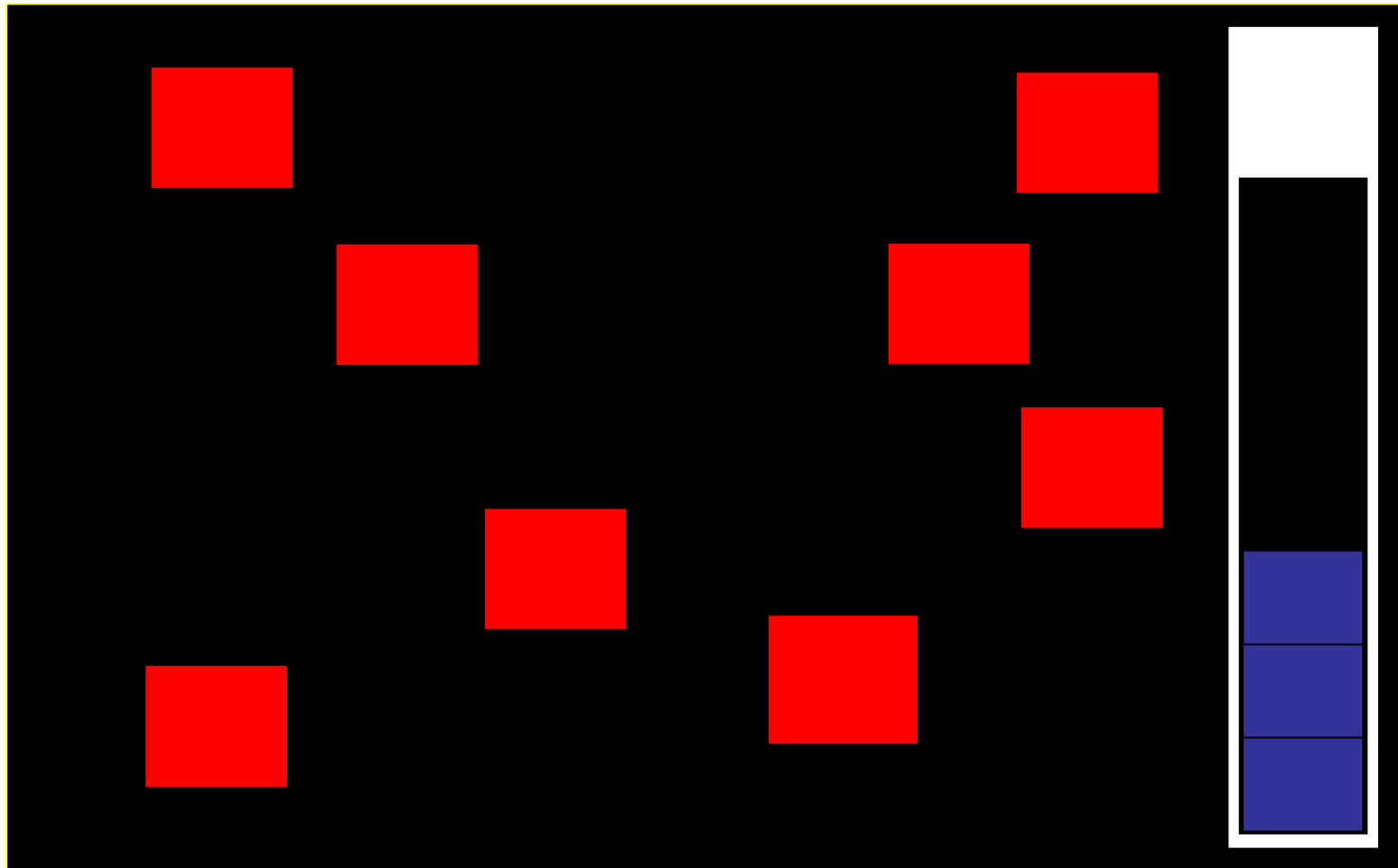
Yuan, K., Steedle, J., Shavelson, S., Alonzo, A. & Oppezzo, M. (2002) Educational Research Review

- 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

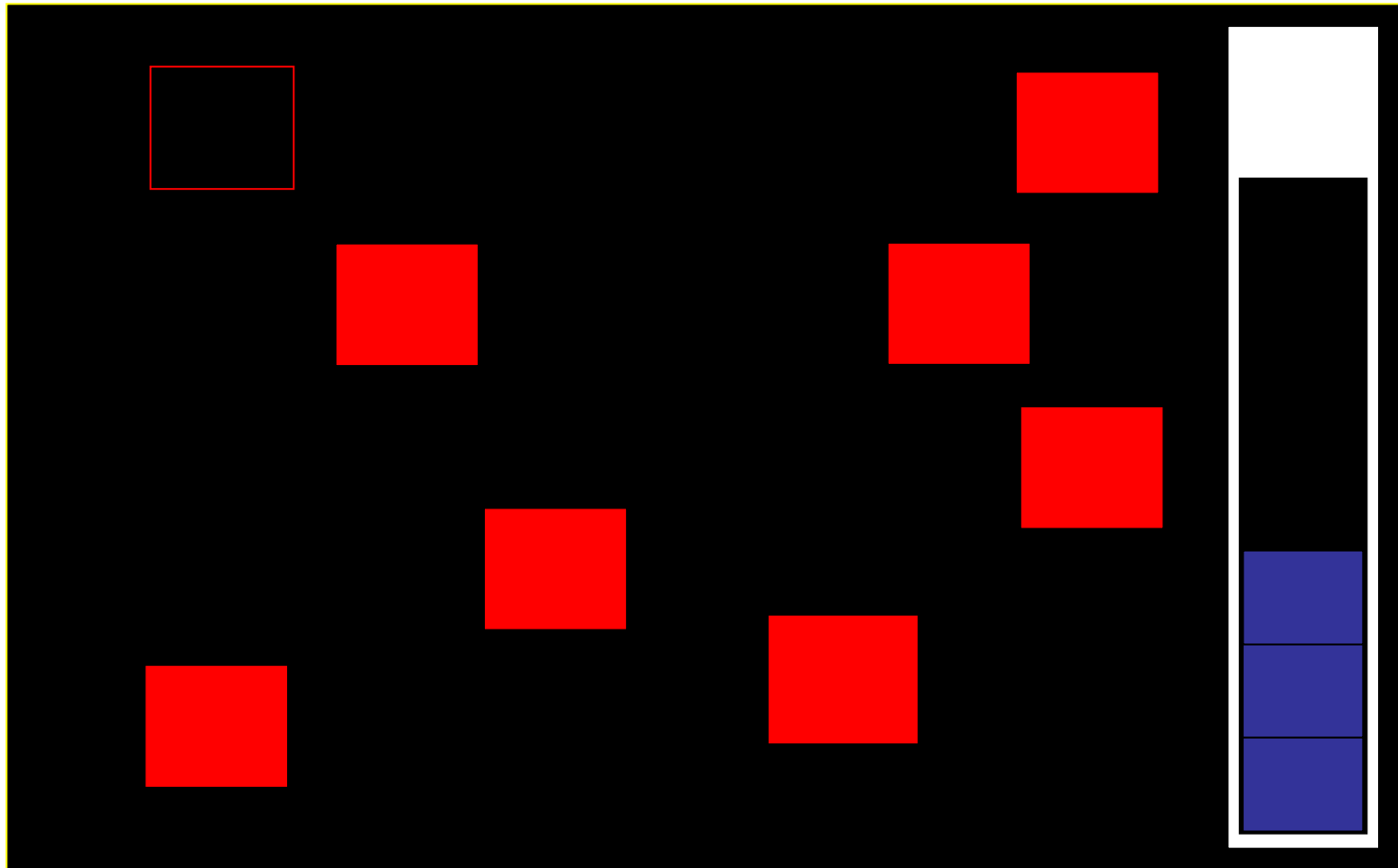
- Working memory is affected in many neuropsychiatric disorders, including depression, attention deficit hyperactivity disorder and schizophrenia

CANTAB Spatial Working Memory (SWM)



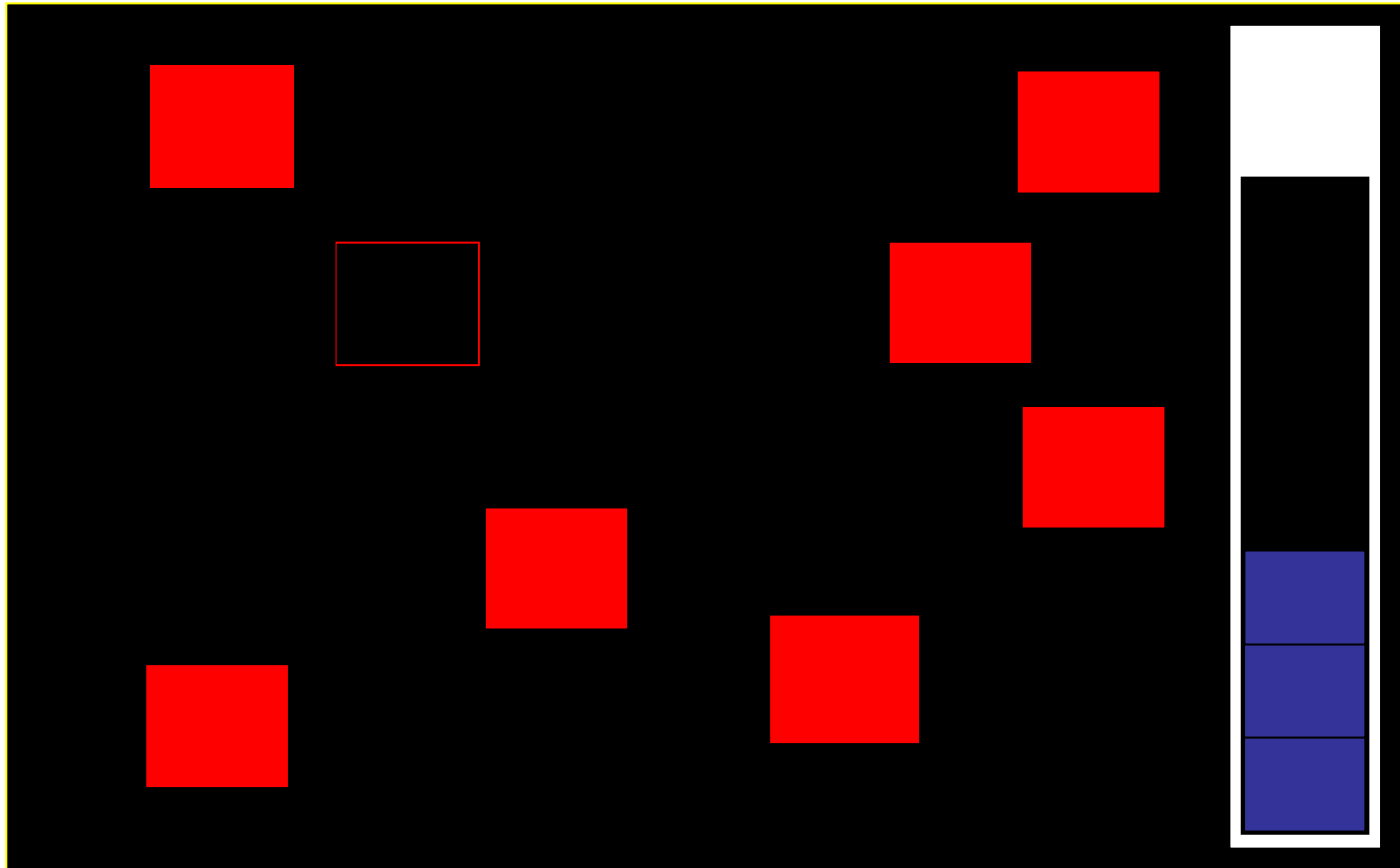
Look for a blue token hidden in 1 of the boxes, without returning to a box where a token has previously been found

CANTAB Spatial Working Memory (SWM)



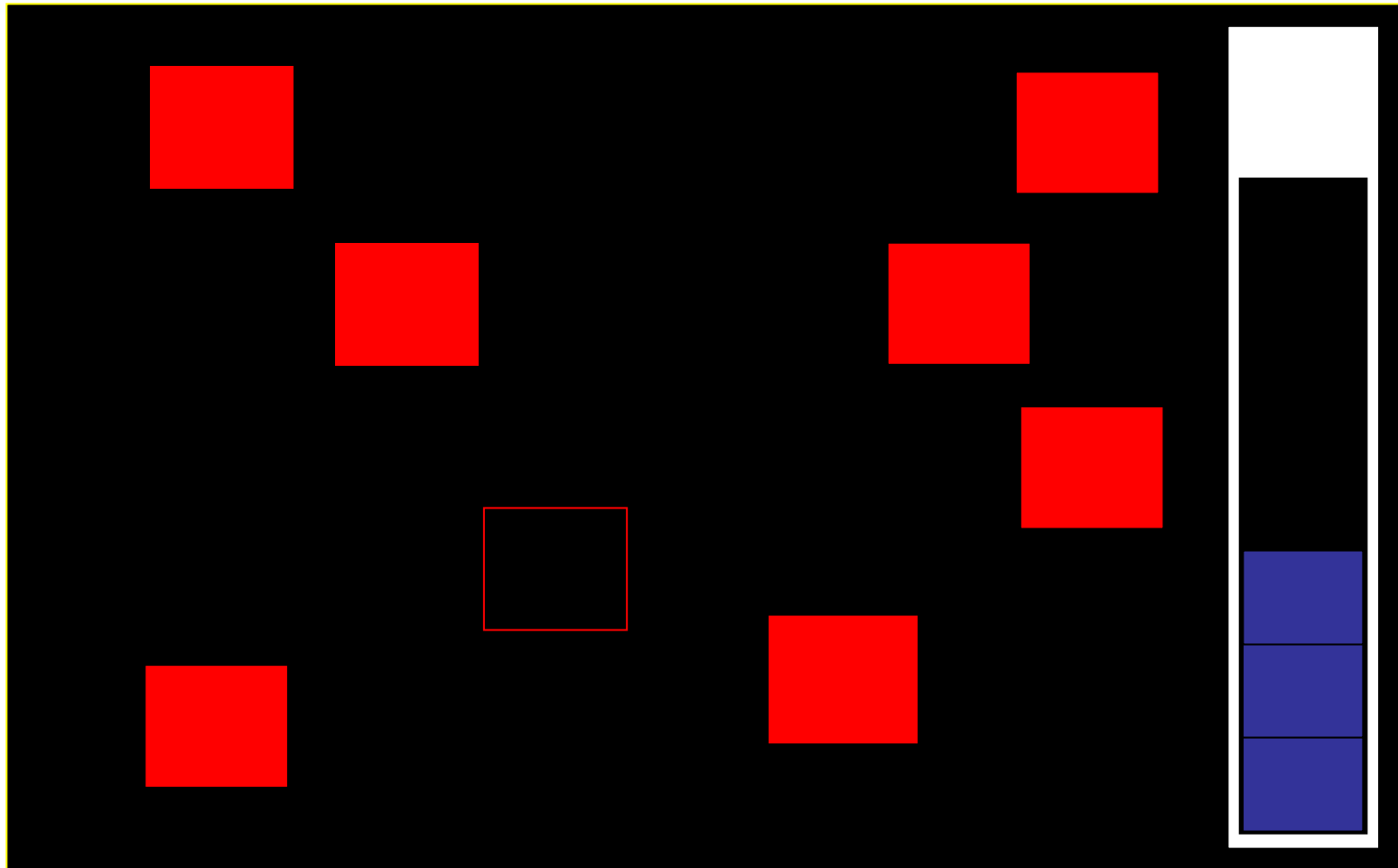
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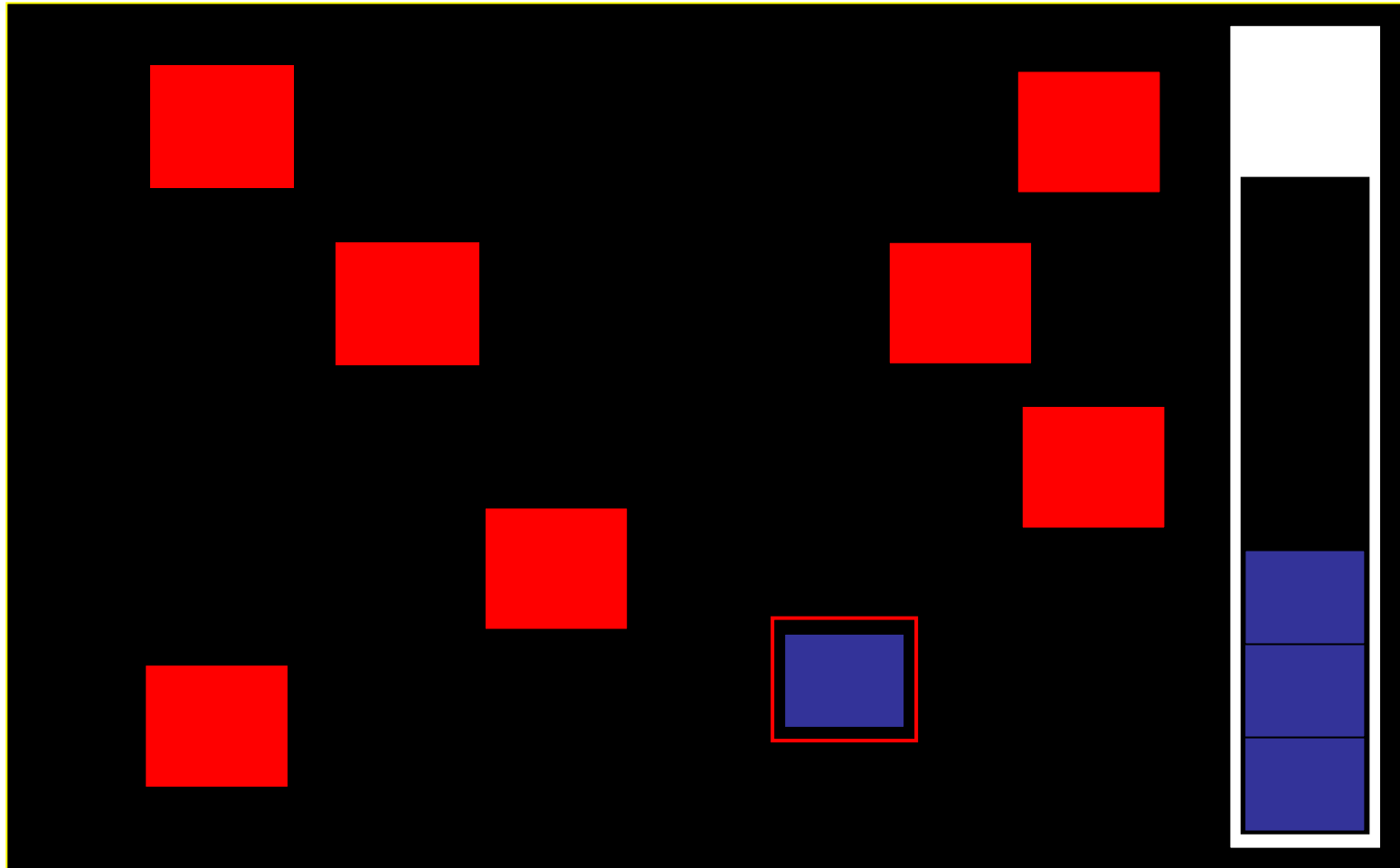
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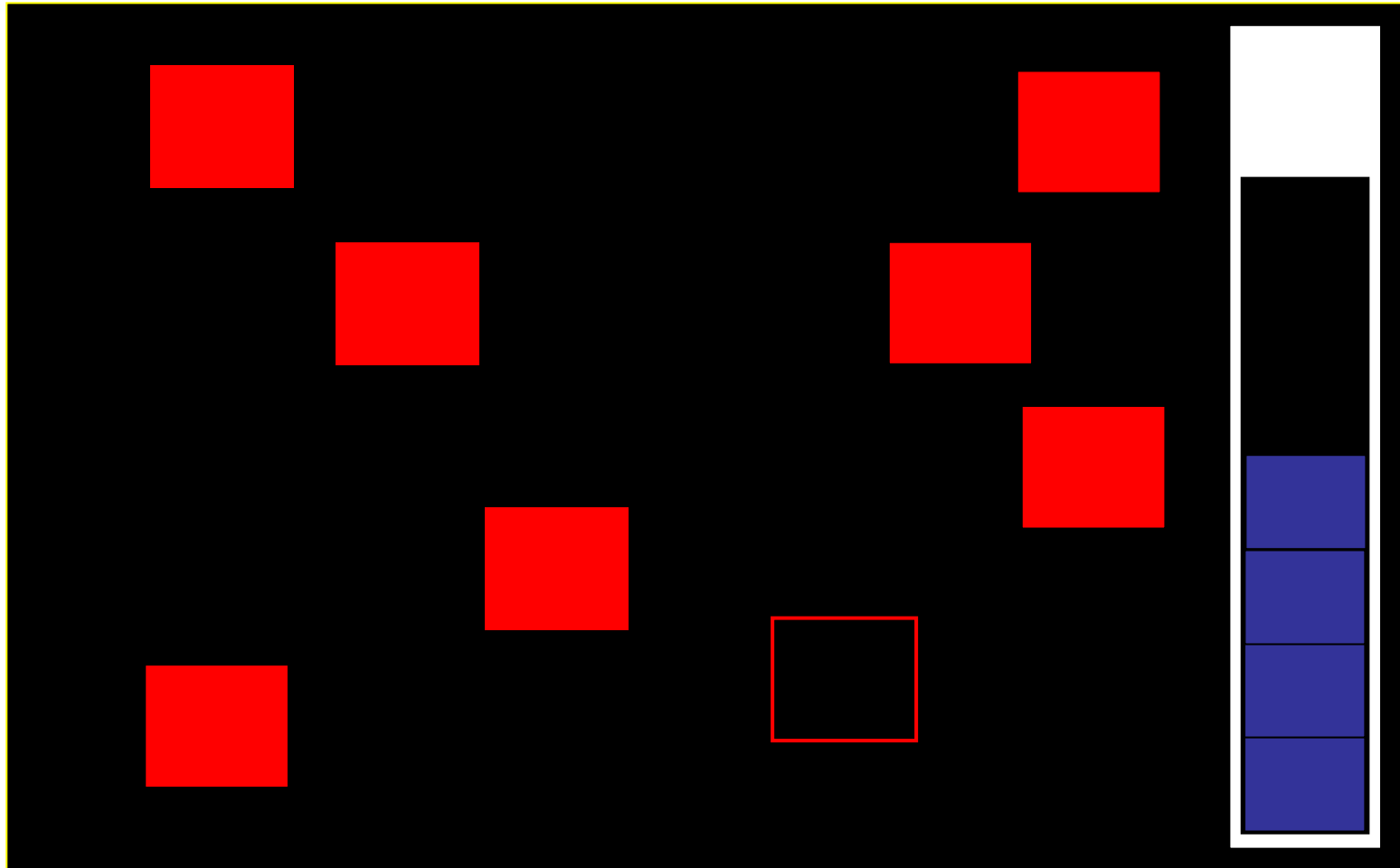
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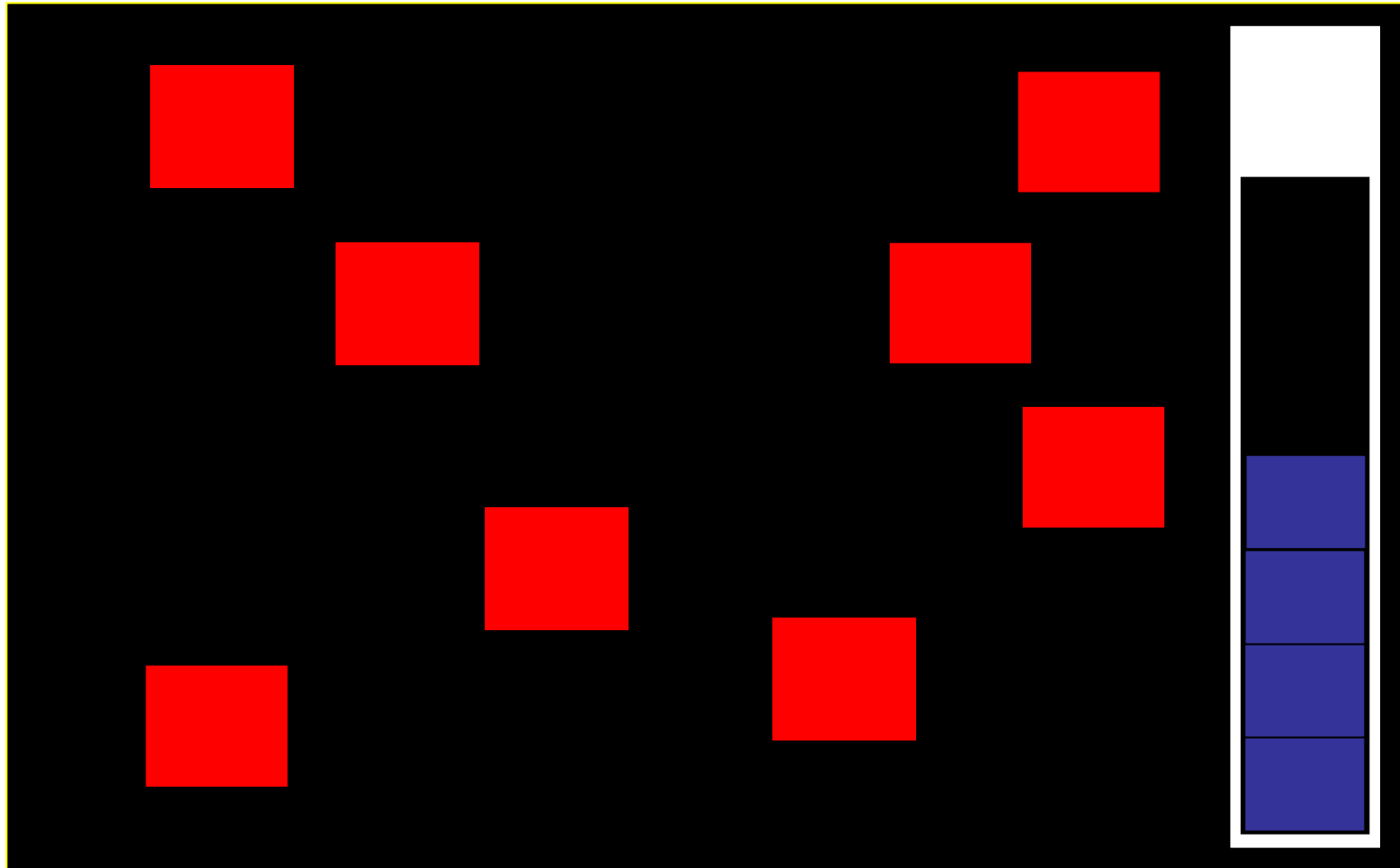
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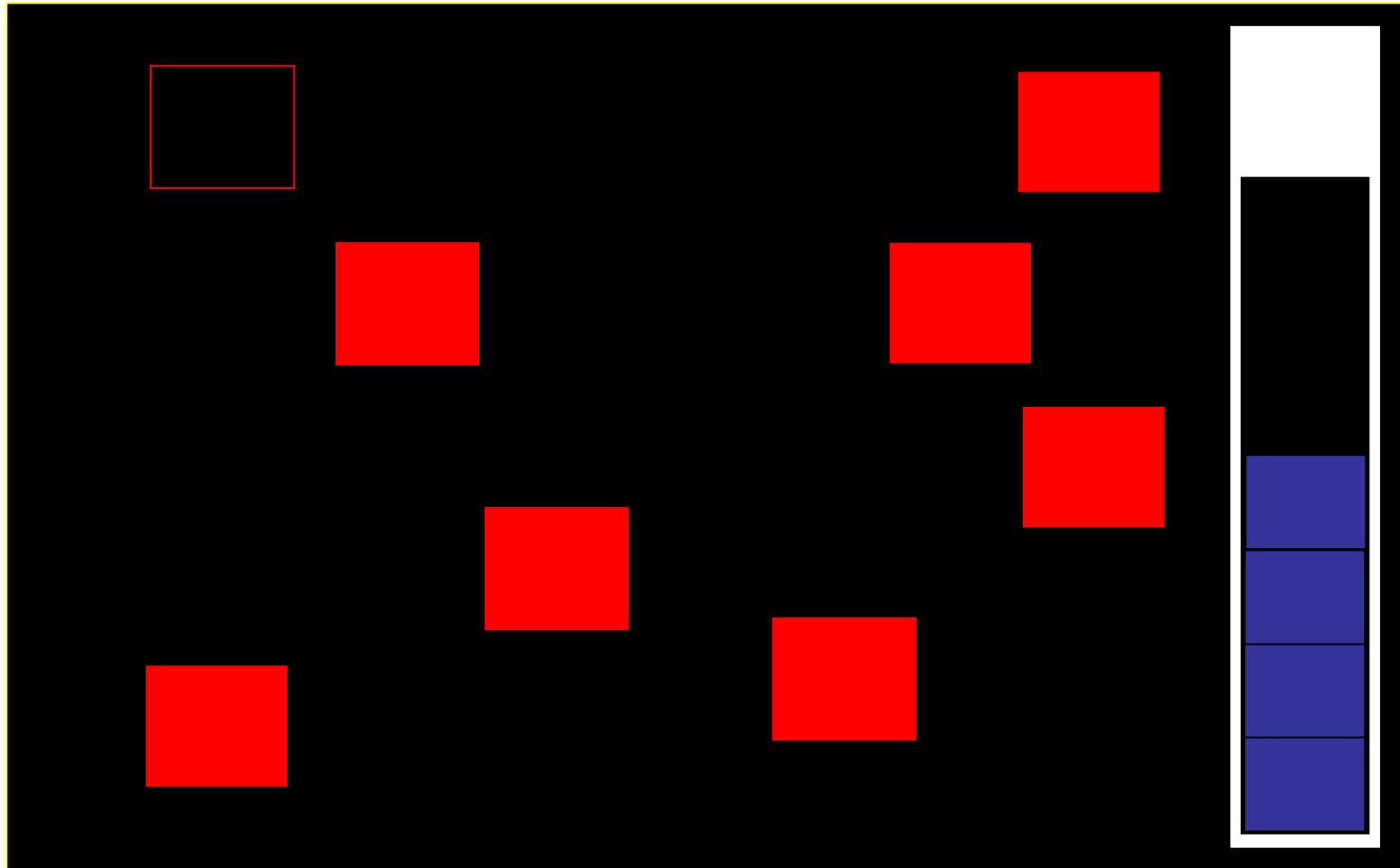
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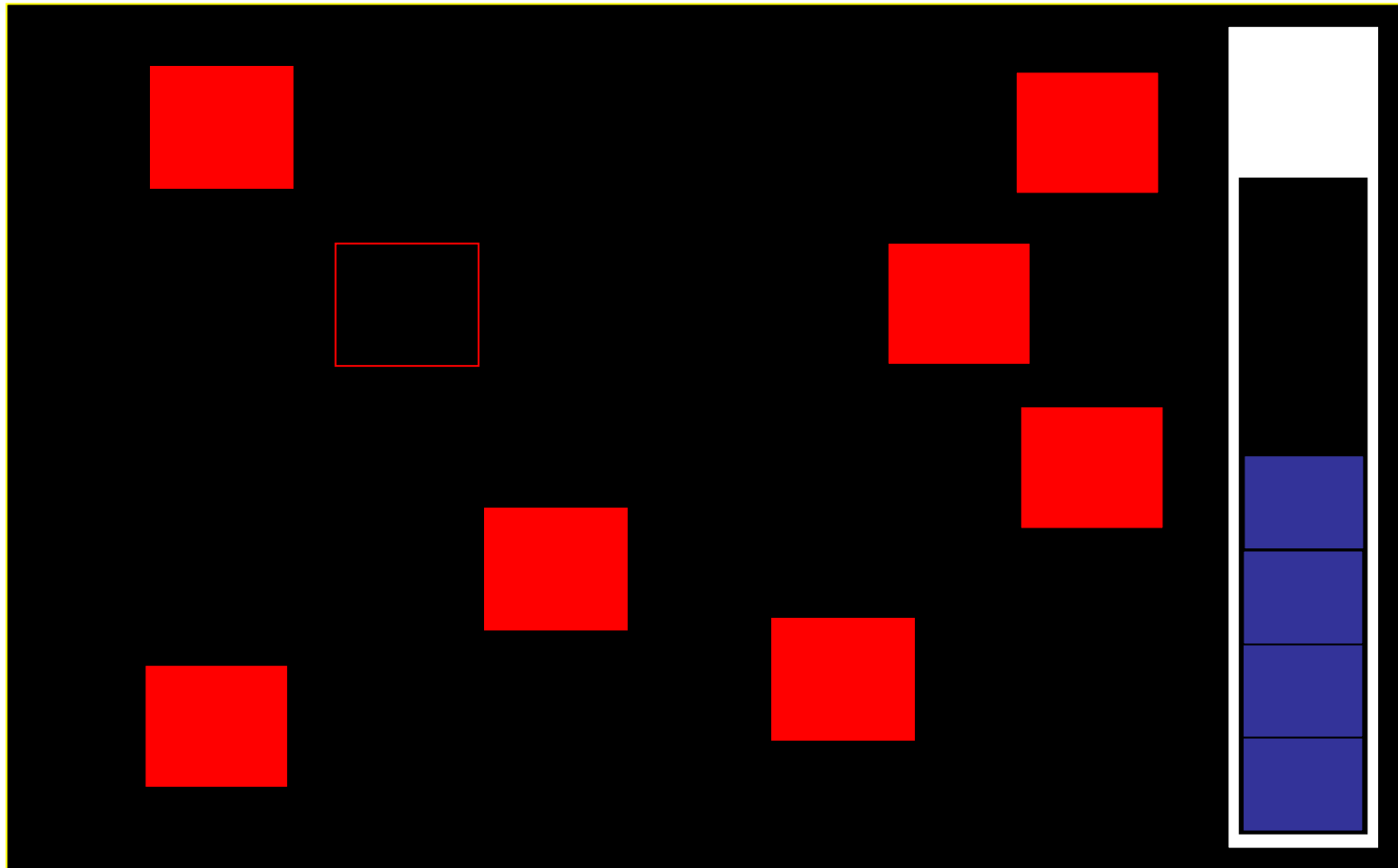
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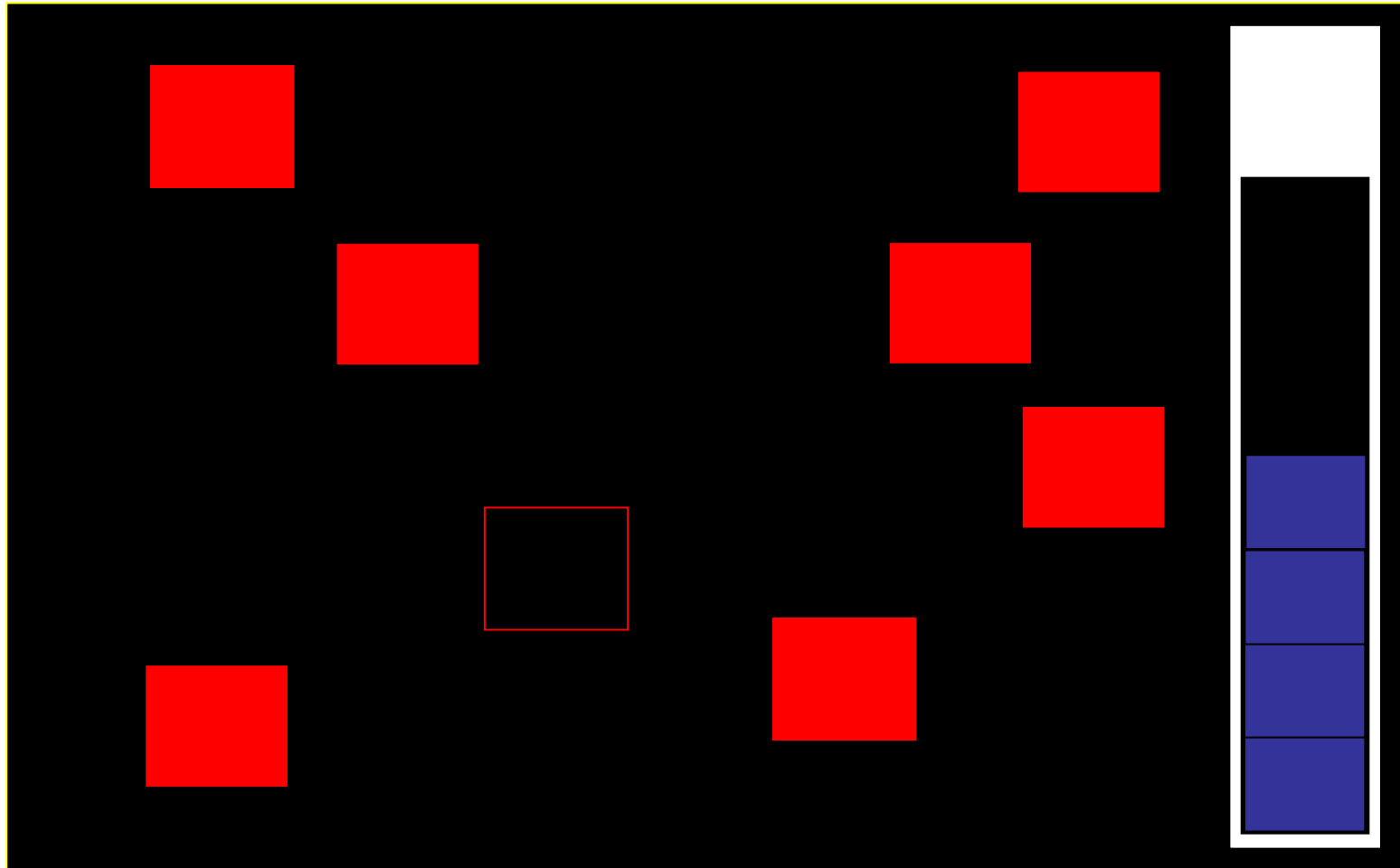
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CANTAB Spatial Working Memory (SWM)



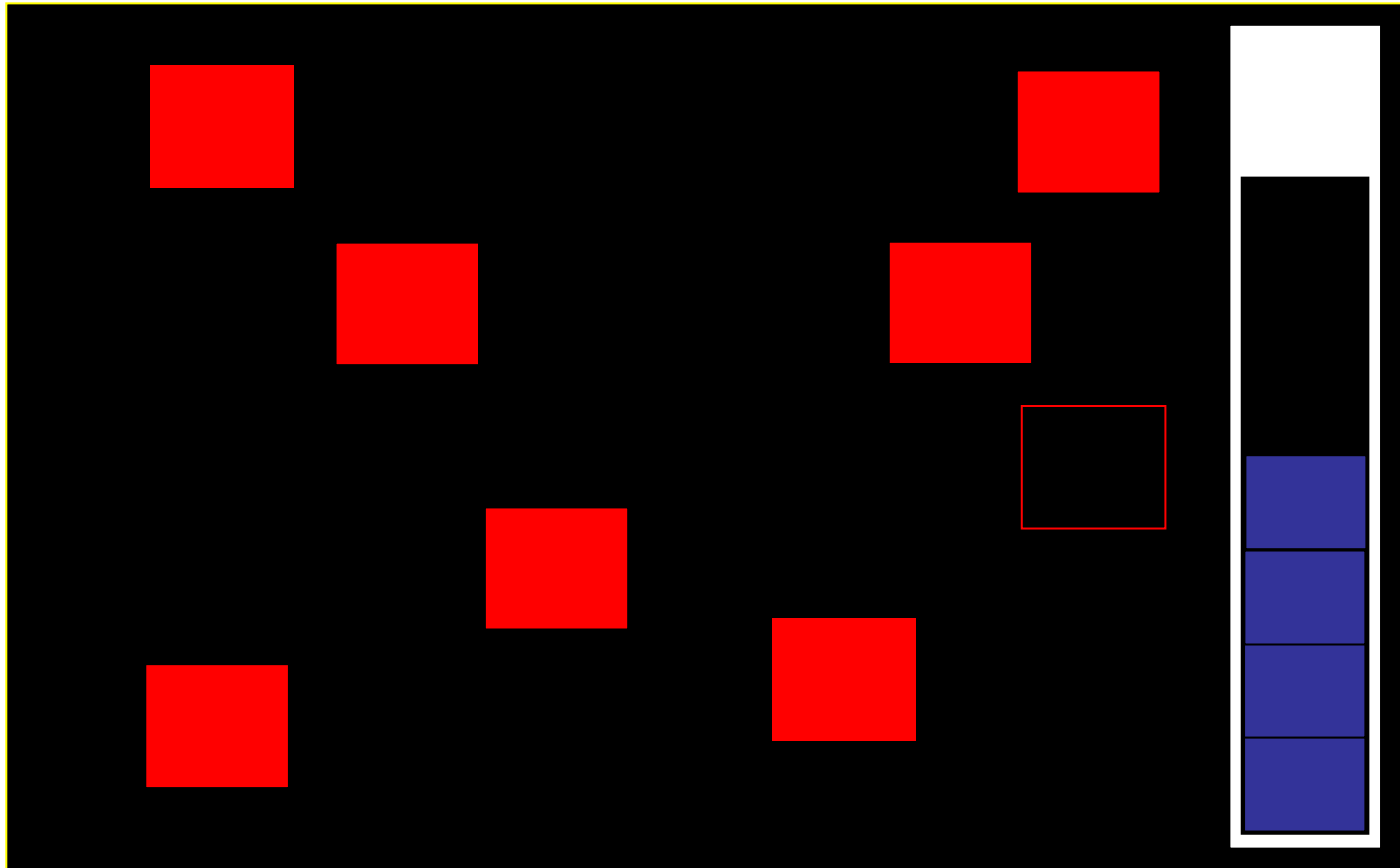
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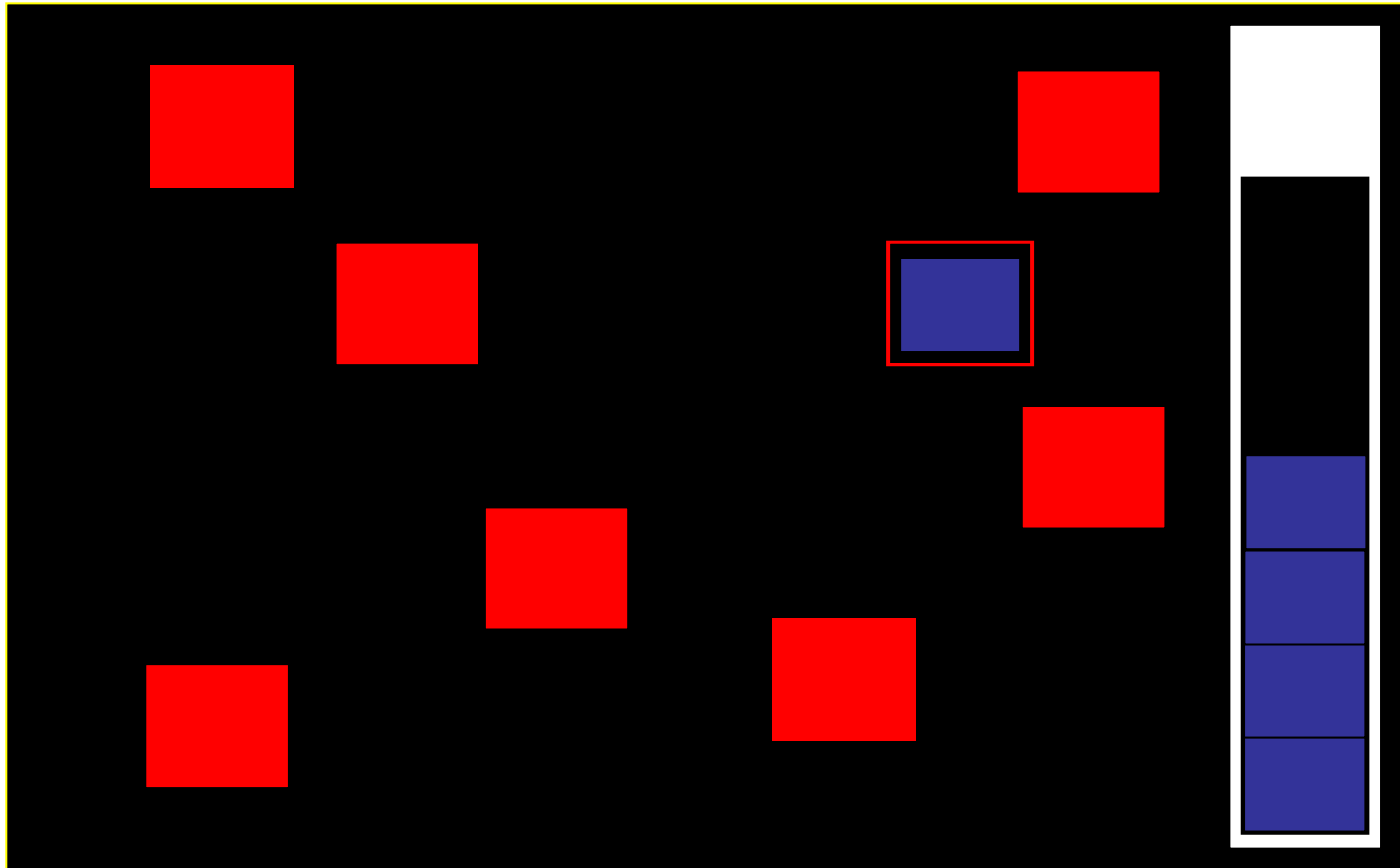
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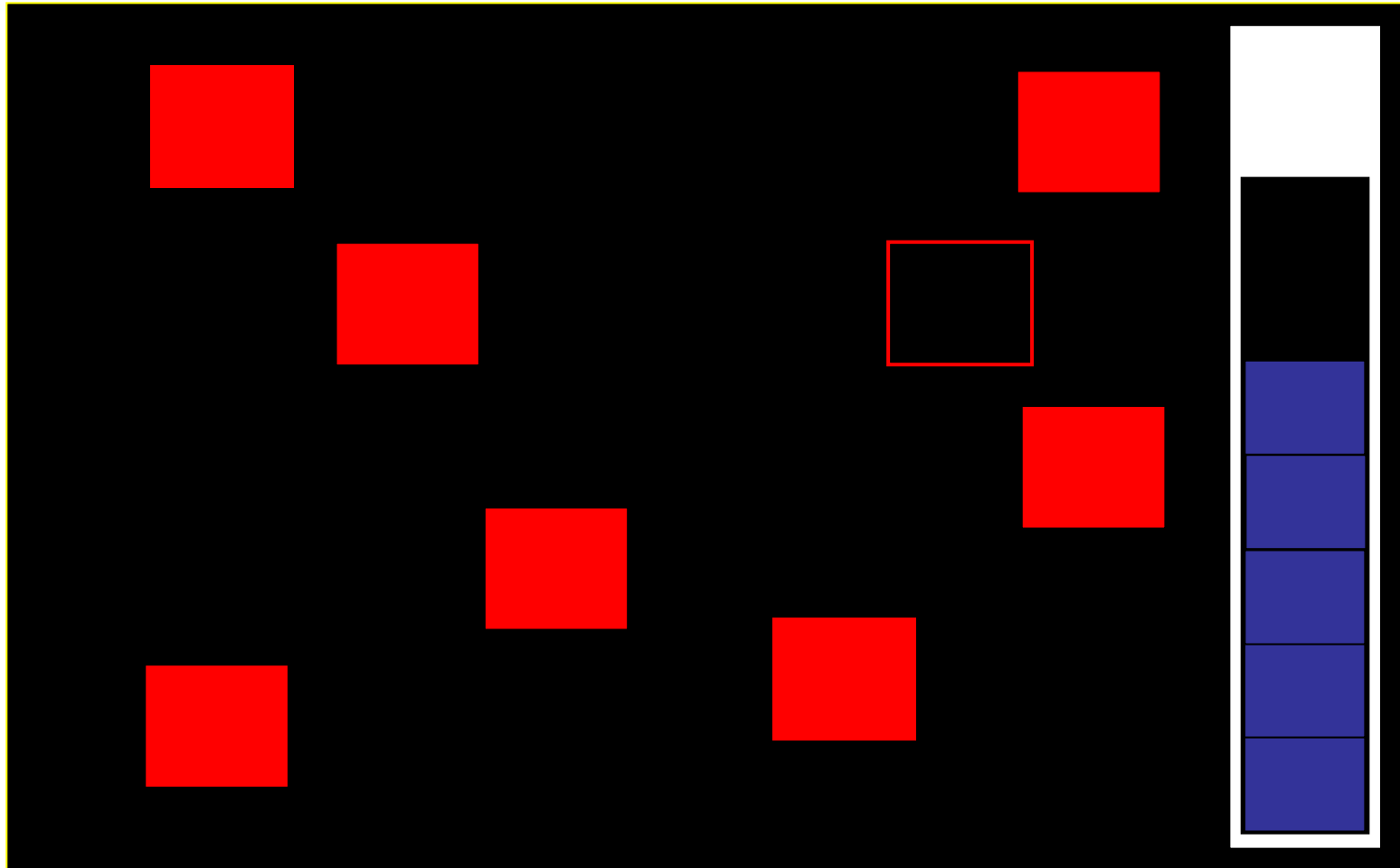
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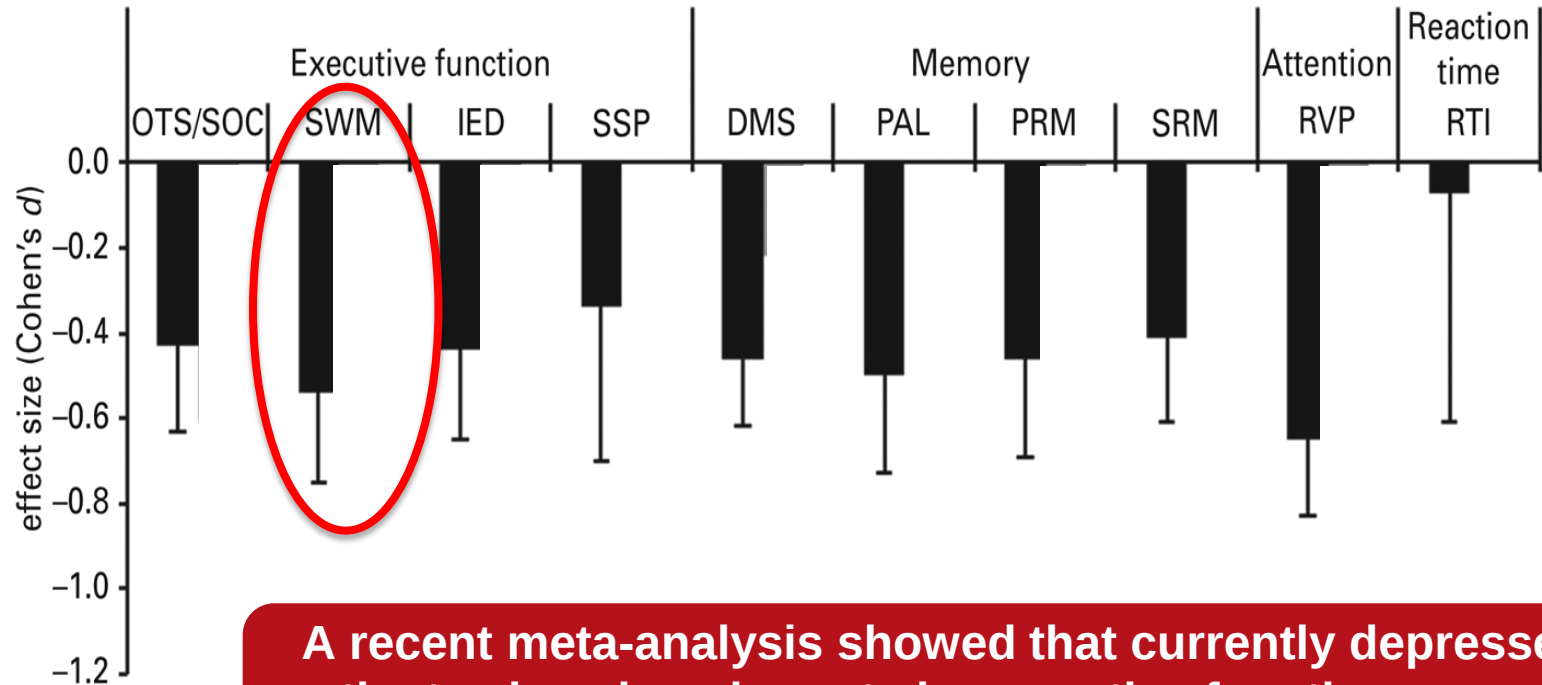
CANTAB Spatial Working Memory (SWM)



Look for a blue token hidden in 1 of the boxes, without returning to a box where a token has previously been found

Cold cognitive impairments in currently depressed patients are seen in attention, memory and executive function

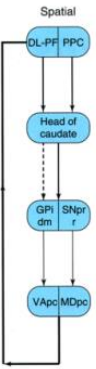
Currently depressed patients



A recent meta-analysis showed that currently depressed patients show impairments in executive function, memory and attention

CGT, Cambridge Gambling Task; **SWM**, Spatial Working Memory; **OTS/SOC**, Stockings of Cambridge; **IED**, Intra-Extra Dimensional Set Shift; **SSP**, Spatial Span; **DMS**, Delayed Matching to Sample; **PRM**, Pattern Recognition Memory; **SRM**, Spatial Recognition Memory; **PAL**, Paired Associates Learning; **RVP**, Rapid Visual Information Processing; **RTI**, Reaction Time

Rock, P. L., Roiser, J.P., Riedel, W. J. & Blackwell, A. D. (2014) *Psychological Medicine*, 44 (10)
Poster presented at the British Association for Psychopharmacology 2012 Summer Meeting



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)**.

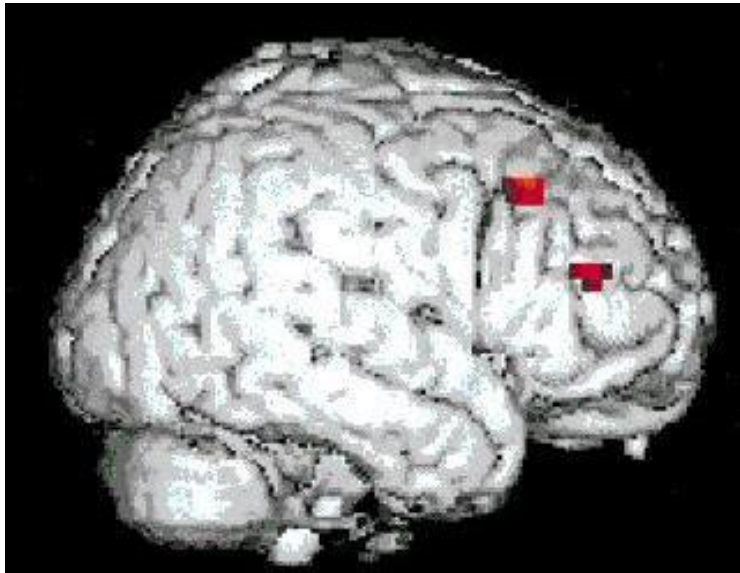
Modafinil (Provigil) action is unclear; Possibilities include: indirect mediation of ACh and/or Adrenergic $\alpha-1$ receptor activity. Appears to effect hypothalamic orexin and histamine, and has a small effect on dopamine transporter activity. **Recent evidence suggests NA** (Minzenberg et al 2008), **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.

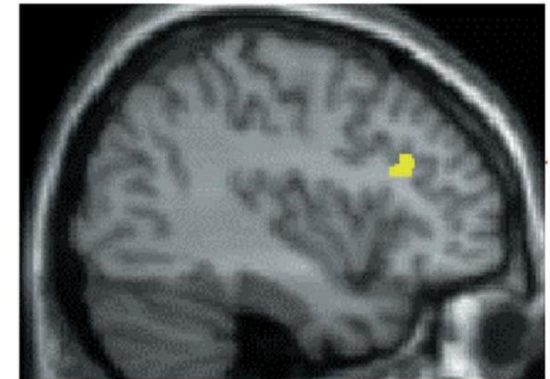
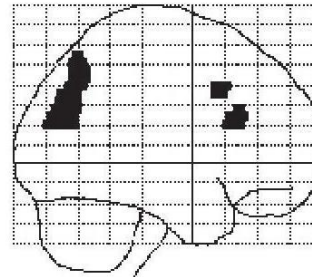
http://www.ecnp.eu/~media/Files/ecnp/Projects%20and%20initiatives/Nomenclature/Review%20articleNEUPSY_10717v2%20pdf.pdf

The neural network involved in the Spatial Working Memory (SWM) task

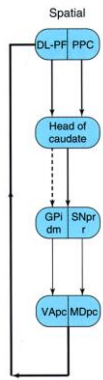
SWM activates a neural network that includes dorsolateral prefrontal cortex



Methylphenidate enhances SWM performance and improves the efficiency of this neural network in healthy people



- Owen, A.M., Herrod, N.J., Menon, D.K., Clark, J.C., Downey, S.P.M.J., Carpenter, T.A., Minhas, P.S., Turkheimer, F.E., Williams, E.J., Robbins, T.W., Sahakian, B.J., Petrides, M. & Pickard, J.D. (1999) Redefining the functional organization of working memory processes within human lateral prefrontal cortex. European Journal of Neuroscience
- Owen, A.M., Evans, A. C. & Petrides, M. (1996) Evidence for a Two-Stage Model of Spatial Working Memory Processing within the Lateral Frontal Cortex: A Positron Emission Tomography Study. Cereb Cortex
- Mehta, M.A., Owen, A.M., Sahakian, B.J., Mavaddat, N., Pickard, J.D. & Robbins, T.W. (2000) Methylphenidate Enhances Working Memory by Modulating Discrete Frontal and Parietal Lobe Regions in the Human Brain. The Journal of Neuroscience



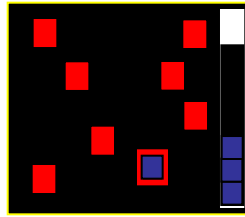
Neural correlates of **cold** cognitive impairments in depression and neuroimaging as a biomarker for prediction of clinical outcome

- Greater load-response activity in the fronto-parietal working memory neural network in un-medicated patients with depression
- A marker of treatment response to fluoxetine was a lower load-response activity at baseline in the dorsal anterior cingulate, left middle frontal and lateral temporal cortices

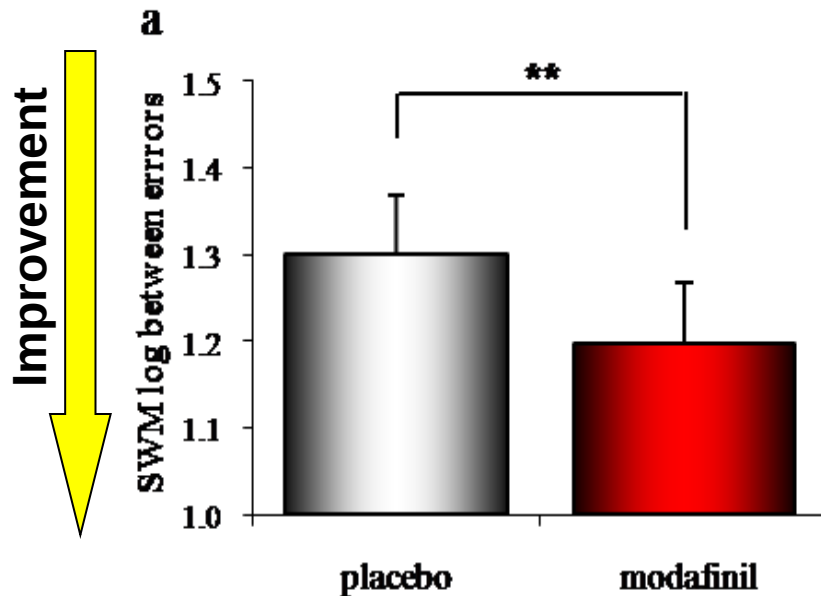
Harvey, Fossati, Pochon, Levy, LeBastard, Lehéricy, Allilaire, Dubois (2005) Neuroimage

Walsh, N. D., Williams, S. C. R., Brammer, M. J., Bullmore, E. T., Kim, J., Suckling, J., Mitterschiffthaler, M. T., Cleare, A. J., Pich, E. M., Mehta, M. A. & Fu, C. H. Y. (2007) Biological Psychiatry

Modafinil improves working memory in patients with first episode psychosis and healthy volunteers

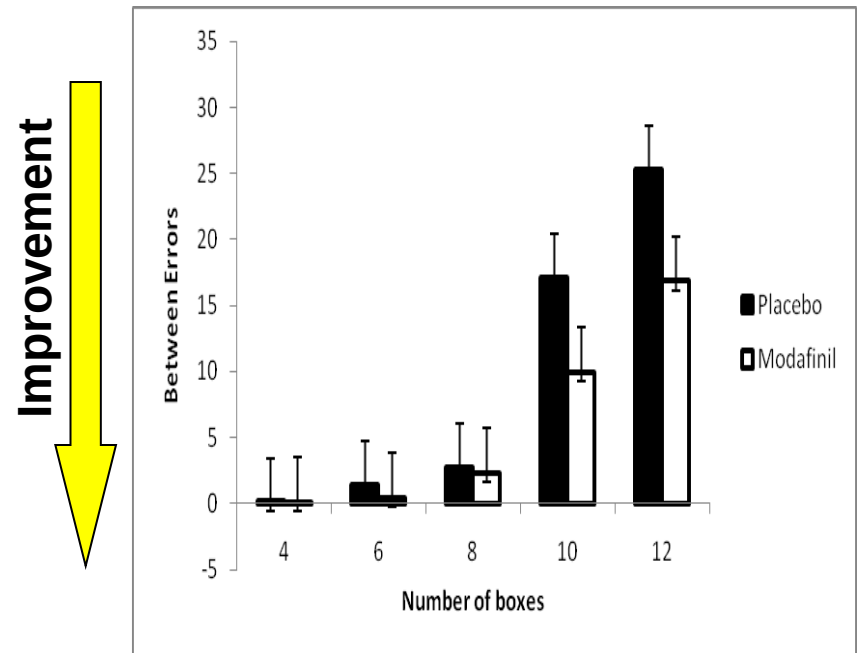


Patients with First Episode Psychosis

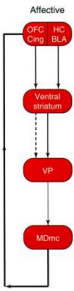


Scoriels L, Barnett JH, Soma PK, Sahakian BJ, Jones, PB (2012) Effects of modafinil on cognitive functions in first episode psychosis. *Psychopharmacology*, 220, 249-258

Healthy Volunteers



Müller U, Rowe JB, Rittman T, Lewis C, Robbins TW, Sahakian BJ (2013) Effects of modafinil on non-verbal cognition, task enjoyment and creative thinking in healthy volunteers. *Neuropharmacology*, 64, 490-495.



Hot cognitive impairments in depression

CANTAB Affective Bias Task

Sample Stimuli

HAPPY

JOYFUL

SUCCESS

CONFIDENT

SAD

GLOOMY

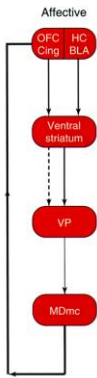
HOPELESS

FAILURE

See also Affective Bias Translational Task for rodents:

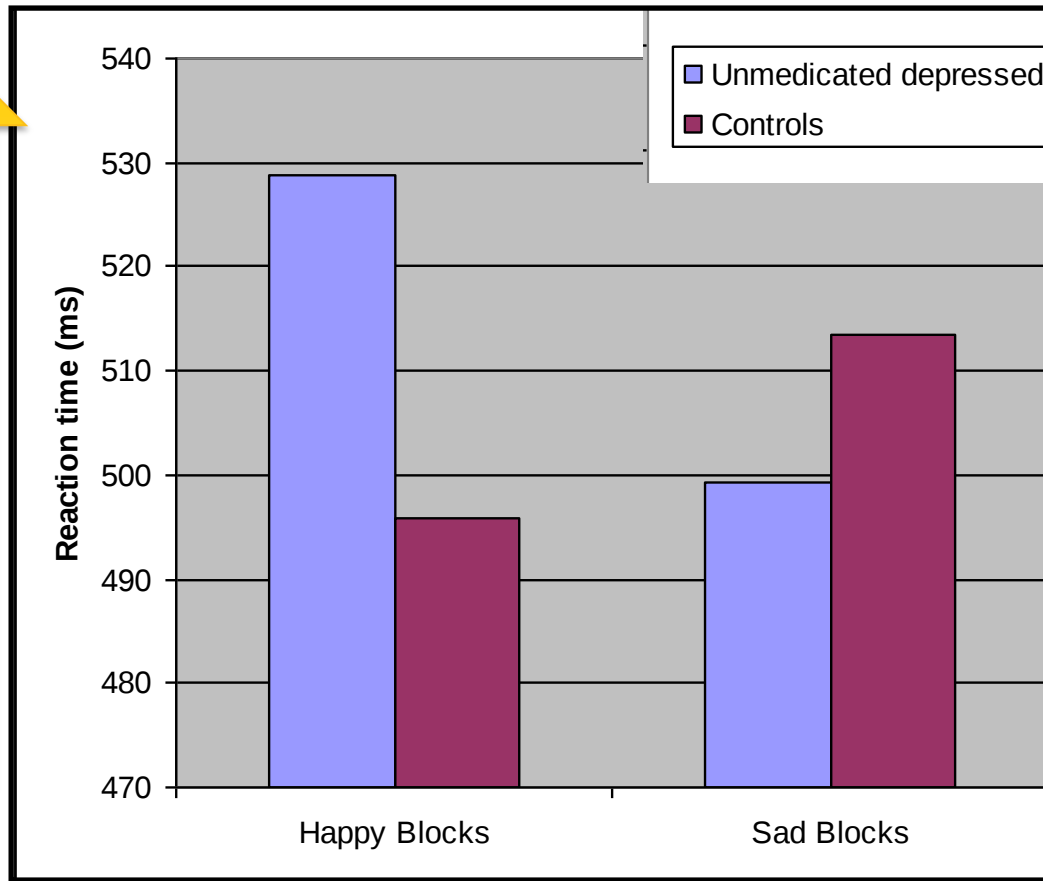
Stuart, Butler, Munafo, Nutt, Robinson (2013) A translational rodent assay of affective biases in depression and antidepressant therapy.

Neuropsychopharmacology, 38, 1625-1635



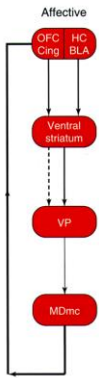
Negative affective bias in depression

Unmedicated patients with major depressive disorder (MDD) are faster to respond to sad compared with happy word targets. In contrast, healthy volunteers are faster to respond to happy words than to sad words (resilience).



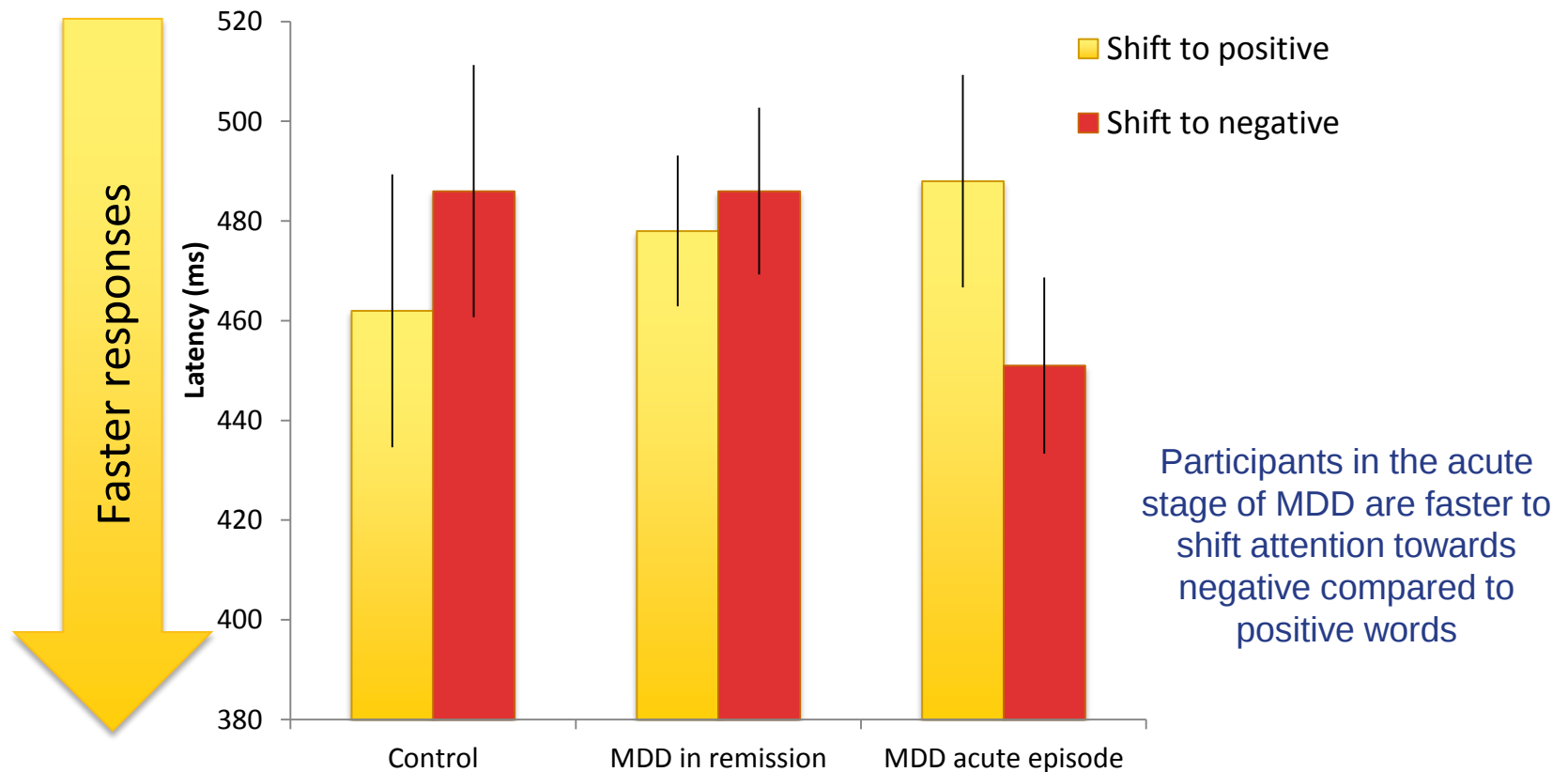
	Major Depressive Disorder	Healthy Volunteers
Age	37.5 (11.9)	36.5 (11.1)
IQ (WAIS abbrev.)	114.85 (12.1)	116.15 (11.9)
MADRS	25.4 (7.1)	0.25 (0.7)

Erickson K, Drevets WC, Clark L, Cannon DM, Bain EE, Zarate CA Jr, Charney DS, Sahakian BJ (2005) Mood-congruent bias in affective go/no-go performance of unmedicated patients with major depressive disorder. American Journal Psychiatry, 162, 2171-2173.



Negative bias to emotional stimuli is present in Major Depressive Disorder and absent in remission

Bias to negative emotions is linked to depressive state



Maalouf FT, Clark L, Tavitian L, Sahakian BJ, Brent D, Phillips ML (2012) Bias to negative emotions: A depression state-dependent marker in adolescent major depressive disorder. *Psychiatry Research*, 198, 28-33.

The noradrenaline reuptake inhibitor Reboxetine improves positive emotional processing in depressed patients

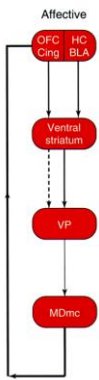
*Harmer, C.J., O'Sullivan, U., Favaron, E., Massey-Chase, R., Ayres, R., Reinecke, A., Goodwin, G. M. & Cowen, P. J. (2009)
Effect of Acute Antidepressant Administration on Negative Affective Bias in Depressed Patients Am J Psychiatry*

Activations in the subgenual cingulate region in response to emotional targets in healthy volunteers

Elliott, R., Rubinsztein, J. S., Sahakian, B. J. & Dolan, R. J. (2000) Neuroreport

Deep Brain Stimulation (Broadmann's Area 25) for Treatment-Resistant Depression **Improves Functional Outcome**

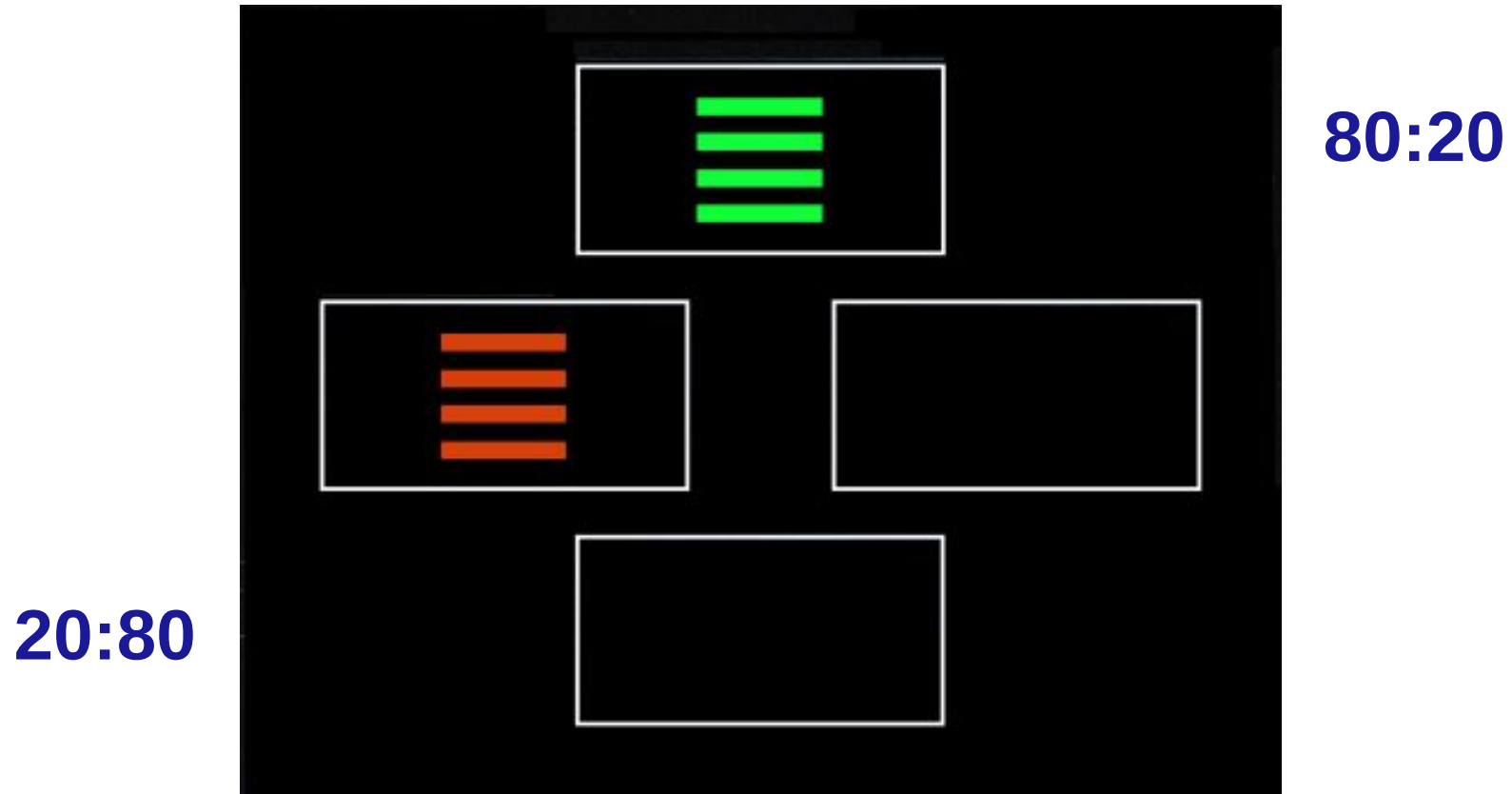
Kennedy, S.H., Giacobbe, P., Rizvi, S.J., Placenza, F.M., Nishikawa, Y., Mayberg, H.S. & Lozano, A.M. (2011) Deep Brain Stimulation for Treatment-Resistant Depression: Follow-Up After 3 to 6 Years. Am J Psychiatry



Rationale for Test Selection: Probabilistic Reversal Learning with Misleading Negative Feedback

Adaptive behaviour in daily living requires that individuals are able to learn in situations where feedback is unclear and potentially spurious or inconsistent.

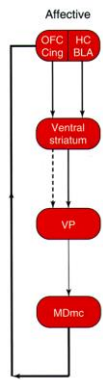
Hot cognition: Probabilistic Reversal Learning with Misleading Negative Feedback



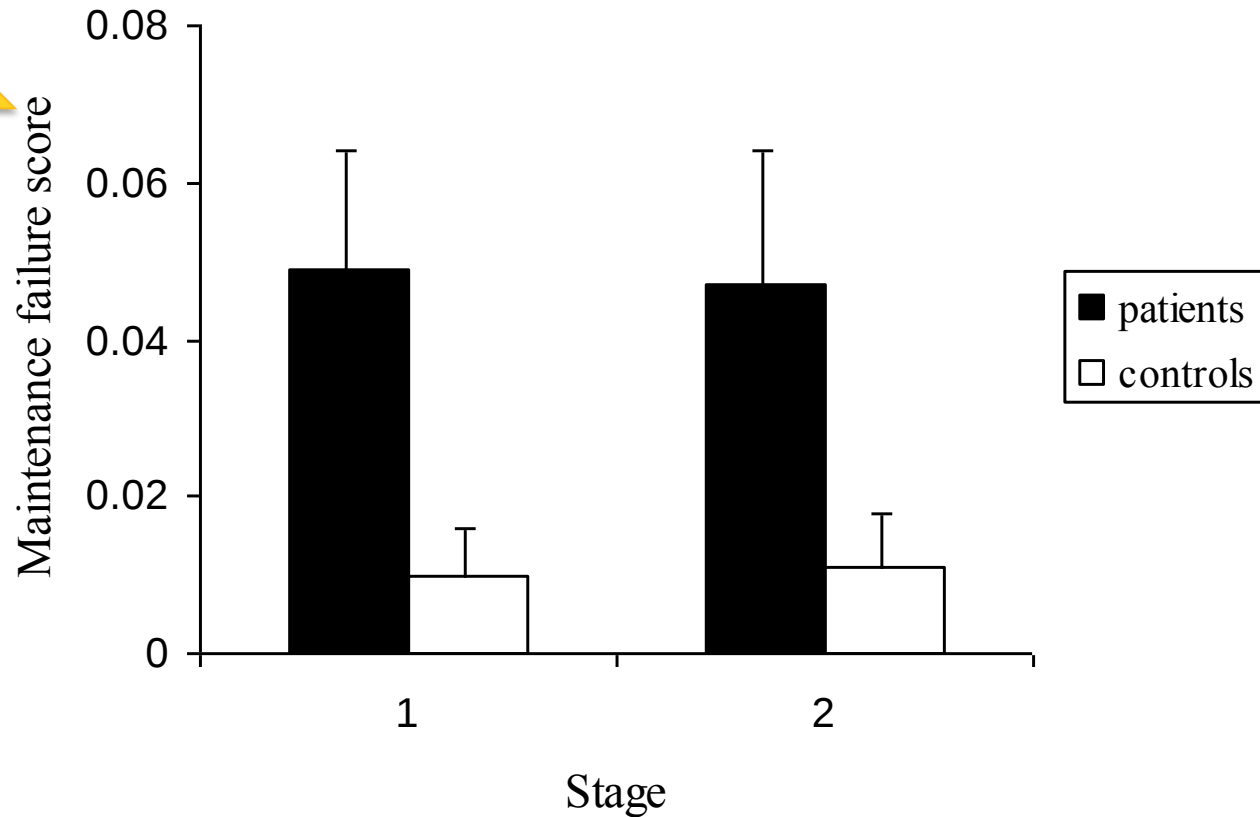
See also: Negative feedback in probabilistic reversal learning translationa task for rodents:

Bari, Theobald, Caprioli, Mar, Aidoo-Micah, Dalley, Robbins (2010) Serotonin modulates sensitivity to reward and negative feedback in a probabilistic reversal learning task in rats. *Neuropsychopharmacology*, 35, 1290-1301.

Oversensitivity to Negative Feedback in Depression

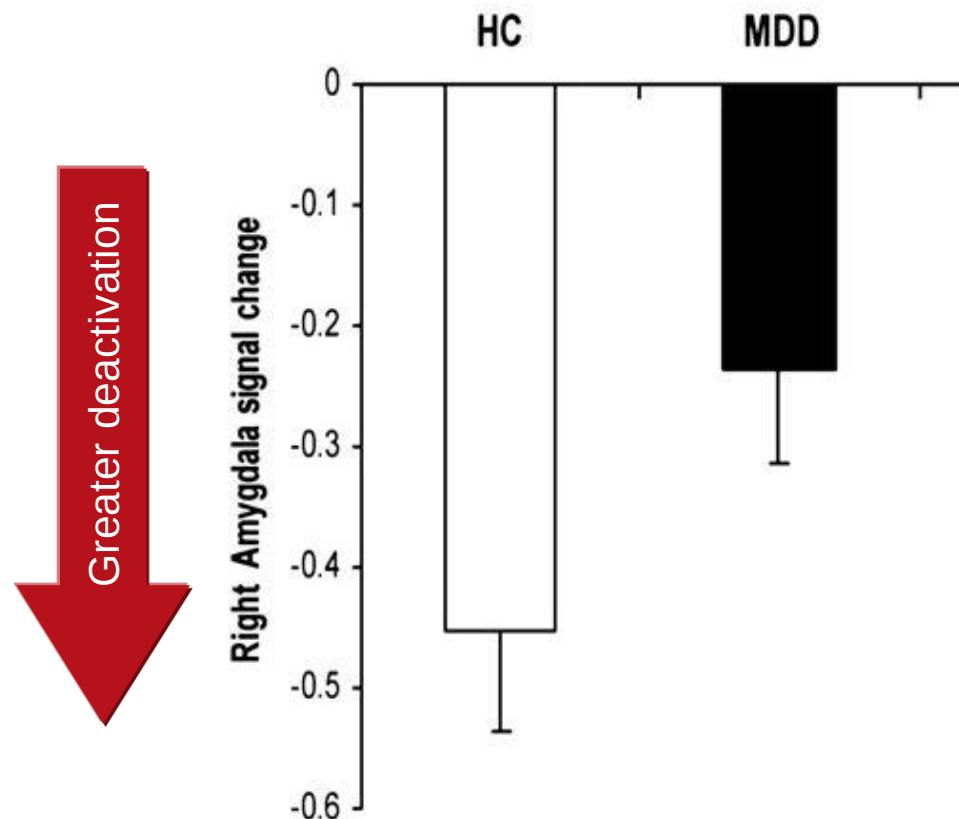


Switching in response to misleading negative feedback



Murphy, F.C., Michael, A., Robbins, T.W., Sahakian, B.J. (2003). Neuropsychological impairment in patients with major depressive disorder: the effects of feedback on task performance. *Psychological Medicine*, 33, 455-467.

Failure of top-down control by prefrontal cortex over the amygdala in patients with depression in response to negative feedback.



This functional neuroimaging study in unmedicated depressed patients demonstrates disrupted top-down control by the prefrontal cortex of the amygdala underlies the hypersensitivity to negative feedback in major depressive disorder.

There was greater dorsomedial PFC and ventrolateral PFC activation in HC subjects compared to MDD subjects.

Greater right amygdala deactivation in HC subjects compared to MDD.

Cognitive treatments are important for top-down control of emotion.

Pharmacological interventions are important for treating negative affective bias and reinstating more positive attitude

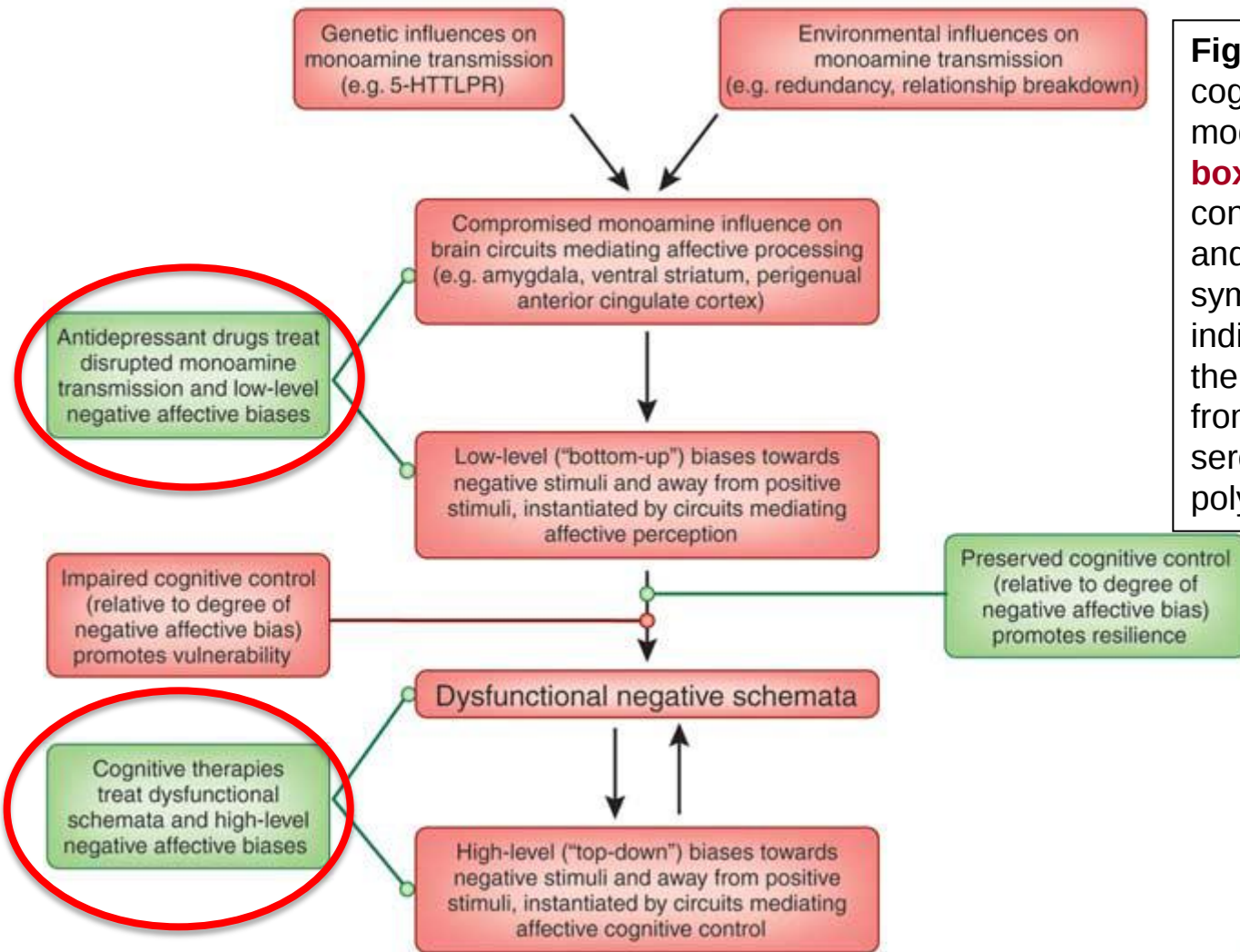


Figure 1. The extended cognitive neuropsychological model of depression. **Red boxes** indicate factors contributing to the development and maintenance of depressive symptoms. **Green boxes** indicate factors contributing to the treatment of and recovery from depression. 5-HTTLPR: serotonin transporter-linked polymorphic region.

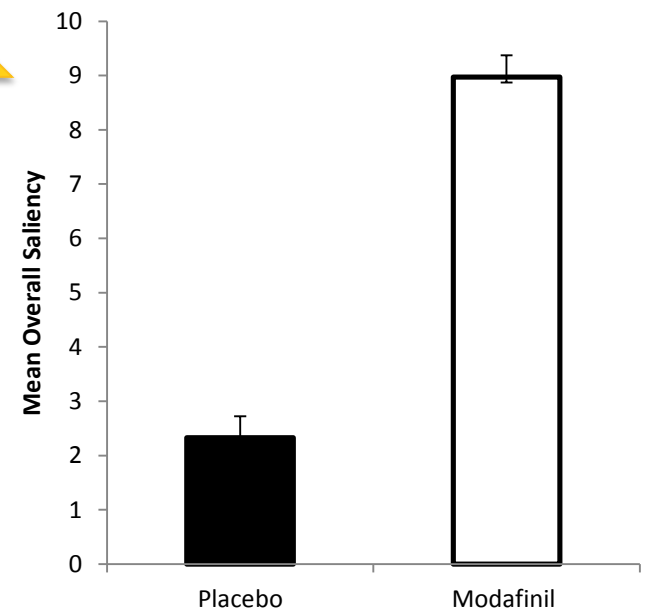
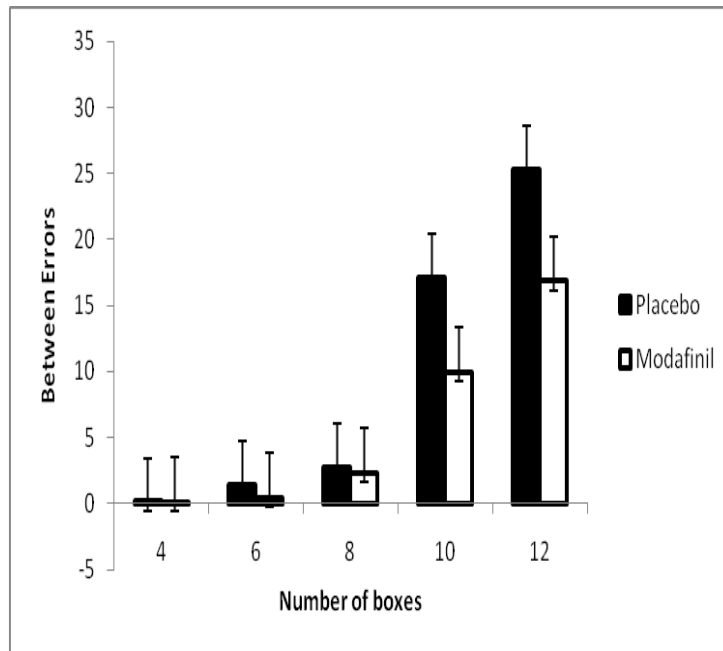
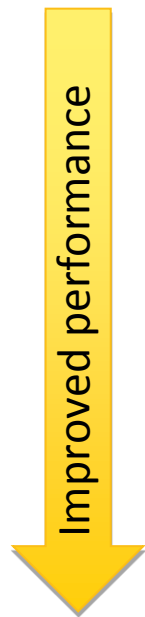
Future Directions

- **Cognitive impairment as a target for treatment in depression**
- **Fast-acting antidepressants**
- Games on iPads or phones to reduce attentional bias or anhedonia and increase motivation
- Development of touchscreen computerised tests of **hot** cognition (eg. EMOTICOM), with domains including emotional processing, social cognition, motivation and reward.

Modafinil enhances working memory and task-related motivation in healthy volunteers

On the CANTAB working memory task healthy volunteers on modafinil made significantly fewer errors than those on placebo.

Modafinil increases task-related motivation in healthy volunteers



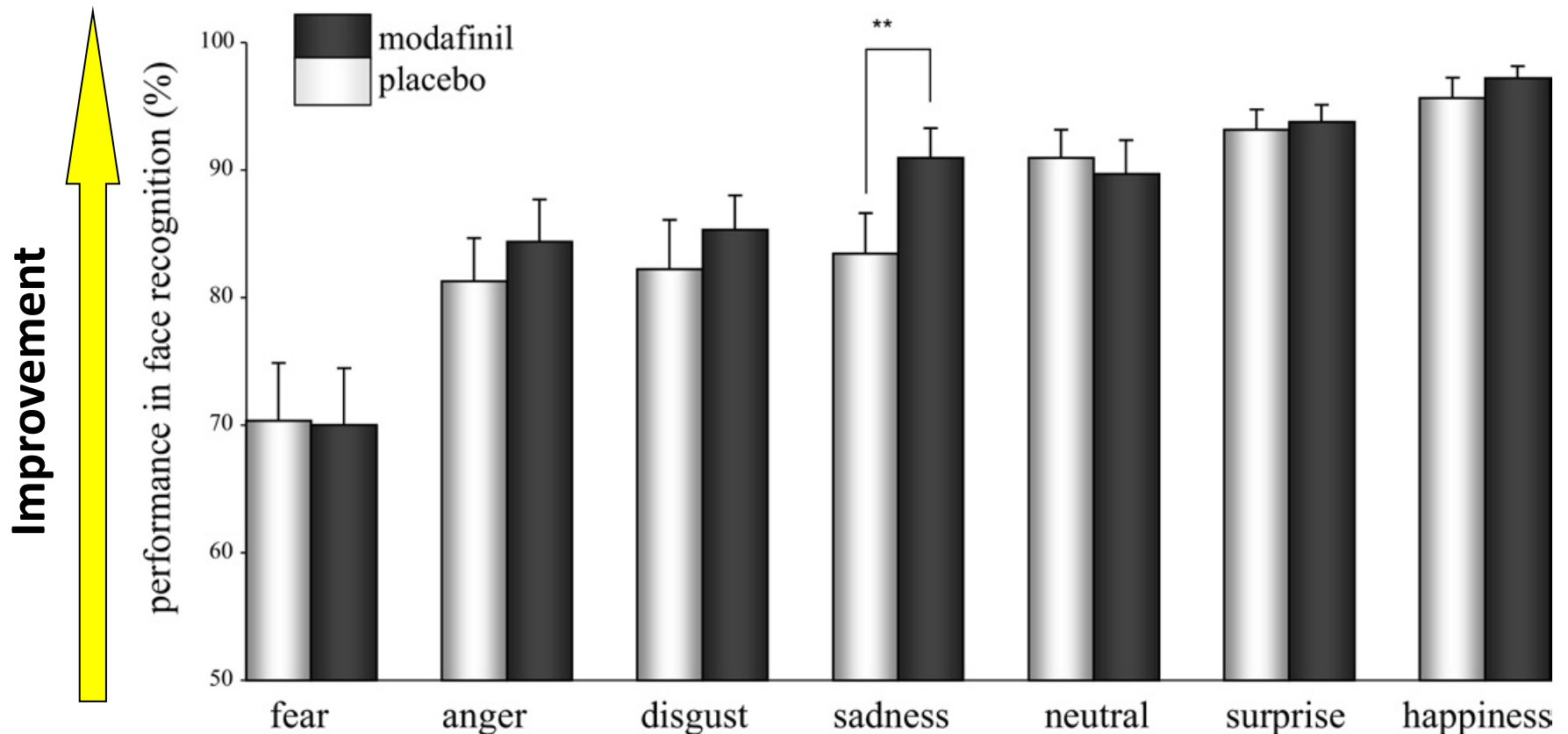
Müller U, Rowe JB, Rittman T, Lewis C, Robbins TW, Sahakian BJ (2013) Effects of modafinil on non-verbal cognition, task enjoyment and creative thinking in healthy volunteers. *Neuropharmacology*, 64, 490-495

Hot Cognitive Enhancement by Modafinil



Happiness

Modafinil improves emotional processing in first episode psychosis



Scoriels L, Barnett JH, Murray GK, Cherukuru S, Fielding M, Cheng F, Lennox BR, Sahakian BJ, Jones PB (2011) Effects of modafinil on emotional processing in first episode psychosis. *Biological Psychiatry*, 69, 457-464

Adding modafinil on to the antidepressant medication improves major depressive disorder

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 2012).

Multimodal action of antidepressant treatments?

Goss AJ, Kaser M, Costafreda SG, Sahakian BJ, Fu CHY (2013) Modafinil augmentation therapy in unipolar and bipolar depression: A systematic review and meta-analysis of randomized controlled trials. Journal of Clinical Psychiatry, 74, 1101-1107

Antidepressants with Effects on Cognition

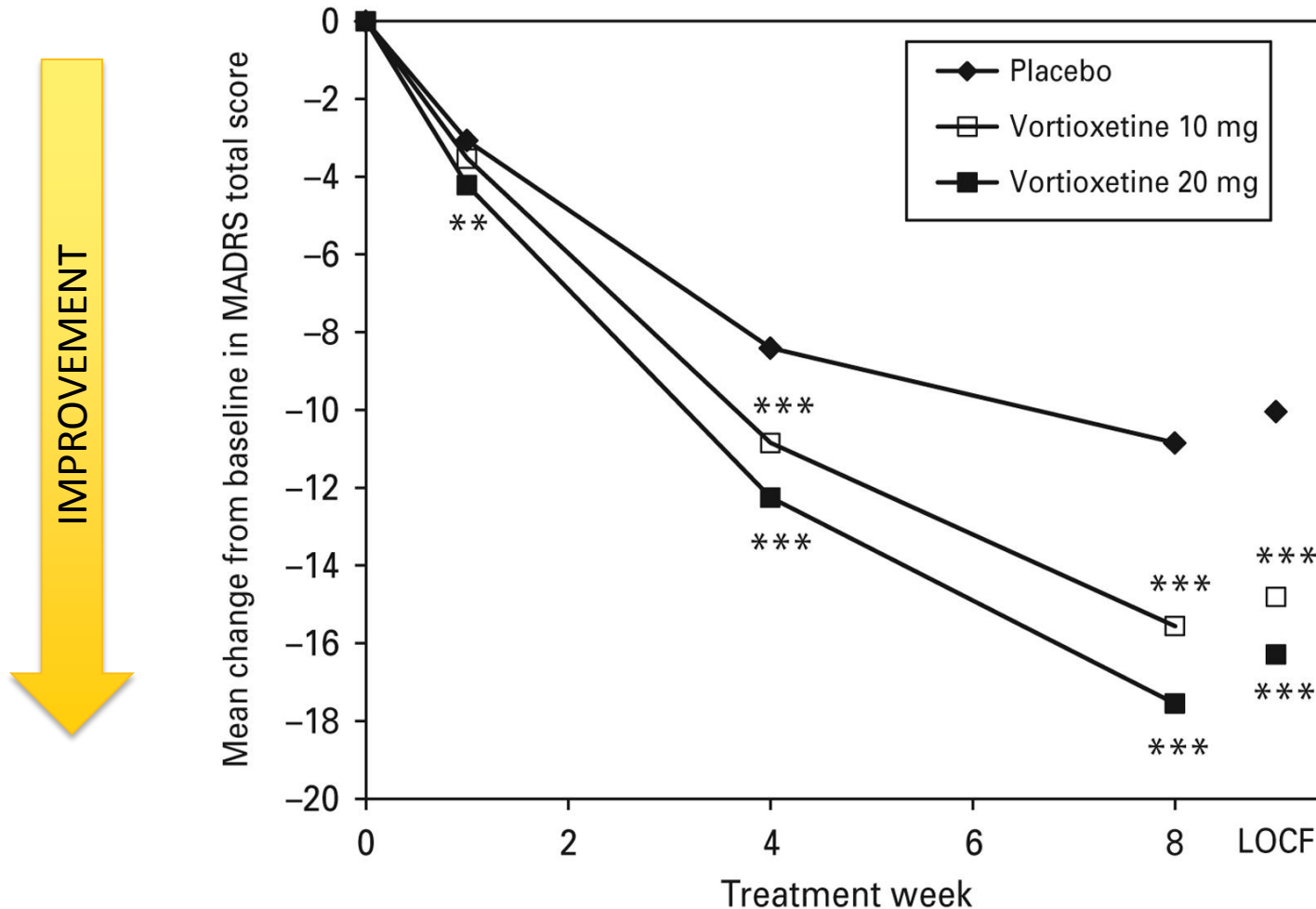
- Vortioxetine has as its principal mode of action a combination of a direct effect on receptor activity and serotonin (5-HT) reuptake inhibition.
- *In Vitro* studies show that vortioxetine is a:
 - 5-HT₃, 5-HT_{1D} and 5-HT₇ receptor antagonist
 - 5-HT_{1B} receptor partial agonist
 - 5-HT_{1A} receptor agonist
 - 5-HT transporter inhibitor.

Bang-Andersen, B., Ruhland, T., Jorgensen, M. et al (2011) Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): A novel multimodal compound for the treatment of major depressive disorder. J Med Chem

Mork, A. Pehrson, A., Brennum, L.T. et al (2012) Pharmacological effects of Lu AA21004: A novel multimodal compound for the treatment of major depressive disorder. J Pharm Exp Ther

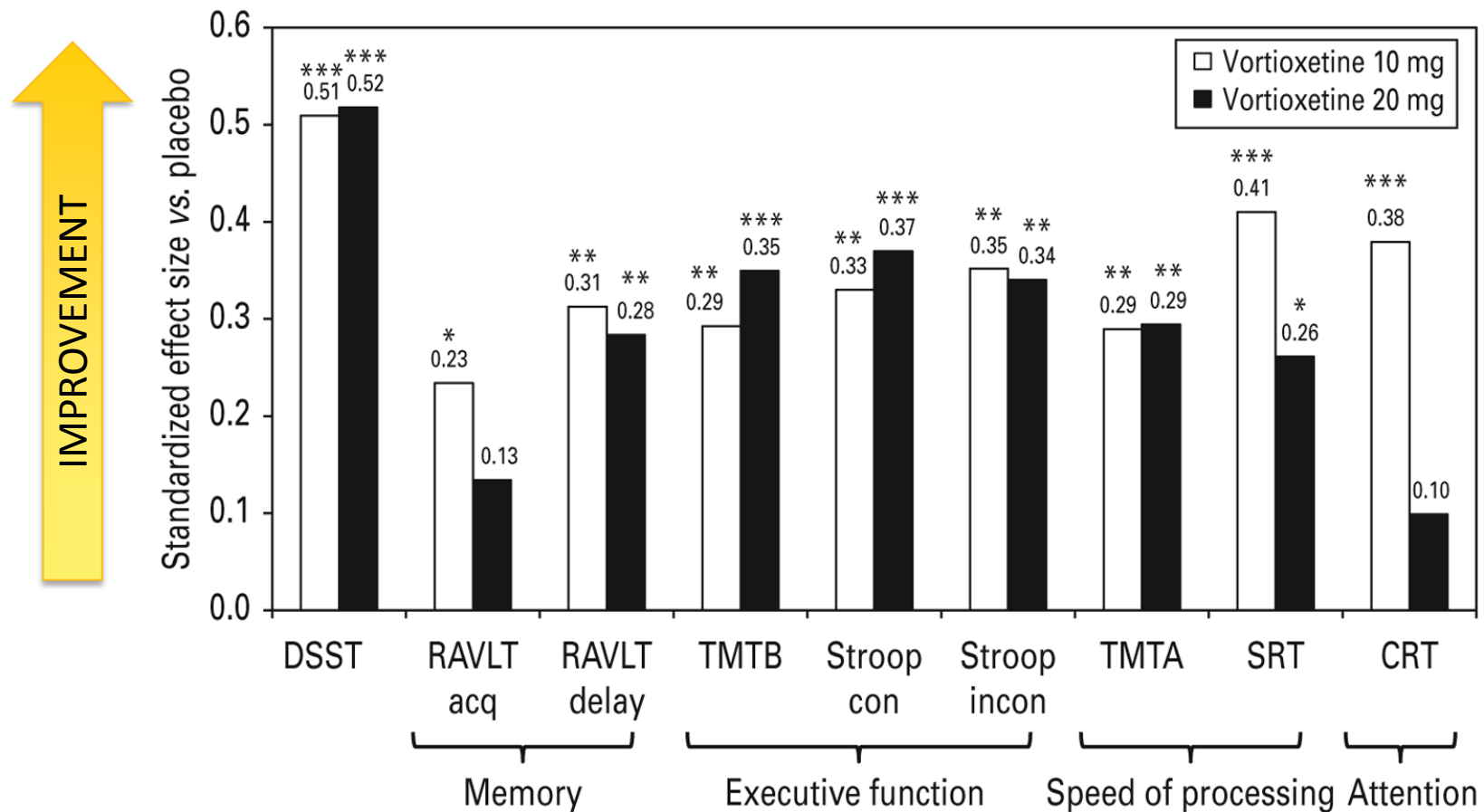
Westrich, L., Pehrson, A., Zhong, H. et al (2012) In vitro and in vivo effects of the multimodal antidepressant vortioxetine (Lu AA21004) at human and rat targets. Int J Psychiatry Clin Pract

Vortioxetine (10 and 20 mg) reduces depressive symptoms



McIntyre, R.S., Lophaven, S. & Olsen, C.K. (2014) A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *International Journal of Neuropsychopharmacology*, 17, 1557-1567

Vortioxetine (10 and 20 mg) improves **cold** cognition



McIntyre, R.S., Lophaven, S. & Olsen, C.K. (2014) A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *International Journal of Neuropsychopharmacology*, 17, 1557-1567

Fast-acting Antidepressants

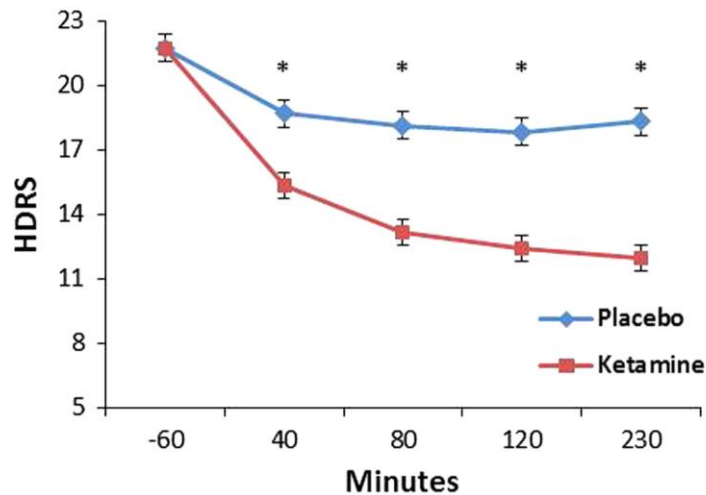
- Ketamine is an NMDA receptor antagonist, which paradoxically **increases glutamate transmission** in the prefrontal cortex.
- This occurs via blockade of tonic firing of GABAergic interneurons, resulting in a '**burst of glutamate**'
- This contributes to **activity-dependent release of BDNF** and increased **synaptogenesis**

Duman, R. & Aghajanian, G.K. (2012) Synaptic dysfunction in depression: Novel therapeutic targets. Science

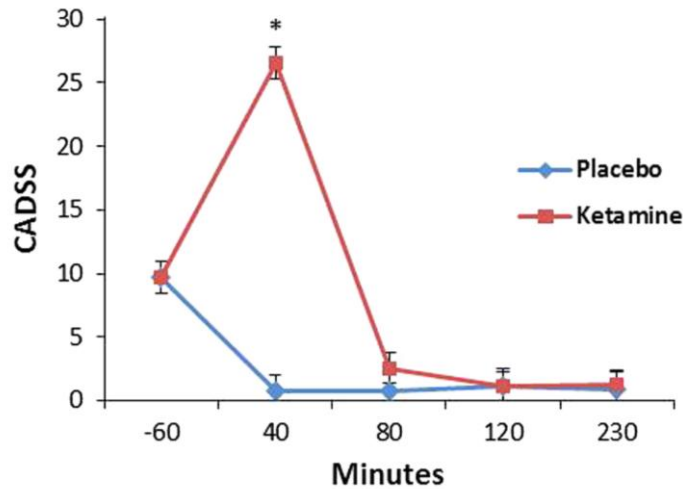
Duman, R.S. & Aghajanian, G.K. (2013) Neurobiology of rapid acting antidepressants: Role of BDNF and GSK-3β. Neuropsychopharmacology

Evidence suggests that the dissociative effects of ketamine may mediate its antidepressant effects

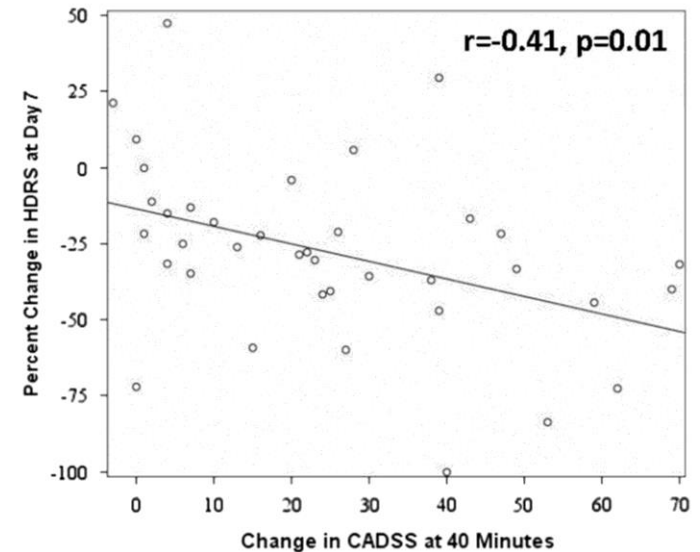
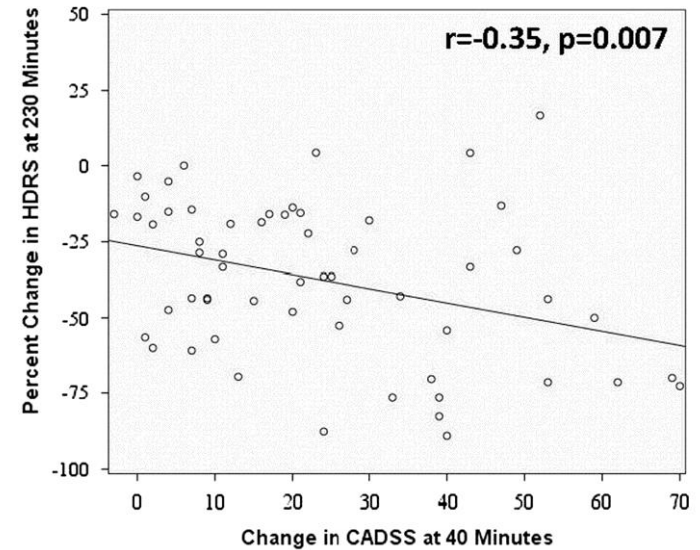
Decreased depression



* p < .05.



* p < .05.



Luckenbaugh, D.A., Niciu, M.J., Ionescu, D.F., Nolan, N.M., Richards, E.M., Brutsche, N.E., Guevara, S. & Zarate, C.A. (2014) Do the dissociative side effects of ketamine mediate its antidepressant effects? *Journal of Affective Disorders*, 159, 56-61

Holistic treatment (eg pharmacological, psychological, cognitive, workplace, social)

- The importance of **early detection** of depression and **early effective treatment**
- Treatment should address **all aspects of depression, including cognition**, to ensure **wellbeing and functional outcome** in the workplace and the home environment
- **Combining treatments** and a **holistic approach** may give the best outcomes for people with depression
- Patients with depression have to take **an active role in their treatment**, and not a passive role. The drug will facilitate improvement, but it also requires an active effort on the individual's part to learn and re-learn
- **This should prevent depression from becoming debilitating, chronic and relapsing**

- Sahakian, B.J. (2014) What do experts think we should do to achieve brain health? *Neuroscience & Biobehavioral Reviews*
- Pulcu, E., Trotter, P.D., Thomas, E.J., McFarquhar, M., Juhasz, G., Sahakian, B.J., Deakin, J.F.W., Zahn, R., Anderson, I.M. & Elliott, R. (2014) Temporal discounting in major depressive disorder. *Psychological Medicine*
- Insel, T.R., Voon, V., Nye, J.S., Brown, V.J., Altevogt, B.M., Bullmore, E.T., Goodwin, G.M., Howard, R.J., Kupfer, D.J., Malloch, G., Marston, H.M., Nutt, D.J., Robbins, T.W., Stahl, S.M., Tricklebank, M.D., Williams, J.H. & Sahakian, B.J. (2013) Innovative solutions to novel drug development in mental health. *Neuroscience and Biobehavioral Reviews*
- Insel, T.R., Sahakian, B.J., Voon, V., Nye, J., Brown, V.J., Altevogt, B.M., Bullmore, E.T., Goodwin, G.M., Howard, R.J., Kupfer, D.J., Malloch, G., Marston, H.M., Nutt, D.J., Robbins, T.W., Stahl, S., Tricklebank M.D. & Williams, J.H. (2012) A plan for mental illness. *Nature*

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