Enhancing Cognition

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We need cognitive enhancing drugs to treat the cognitive disability of people with mental health disorders and brain injury

- Disorders such as attention deficit hyperactivity disorder (ADHD), schizophrenia and Alzheimer’s disease all have associated cognitive problems.

- Cognitive enhancing drugs (Smart Drugs) are needed to treat cognitive disabilities and improve functional outcome, quality of life and wellbeing for people with neuropsychiatric disorders and brain injury.

**Estimated Total Annual Costs**

*Including health service costs, lost earnings, lost productivity and human costs*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Cost</th>
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<tbody>
<tr>
<td>Depression</td>
<td>£20.2-23.8 billion</td>
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<tr>
<td>Anxiety</td>
<td>£8.9 billion</td>
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<tr>
<td>Schizophrenia</td>
<td>£13.3 billion</td>
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<tr>
<td>Dementia</td>
<td>£17 billion</td>
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<tr>
<td>Somatisation disorder</td>
<td>£17.6 billion</td>
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</tbody>
</table>

- Department of Health (2011) No health without mental health: The economic case for improving efficiency and quality in mental health
- Fineberg, Haddad, Carpenter, Gannon, Sharpe, Young, Joyce, Rowe, Wellsted, Nutt, Sahakian (2013) *Journal of Psychopharmacology*
Some Possible Methods of Boosting Your Brain Power

- Pharmacological (Smart Drugs)
- Neuroprosthetics for cognition
- Devices (eg tDCS, TMS)
- Education
- Cognitive training/ Brain training
- Physical exercise

Learning helps to generate new brain cells

New brain cells in control

‘New’ brain cells after spatial learning


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

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
Using Innovative Technology to Assess Cognition, Including Working Memory

Invention

- CANTAB was co-invented by Trevor Robbins and Barbara Sahakian
- CANTAB computerised tests which use a touch-sensitive screen.
- Used in over 500 universities, research institutes and hospitals in over 50 countries
- Validated by over 1,200 peer-reviewed publications

“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.”

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

The importance of working memory for academic achievement

- 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

- 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 ADHD and schizophrenia*
Look for a blue token hidden in one of the boxes, without returning to a box where a token has previously been found.
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Neuroimaging at the Wolfson Brain Imaging Centre
Methylphenidate improves spatial working memory performance in adult patients with ADHD


Better Performance

Improvement

Turner, Blackwell, Dowson, McLean, Sahakian (2005) Psychopharm

Working memory is impaired in adult patients with ADHD
Methylphenidate (Ritalin) improves working memory & increases ‘efficiency’ of dorsolateral prefrontal cortical network in healthy volunteers.

**Graph**

- **Y-axis:** Mean Total Errors
- **X-axis:** Session (1, 2)
- **Bars:**
  - Dark grey: Drug
  - Light grey: Placebo

**Notes:**

- Elliott, Sahakian, Matthews, Bannerjea, Rimmer, Robbins (1997) *Psychopharm*

**Images**

- (a) Brain scan in sagittal view
- (b) Brain scan in transverse view

**References:**

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

Healthy Volunteers

Patients with First Episode Psychosis

*Müller, Rowe, Rittman, Lewis, Robbins, Sahakian (2013)*
*Neuropharmacology*

*Scorieds, Barnett, Soma, Sahakian, Jones (2011)*
*Psychopharmacology*
Modafinil also has effects on ‘hot’ cognition

It improves emotional processing in first episode psychosis

EMOTICOM (CANTAB for ‘hot’ cognition)

Domains:

• Emotional Processing
• Social Cognition
• Impulsivity
• Motivation and Reward

200 Healthy Volunteers Tested

MRC funded research: R Elliott, BJ Sahakian, TW Robbins, J Roiser, M Mehta

With Amy Bland and Thea Schei
The prescribing of methylphenidate has continued to increase in both the NHS and private sectors. This is likely to be attributable to its use in the management of childhood and adult ADHD and, due to its potential for diversion, and misuse, its use should also be monitored carefully.

Prof Sahakian is regularly approached by students who say they feel under pressure to take the drugs for fear of falling behind their peers.

13 August 2013

It is no longer caffeine but pills to which a rising number of students turn when revising.

“The prescribing of methylphenidate has continued to increase in both the NHS and private sectors. This is likely to be attributable to its use in the management of childhood and adult ADHD and, due to its potential for diversion, and misuse, its use should also be monitored carefully.”
Increasing Lifestyle Use of ‘Smart Drugs’ by Healthy People

<table>
<thead>
<tr>
<th>Study</th>
<th>% of People Using Smart Drugs</th>
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<tbody>
<tr>
<td><em>Nature</em></td>
<td>20%</td>
</tr>
<tr>
<td><em>Varsity</em> (Student Newspaper at the University of Cambridge)</td>
<td>10%</td>
</tr>
<tr>
<td><em>The Tab Student Newspaper</em></td>
<td>20%</td>
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<tr>
<td><em>The New Scientist &amp; BBC Newsnight</em></td>
<td>38%</td>
</tr>
<tr>
<td>Zurich and Basel Universities, The Swiss Federal Institute of Technology</td>
<td>7.6%</td>
</tr>
<tr>
<td>Data from US Universities</td>
<td>13.3%</td>
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<td></td>
<td>16.2%</td>
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</tbody>
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- In 2008, the global market share of modafinil was more than **$700 million** per year
- It is estimated that around **90%** of modafinil use is ‘off-label’ by **healthy individuals**.

Why are healthy people using cognitive enhancing drugs?

- **Increased performance / ‘competitive edge’** (effect sizes are generally small to moderate)
  Small percentage increments in performance can lead to significant improvements in functional outcome; it is conceivable that a 10% improvement in memory score could lead to an improvement in an A-level grade or degree class
  \[(Academy of Medical Sciences Report on Brain Science, Addiction and Drugs, 2008)\]

- To reduce the **effects of jetlag** and to stay awake for longer periods of time

- **Increased motivation and enjoyment of tasks**
  People report that they find it easier to carry out tasks that they had been putting off

Significant increase in pleasure rating for the modafinil group on all tasks
  \((p<0.001)\)

\[Muller, Rowe, Rittman, Lewis, Robbins, Sahakian (2013) Neuropharmacology\]
Modafinil reduces impulsivity and improves cognitive flexibility in sleep deprived doctors.

**Cambridge Gamble Task**

- Graph showing the delay aversion measure for Modafinil and Placebo.
- Ratio of coloured boxes: 9:1, 8:2, 7:3, 6:4.

**Cognitive Flexibility**

- Stages completed:
  - Modafinil: 9
  - Placebo: 8.4 to 8.9

*Sugden, Housden, Aggarwal, Sahakian, Darzi (2011) Annals of Surgery*
What are the potential harms and concerns in regard to pharmacological cognitive enhancement?

- There could be long-term side-effects, especially in the developing brain. Long-term studies in healthy people are required
- People could be coerced, or forced, into taking cognitive enhancers (24/7 society)
- There could be greater inequality, with access dependent on wealth
- **Cheating**, unfair advantage over others
  
  Duke University includes ‘the unauthorized use of prescription medication to enhance academic performance’ as cheating. ([https://studentaffairs.duke.edu/conduct/z-policies/academic-dishonesty](https://studentaffairs.duke.edu/conduct/z-policies/academic-dishonesty))
- Abuse potential for certain PCEs (e.g., methylphenidate)
- **Dangers of buying prescription drugs over the internet**
- You could be “over-enhanced” e.g. plagued by unwanted memories
- We run the risk of becoming a homogeneous society
- Our perception of ourselves could change (mechanistic beings) and we will be unable to take credit for our achievements
- Virtues such as motivation and working hard could become outdated (students will just take a drug)
MHRA 2014 Seizure of Smart Drugs in UK

- With over 20,000 units, of **13 different types of cognitive enhancement** drugs, the seizure represents an approximate value of **£200,000**.
- The drugs seized included noopept, phenylpiracetam, oxiracetam, centrophenoxine, sunifiram, citicoline and aniracetam.

**Piracetam**
One of the original racetams. In published reports, it is said to **enhance brain metabolism and neuroprotection**.

**Nefiracetam**
Binds to GABA-A and potentiates activity at the NMDA and acetylcholine nicotinic receptors.

**Aniracetam**
Has been shown to modulate the AMPA receptor and that it has actions on D2, nACh and 5-HT2A receptors.

**Noopept**
Derived from the racetam family of drugs and shares similar mechanisms of actions, but is **far more potent** than the prototypical racetam drug, piracetam.

**Sunifiram**
Entirely experimental and has **never been tested on humans in clinical trials**.

“There are also no long-term safety studies of the effects of these cognitive-enhancing drugs in healthy people. Healthy people are using these drugs without consultation from a doctor.”

Barbara Sahakian in The Guardian
As a society, we need to consider which forms of cognitive enhancement (e.g. pharmacological, exercise, lifelong learning) are acceptable and for which groups (e.g. military, doctors) under what conditions (e.g. war, shift work) and by what methods we would wish to improve and flourish.


**Human Enhancement and the Future of Work**


**Presidential Commission on Bioethics** Plays Early Role in BRAIN Initiative, Releases Gray Matters

Top Priority: Cognitive enhancement and justice


**UK Government Foresight Project on Mental Capital and Wellbeing** (Beddington et al. 2008) *Nature*

**Brain Project**

**The Oxford Handbook of Neuroethics**

BARBARA SAHAKIAN AND JAMIE NICOLE LABUZETTA

**2015 INS Annual Meeting**

Chicago IL - October 15-16

International Neuroethics Society

www.neuroethicsociety.org
Cognitive Training

• Engaging in mentally stimulating activities from middle age is correlated with lower incidence of dementia
  (Wilson et al, 2002, Neurology)

• Cognitive training has been shown to improve cognitive abilities and slow cognitive decline in older adults
  (Willis et al, 2009, JAMA)

• Hippocampal volume has been shown to relate to visuospatial/navigation ability in taxi drivers
  (Maguire et al, 2006, Hippocampus)
Increased brain activity after training of working memory

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)

Cognitive training for schizophrenia

Cognitive training effect sizes:

• Cognition = 0.45 (moderate)
• Psychosocial function = 0.42 (moderate)
• Psychiatric symptom severity = 0.18 (small)

Effect sizes are described as small, moderate or large

Playing the Wizard Memory Game Improved Performance in Patients with Schizophrenia on CANTAB PAL, a Test of Learning and Memory. They Also Found the Game Enjoyable

The cognitive training group made fewer errors (a), needed less trials to target (b) and correctly located more patterns at the first attempt of the eight pattern stage (c) of the CANTAB PAL task than the treatment as usual group. The Cognitive Training group indicated that they enjoyed playing the game and were motivated to continue across all the hours of cognitive training (all ratings higher than 65%) (d). Screen shot of the Wizard Memory Game (e).

Technology Transfer – Partnership with Peak

• In April 2015, Professor Sahakian and colleagues teamed up with the games developers Peak to produce scientifically-tested brain training apps

• Allows the Wizard memory game to become widely available, inexpensively.


University of Cambridge and Peak Memory Advanced Training Plan

Available on the App Store
**Ampakines improve cognition in healthy aged volunteers**

**Improvement**

- Insel, Voon, Nye, Brown, Altevogt, Bullmore, Goodwin, Howard, Kupfer, Malloch, Marston, Nutt, Robbins, Stahl, Tricklebank, Williams, Sahakian (2013) *Neuroscience and Biobehavioral Reviews*
- Sahakian, Malloch, Kennard (2010) *The Lancet*

**Disease Modifying Drugs and Novel Cognitive Enhancing Drugs**

- Offered long-term evidence to show that its amyloid-busting drug solanezumab has a distinct impact on Alzheimer's disease among early-stage patients.

- Bapineuzumab (AAB-003) will go into patients in earlier stages of the disease, said Husseini Manji, J&J’s global head of neuroscience.


**Cognitive Enhancement – Special Issue of Current Opinion in Behavioral Sciences**

(http://www.sciencedirect.com/science/journal/23521546/4)

**Special Issue on Cognitive Enhancers: Molecules Mechanisms and Minds, 2013**

**Conclusions:** New cognitive enhancing drugs are in development. However, we also need other methodologies, including technical solutions, such as cognitive training using games. These methods of enhancement could be combined for greater effects.
Acknowledgments to Collaborators

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Colin Sugden, Rajesh Aggarwal, Professor Lord Ara Darzi

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