# Experimental design and approaches: opportunities to facilitate new target and validation strategies for cognitive dysfunction in depression

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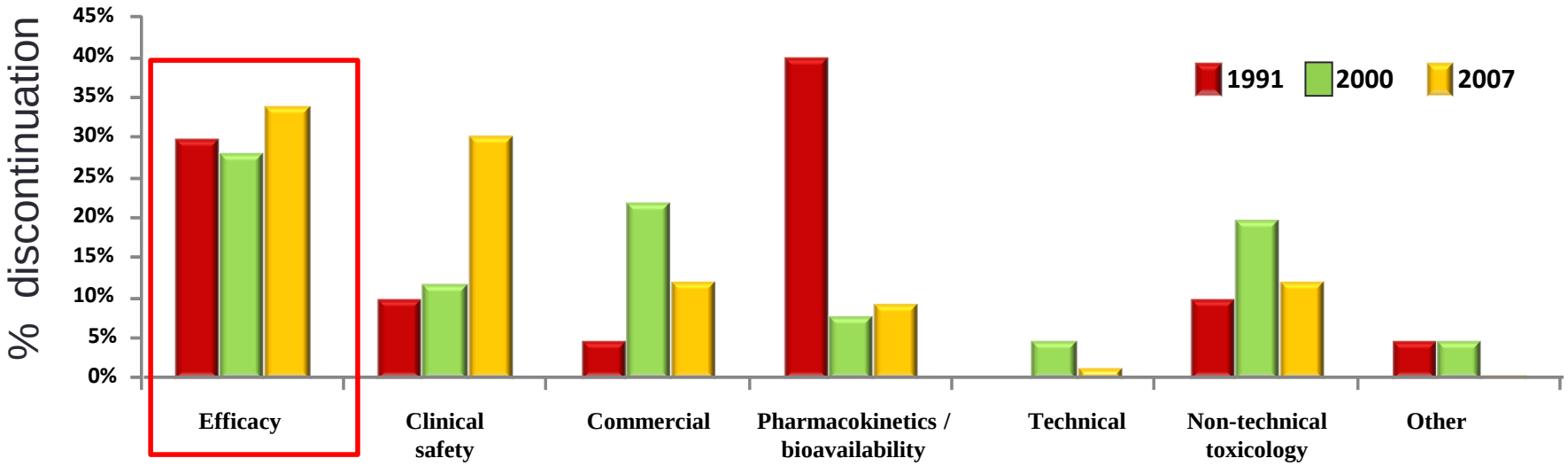
# Outline

- **Why do we need experimental medicine models for antidepressant drug action?**
- **Use of experimental medicine models for detecting early effects on negative biases in cognition (“Hot”)**
- **Use of experimental medicine models for detecting pro-cognitive actions (“Cold”)**

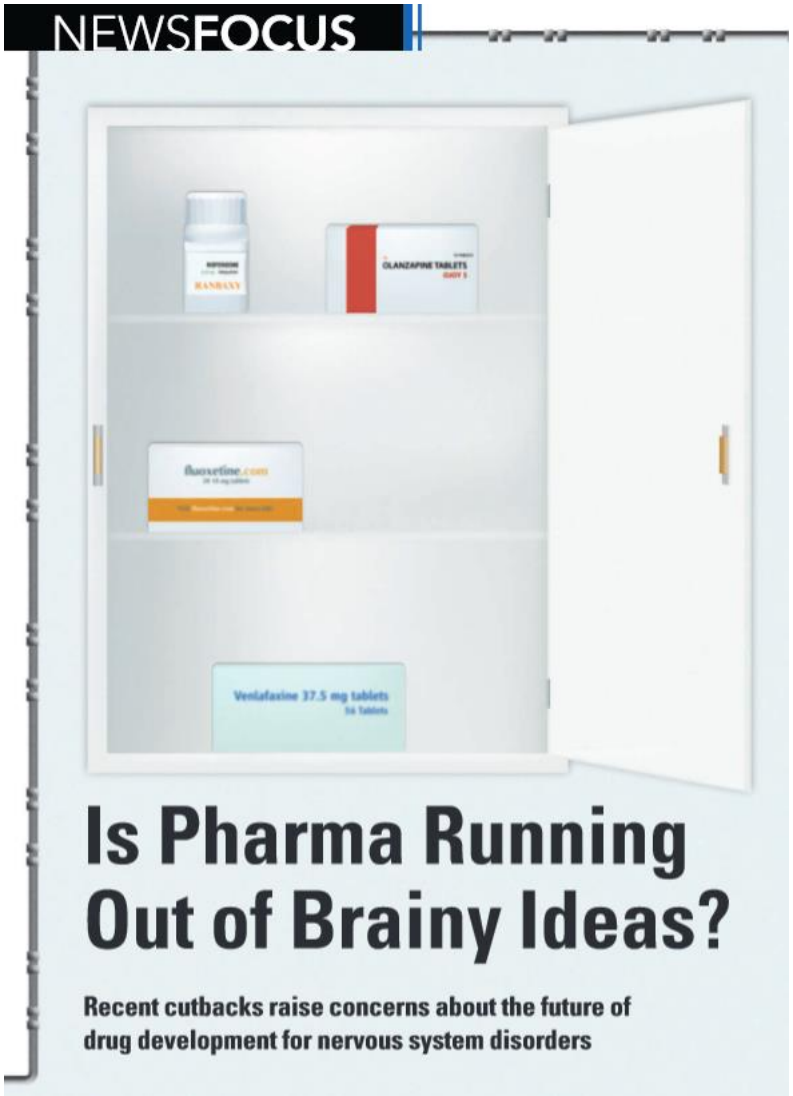
# Lack of efficacy is now the main reason for failure in drug development




- In 1991 unpredictable pharmacokinetics was the main reason for a drug to fail in development
- Now, lack of efficacy is the main reason for failure

Kola & Landis. *Nat Rev Drug Discov*. 2004;3:711;
CMR International. 2010 Pharmaceutical R&D FactBook.

# What is experimental medicine and how can it help?

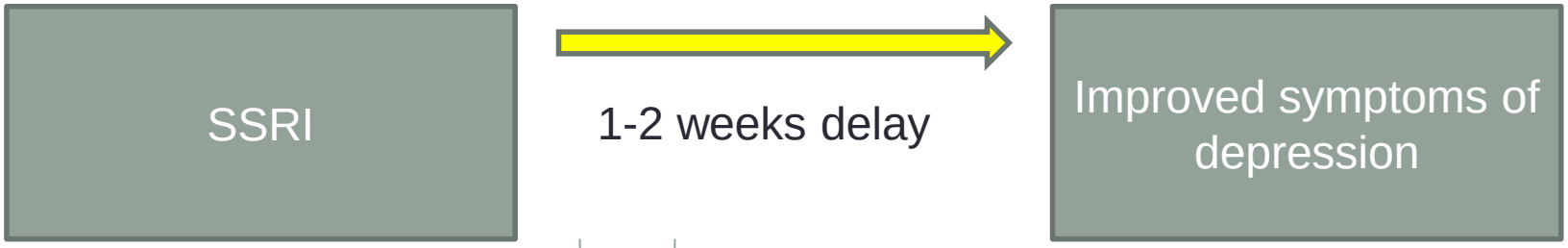



- Novel candidate treatments for psychiatry are often screened using preclinical animal models. Current models have low predictive validity; most drugs fail late in development because of problems in efficacy

- Experimental medicine may offer a solution: a model of the disease process in humans which is sensitive to effective treatments and can be used to screen, understand and predict treatment action

Miller, Science 2010

# Experimental medicine for antidepressant drug action




Drug development focused on serotonin, leading to ‘me too’ drugs

Changes in neural and psychological processes important for later clinical change?

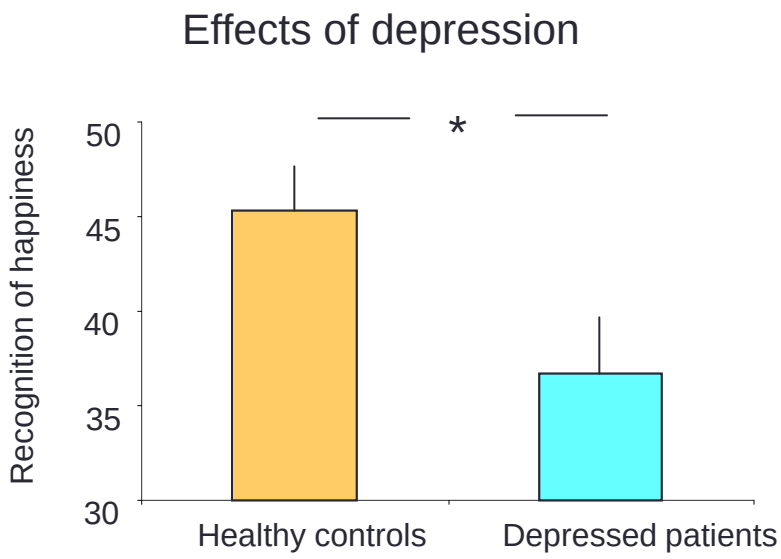
More recent development focused on neurobiological mechanisms also expressed with delay (e.g. plasticity changes)

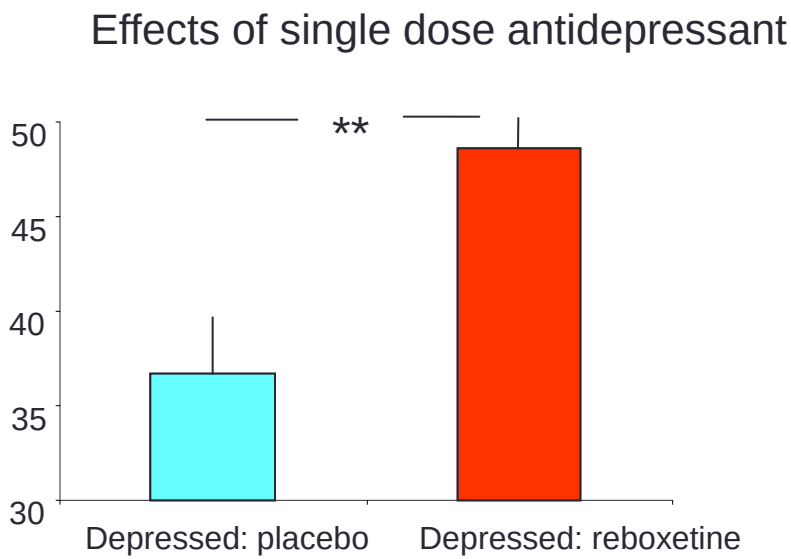
# Early changes in emotional processing are seen with antidepressant drug treatments (hot cognition)

- Negative biases in emotional processing are important in the maintenance of depression (see Roiser & Sahakian 2013)
- Early changes in negative bias are seen with antidepressant drug treatment (Harmer et al 2009: Roiser & Sahakian 2013).
- Antidepressants may not act as direct mood enhancers but rather change information processing in a positive direction which leads to clinical change gradually (after interaction with social and emotional environment).

Roiser and Sahakian (2013) CNS Spect 18, 139-49
Harmer et al (2009) Brit J Psych 195, 102-108

# Example antidepressant drug effects




Harmer et al 2009 Am J Psych

# Early and reliable changes in emotional processing predictive of treatment action

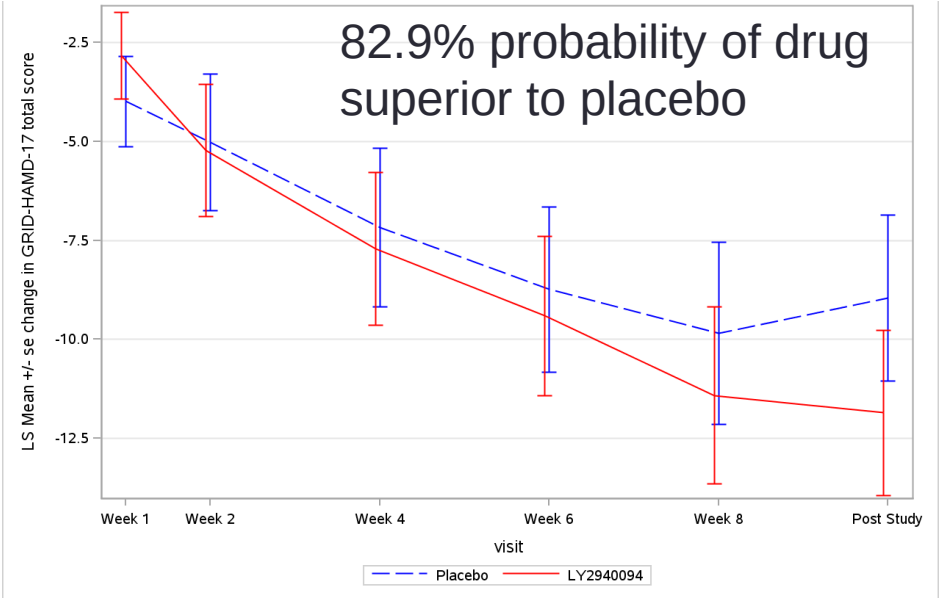
- **Is the model sensitive to established antidepressants?**
- **Do early effects predict treatment response?**
- **Can it discriminate between ineffective vs effective agents?**
- **Is it sensitive to novel mechanisms of action?**
  - e.g. NMDA antagonism
- **Can it be used to generate hypotheses, dosing information or subgroups useful for RCT testing?**
- **Can this approach be used in healthy people as well as depressed patients?**

See Harmer et al 2009; Pringle et al 2013; Roiser & Sahakian 2013; Shiroma et al. 2014

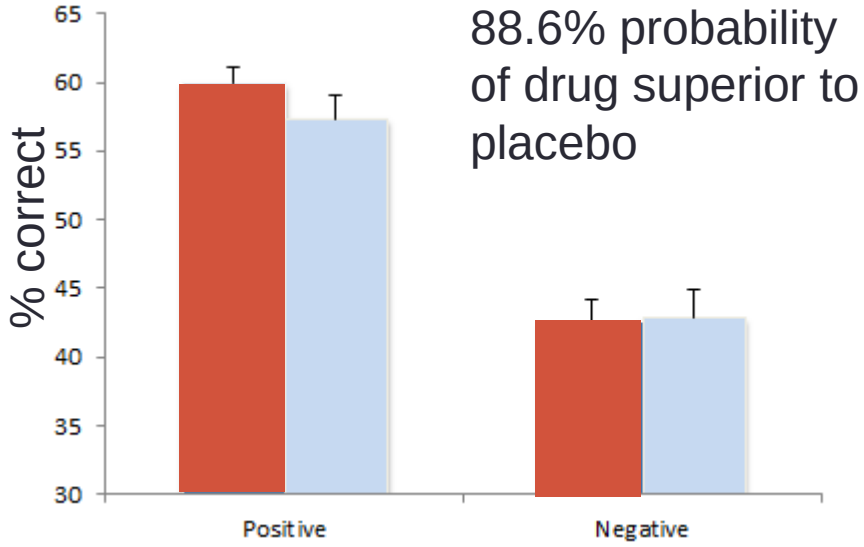
# A drug early in development

- A Selective Nociceptin Receptor Antagonist **LY2940094**
- *RCT* in depressed patients: clinical response at week 8: emotional processing at week 1
- Can emotional processing provide an early marker of likely efficacy?

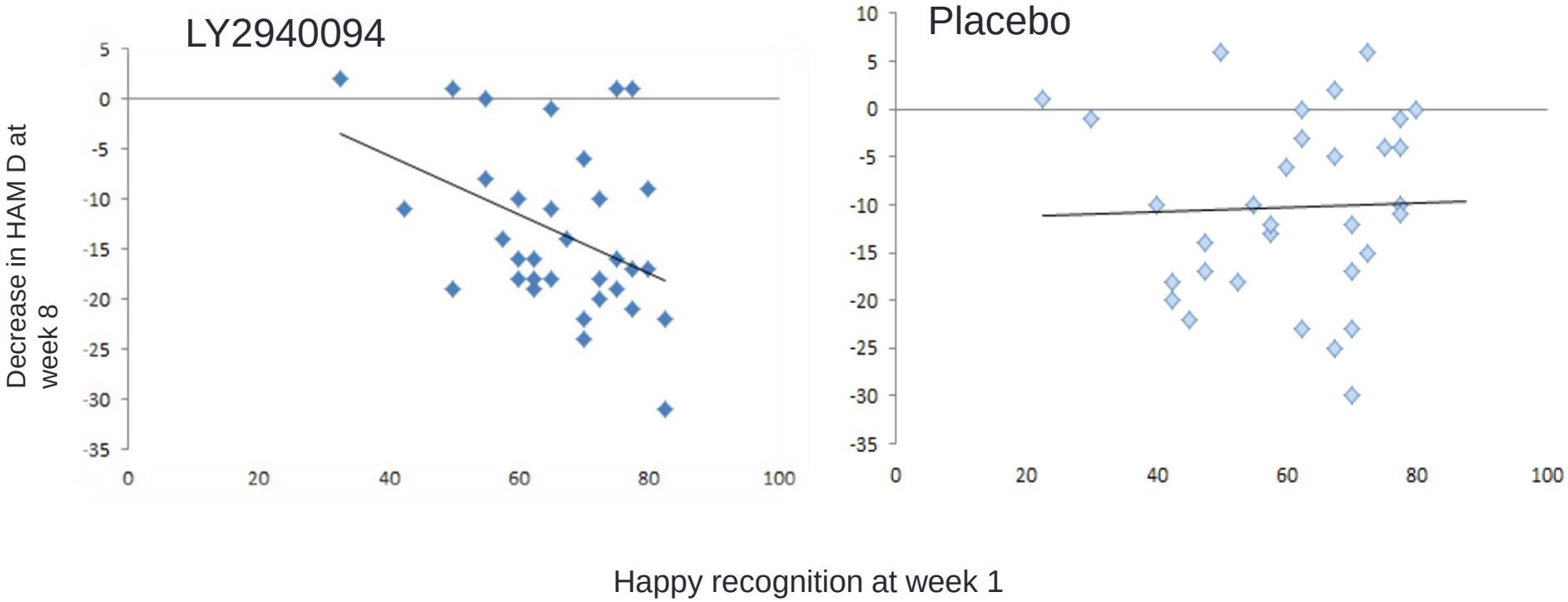
**Clinical Response: week 8**




**Emotional processing response: week1**



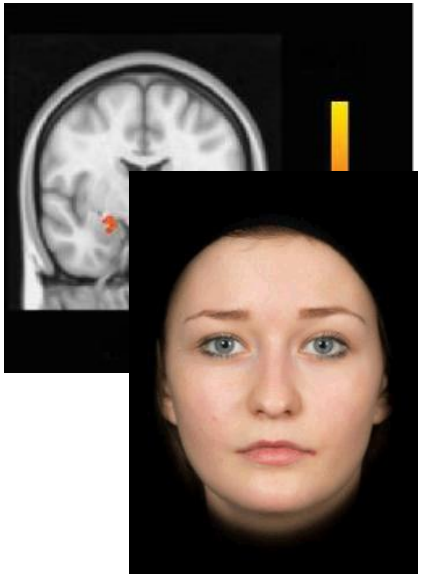
# Increased happy face recognition predicted clinical response to drug




There was a subgroup of patients who responded to the drug: this subgroup was predicted by positive bias in facial expression processing

# Summary: emotional processing

- Early changes in negative bias are seen with a range of treatments for depression
- These predict later therapeutic responses
- These markers are being used by 5 pharmaceutical companies to explore new candidate treatments for depression and anxiety at an early stage of development



# Cognitive deficits in depression (cold cognition)

- Depressed patients show consistent impairments in memory, executive function and attention (Clark *et al 2009*)

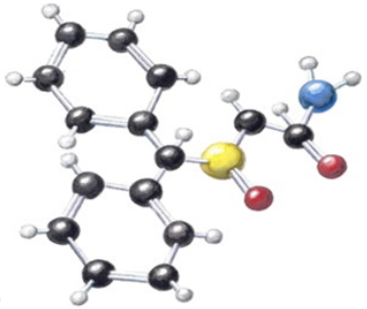
- Historically, considered a epiphenomenon of low mood in depression, but recent evidence suggests dysfunction persists into periods of remission and holds a special relationship to functional recovery (Bortolato et al., 2014)

- Can we use an experimental medicine model to understand and predict mechanisms of action of novel treatments on cognition?
  - A need to separate out effects on mood and effects on cognition.

Clark et al (2009) Annu Rev Neurosci 32, 57-74
Bortolato et al 2014 CNS Neurol Disord Drug Targets 13, 1804-18

# Experimental models for cognition

CANTAB: A translational pathway *e.g.*



Psychopharmacology (Berl). 2003 Jan;165(3):260-9. Epub 2002 Nov 1.

**Cognitive enhancing effects of modafinil in healthy volunteers.**

Turner DC[1], Robbins TW, Clark L, Aron AR, Dowson J, Sahakian BJ.

Modafinil Improves Cognition and Attentional Set Shifting in Patients with Chronic Schizophrenia

Danielle C Turner*,[1], Luke Clark[2], Edith Pomarol-Clotet[1], Peter McKenna[1], Trevor W Robbins[2] and Barbara J Sahakian*,[1]

**Modafinil Improves Cognition and Response Inhibition in Adult Attention-Deficit/Hyperactivity Disorder**

Danielle C. Turner, Luke Clark, Jonathan Dowson, Trevor W. Robbins, and Barbara J. Sahakian

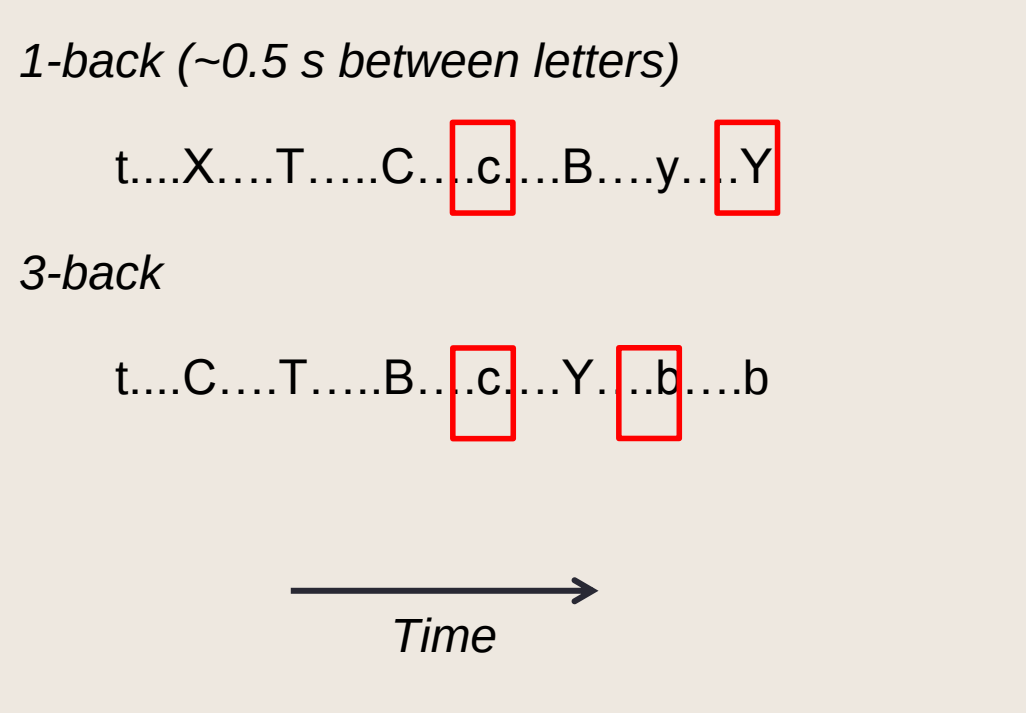
Ann Surg. 2012 Feb;255(2):222-7. doi: 10.1097/SLA.0b013e3182306c99.

**Effect of pharmacological enhancement on the cognitive and clinical psychomotor performance of sleep-deprived doctors: a randomized controlled trial.**

Sugden C[1], Housden CR, Aggarwal R, Sahakian BJ, Darzi A.

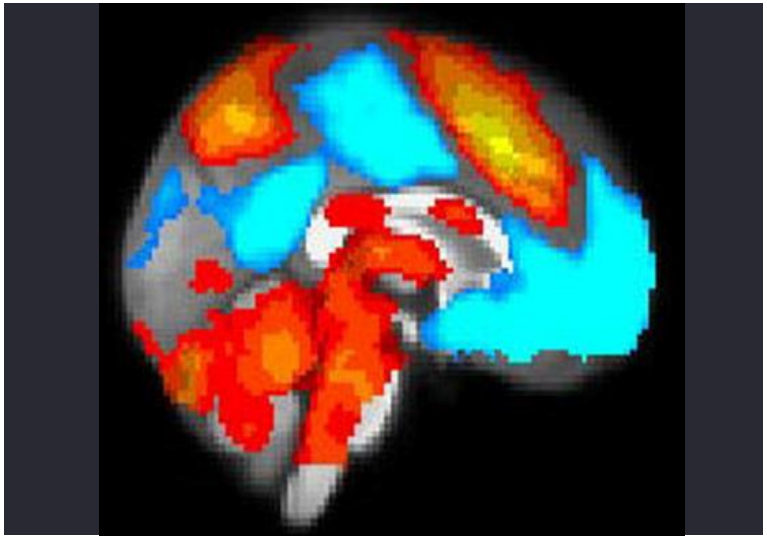
# The neural basis of impaired executive function in depression

- N back task: a working memory task commonly used in both healthy and clinical populations
- 4 levels of increasing difficulty



# Neural mechanisms of 'cold' cognition in depression: n-back

- Depression is associated with increased activation in the task-positive network (eg dlPFC)[1-4] and reduced deactivation in the default mode network (eg hippocampus)[4-6]



**Task-positive networks** come on-line during effortful working-memory demands

**Default mode networks** are activated during internal self-referential processing and switched off during external cognitive tasks

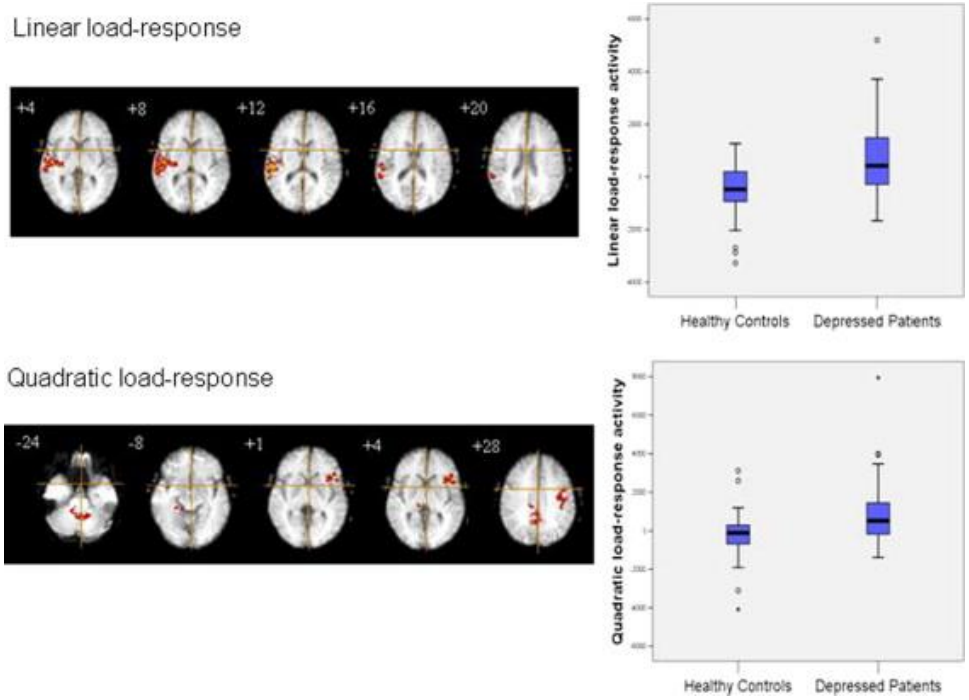
| | |
|---|---|
| **RED** | significantly activated by task |
| **BLUE** | significantly deactivated |

dlPFC, dorsolateral prefrontal cortex

1. Fitzgerald PB et al. Hum Brain Mapp 2008;29:490-501;
2. Matsuo K et al. Mol Psychiatry 2007;12:158-66;
3. Walter H et al. J Affect Disord 2007;101:175-85; 4. Harvey PO et al. Neuroimage 2005;26:860-9;
5. Norbury R et al. Psychol Med 2013;44:1197-203; 6. Rose EJ et al. Neuroimage 2006;29:203-15

# Antidepressant effects on cognition

- Cognitive deficits are often experienced as residual symptoms in depression and are difficult to fully resolve with current antidepressant drug treatments (Bortolato et al., 2014)




**Walsh et al 2009:** fluoxetine treatment did not resolve overactive circuits in depression

Walsh ND et al. Biol Psychiatry 2007;62:1236-43;
Bortolato et al 2014 CNS Neurol Disord Drug Targets 13, 1804-18

# Can vortioxetine modulate the neural underpinnings of working memory?

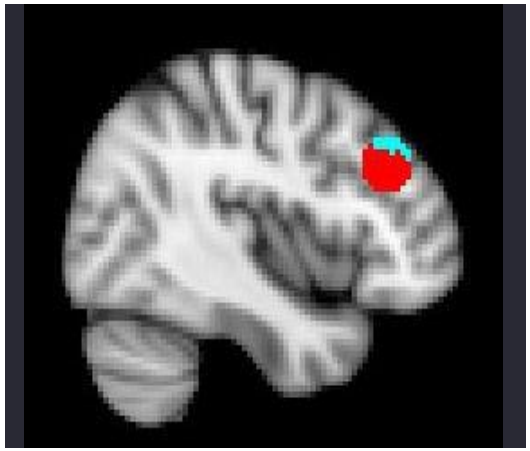
- Vortioxetine – a novel mulitmodal antidepressant. Three RCTs show positive effects on cognition in depression (McIntyre et al., 2014; Katona et al 2012)

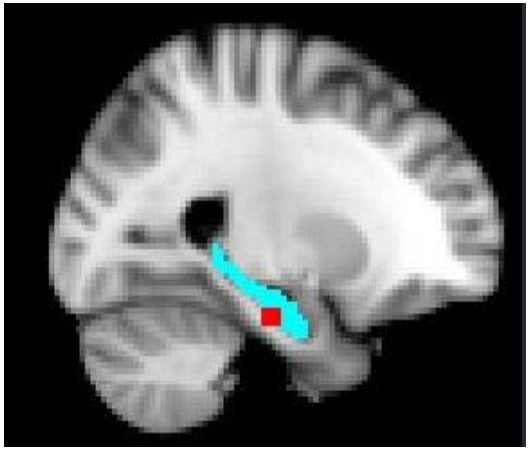
- Can we use an experimental medicine model to explore mechanisms of action and separate mood from cognitive effects?
  - Focused on remitted depressed and healthy controls

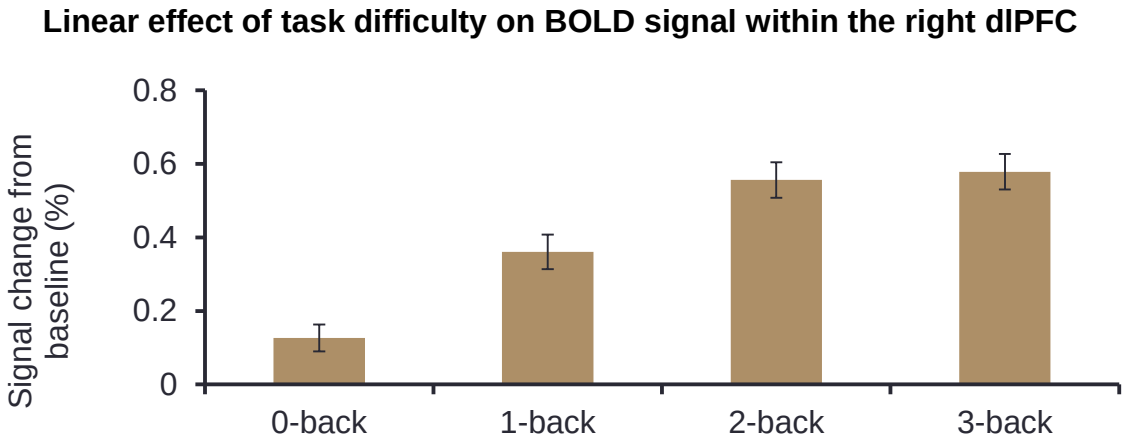
- 3 centres (Oxford; Manchester; Institute of Psychiatry at King's College London)

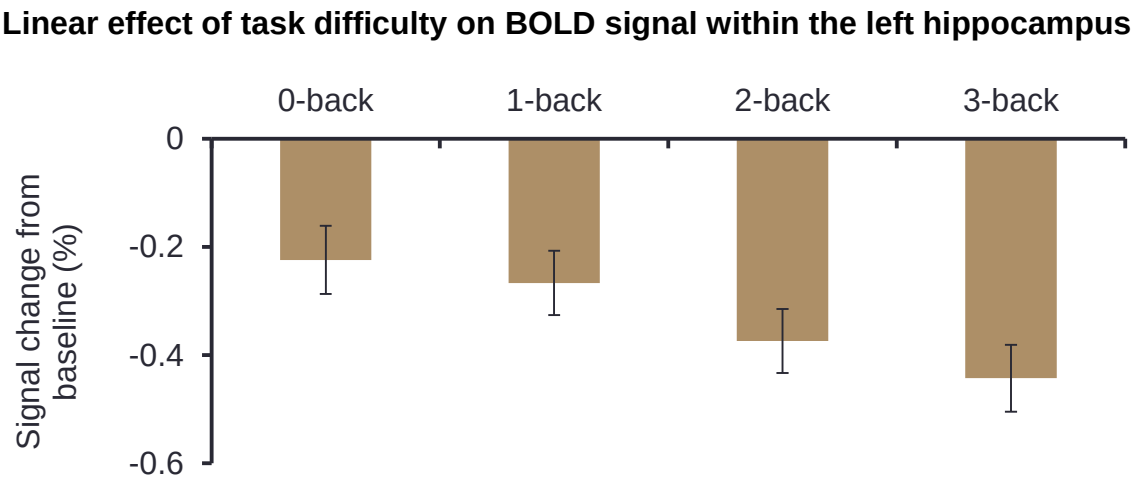
# fMRI activity is related to difficulty

- Regions within the predefined ROIs that show a linear effect of task difficulty



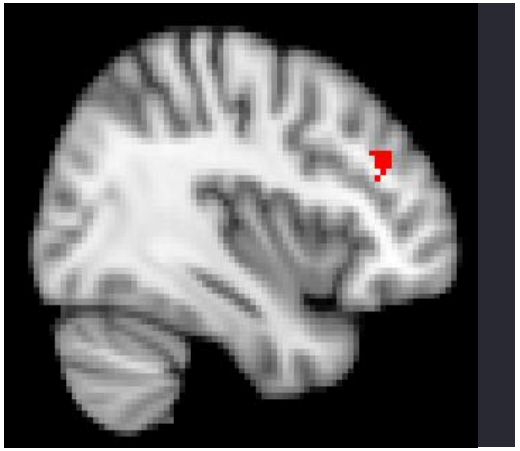




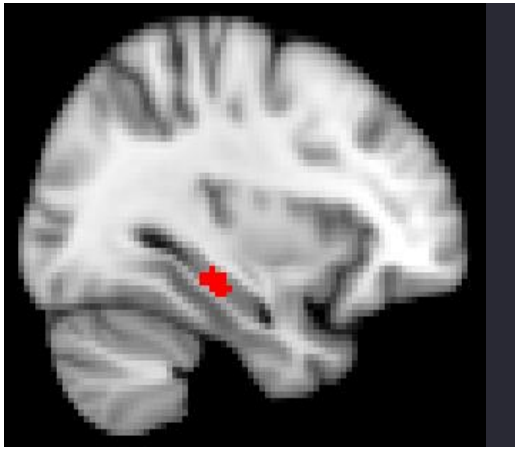




fMRI, functional magnetic resonance imaging; ROI, region of interest; BOLD, blood-oxygen level dependent; dlPFC, dorsolateral prefrontal cortex

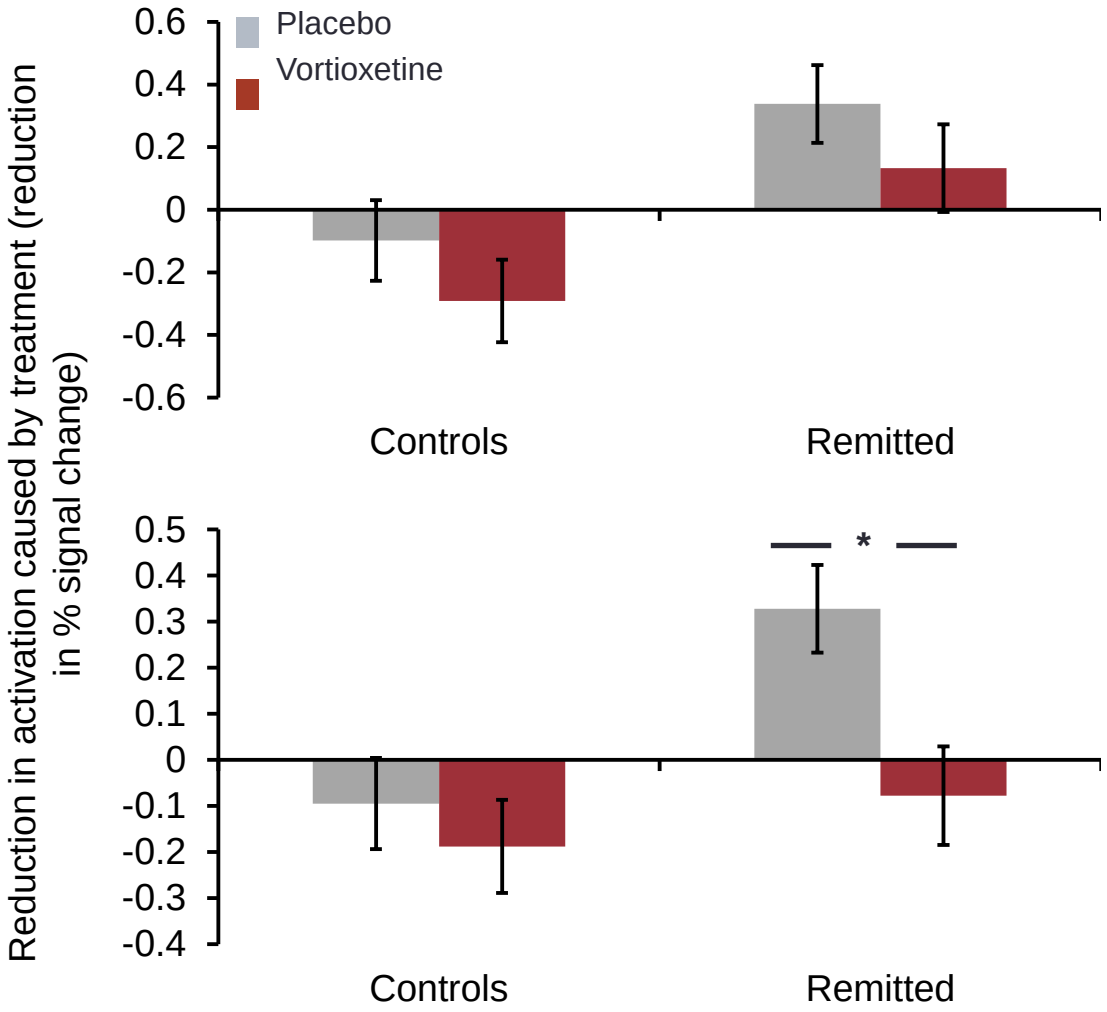
# Effect of vortioxetine on dlPFC and hippocampus across



Cluster corrected p=0.03



Cluster corrected p=0.03




No treatment x subject group interaction in either ROI

*p<0.05 vs placebo
dlPFC, dorsolateral prefrontal cortex; ROI, region of interest

# Summary

- Vortioxetine improves subjective and objective measures of cognition after 10 days compared to placebo
- Vortioxetine reduces neural activity during the n-back task in the hippocampus and dlPFC
- These regions have previously been reported to be hyperactive in patients with depression, therefore providing a mechanism for its effect on executive function
- Similar effect in remitted patients and healthy control individuals – providing evidence for a direct effect

; dlPFC, dorsolateral prefrontal cortex

# Conclusions

- Deficits in cognition are important across many psychiatric disorders
- Developing new treatments to target cognition has proved to be challenging
- An experimental medicine model can provide answers to key questions early in development but needs to show
  - Sensitivity, discrimination, prediction
- Screening using healthy volunteers can be challenging and may involve designing novel tasks to fully capture pro-cognitive actions