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.


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

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*
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)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Estimated number of subjects affected</th>
<th>Total costs - Estimated in Millions of Euros (2010)</th>
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<tbody>
<tr>
<td></td>
<td>Direct health care costs</td>
<td>Direct non-medical costs</td>
</tr>
<tr>
<td>Major depression</td>
<td>30.3 million</td>
<td>24,156</td>
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- 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.

- The economic case appendix, No health without mental health, Department of Health.
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

DA, NA, 5-HT


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

www.cantab.com
Using Innovative Technology in Mental Health

Cantab Mobile

NHS

Approved Class II European Medical Device
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
Deep Phenotyping

Preclinical/Asymptomatic
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


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


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


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

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


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*

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


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
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).

Bias to negative emotions is linked to depressive state

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

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

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

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.
See also: Negative feedback in probabilistic reversal learning translationa task for rodents:
Oversensitivity to Negative Feedback in Depression

Switching in response to misleading negative feedback

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.

Elliott, Sahakian, Roiser, Mehta, Robbins
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

Hot Cognitive Enhancement by Modafinil

Modafinil improves emotional processing in first episode psychosis

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?

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-HT$_3$, 5-HT$_{1D}$ and 5-HT$_7$ receptor antagonist
  - 5-HT$_{1B}$ receptor partial agonist
  - 5-HT$_{1A}$ receptor agonist
  - 5-HT transporter inhibitor.

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Vortioxetine (10 and 20 mg) reduces depressive symptoms

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

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 interneurones, resulting in a ‘**burst of glutamate**’

- This contributes to **activity-dependent release of BDNF** and increased **synaptogenesis**

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*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.

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
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