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REVIEW

The ethics of elective psychopharmacology

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Abstract

Pharmacological cognitive enhancers (PCEs) are used to improve cognitive functions, such as attention, learning, memory and planning in patients with impairments in cognition resulting from traumatic brain injury (TBI) or from neuropsychiatric disorders such as Alzheimer's disease (AD), mild cognitive impairment, schizophrenia, and attention deficit hyperactivity disorder (ADHD). Moreover, PCEs have been shown to improve cognition in healthy volunteers with no psychiatric disorders. This article describes the rationale behind the need for their use in neuropsychiatric patients and illustrates how PCEs can ameliorate cognitive impairments, improve quality of life and wellbeing, and therefore reduce the economic burden associated with these disorders. We also describe evidence that PCEs are being used as cognitive enhancers by healthy people. Crucially, as the lifestyle use of these drugs becomes very popular in the healthy population, a final aim is to present an overview of the current and future neuroethical considerations of enhancing the healthy brain. As information regarding their actual use, benefits and harms in various healthy populations is currently lacking, we propose research that aims to obtain relevant empirical data, monitor the short- and long-term effectiveness and side-effects, and initiate accurate surveys to determine current patterns and quantity of usage of PCE drugs by healthy people. Furthermore, in order to instigate a dialogue between neuroethics and neuropsychopharmacology, we urge scientists to explore and communicate the social and ethical implications of their research to the public. Finally, we discuss and highlight other means of enhancing cognition in both patients and healthy adults, including education and physical exercise.

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Pharmacological cognitive enhancers (PCEs)

Cognitive impairment is a core deficit of a number of neuropsychiatric disorders (Goldberg & Green, 2002; Weickert *et al*. 2000) and drugs that improve facets of cognition such as attention, learning, memory and executive functions are known as PCEs (Morein-Zamir *et al*. 2008; Sahakian & Morein-Zamir, 2010). These drugs alter neurotransmitter modulation of cognition leading to improvements in cognitive deficits in patients with traumatic brain injury (TBI) (Teitelman, 2001), depression (Vaishnavi *et al*. 2006), addiction (Shearer & Rodgers, 2009), multiple sclerosis (Kraft & Bowen, 2005; Zifko *et al*. 2002), Parkinson's disease (Nieves & Lang, 2002), and those suffering from Alzheimer's disease (AD), schizophrenia, and attention deficit hyperactivity disorder (ADHD). The goal for their use is to ameliorate impaired functional outcomes. There is substantial opportunity for meeting the challenge of improving cognition and mental wellbeing in those with mental health problems and for reducing substantially the factors that contribute to the loss of mental, social and economic capital (Beddington *et al*. 2008).

A good illustration is AD, which is a neurodegenerative disorder characterized by a decline in cognitive and behavioural functioning. It is the commonest

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cause of dementia and one of the most disabling and burdensome health conditions worldwide (Ferri *et al*. 2005). There are currently 820 000 people with dementia in the UK, which costs £23 billion per year (Alzheimer's Society, 2007). Globally, if no effective prevention strategies or neuroprotective medications are developed, 81.1 million people will suffer from dementia by 2040 (Ferri *et al*. 2005). However, a treatment that would reduce severe cognitive impairment in older people by just 1% a year would cancel out all estimated increases in the long-term care costs due to ageing population (Comas-Herrera *et al*. 2007).

Cognitive enhancers hold significant benefits in ameliorating these cognitive impairments in AD and countering these economic and social burdens (Alzheimer's Research Trust, 2010; Kaduszkiewicz *et al*. 2005). For example, cholinesterase inhibitors (ChEI), such as donepezil, that inhibit centrally active acetylcholinesterase (AchE) and boost acetylcholine in the brain, compensate for the degeneration of neurons in the neocortex that regulate attention and memory (Stahl, 2009), and are effective in the treatment of mild and moderate AD (Eagger *et al.* 1991*a*, *b*; NICE, 2010).

Selective ChEIs release growth factors, interfere with amyloid deposition, or modulate nicotinic receptors (Pepeu & Giovannini, 2009; Stahl, 2009) while future drugs may exert their beneficial effects by activating various neurotransmitters including noradrenaline (NA), dopamine (DA), serotonin (5-HT), GABA and glutamate (Keowkase *et al*. 2010). Furthermore, drugs that activate synaptic NMDA receptors work synergistically with AMPA receptors to produce long-lasting changes in the synaptic functioning and enable the encoding of new memories. This promotes the phosphorylation of CREB that slows down the pathological changes observed in AD (Snyder *et al*. 2005). However, these drugs only minimize the neural damage caused by glutamate's neurotoxic effects and evidence is needed of improved episodic memory in AD patients. Importantly, some drugs have significant side-effects. For example, donepezil is contraindicated for people with liver problems (Mount & Downton, 2006) while others have modest clinical efficacy in early (Lanctot *et al*. 2003) and advanced stages (Alzheimer's Association, 2005). Furthermore, about 30–40% of patients with AD may not respond to ChEI, and approximately 29% of patients treated with ChEI leave clinical trials because of adverse events (Birks, 2006). Therefore, it is important to develop novel and effective neuroprotective agents that selectively target the underlying neuropathology associated with amnestic mild cognitive impairment and AD. Developing these drugs could be advantageous to the individual and to society, particularly given the significant ageing population in the UK and the USA. It is not within the scope of this review to cover in detail the range and action of all the current and novel PCEs and therefore the reader is referred to Stahl (2009) and The Academy of Medical Sciences (2008).

Notwithstanding, PCEs might also improve the quality of life in patients with TBI, which is the most common cause of disability in young people (Colantonio *et al*. 2010; Norup *et al*. 2010). For example, survivors of TBI often suffer from chronic cognitive deficits (Salmond *et al*. 2005, 2006) in areas such as sustained attention and learning which implicate impaired cholinergic function (Polo *et al*. 2002; Salmond & Sahakian, 2005). Furthermore, voxel-based morphometry studies reveal structurally reduced grey-matter density and changes in hippocampus and neocortex in TBI patients. This is further consistent with the cholinergic dysfunction account that commonly contributes to the development of TBI-induced cognitive impairments (Salmond *et al*. 2005). Consequently, the use of ChEIs that increase cholinergic function may be of benefit to TBI patients (Tenovuo *et al*. 2009). However, whether PCEs improve apathy, which is often considerably disabling and detrimental to rehabilitative efforts in TBI patients, needs to be determined in future research (Keenan *et al*. 2005; Padala *et al*. 2007).

Equally, patients with schizophrenia can also benefit from PCEs through improvements in executive functions (Barnett *et al*. 2010). Schizophrenia is a complex, lifelong disorder that significantly impairs cognitive and motivational function in approximately 1% of the world's population. Although psychotic symptoms, such as hallucinations and delusions, can be managed with antipsychotic treatment (Canuso *et al*. 2009), patients continue to suffer dysfunctions in cognition, affect and motivation, which account for substantial decrements in social and occupational functioning (Harvey *et al*. 2007; Matza *et al*. 2006; Velligan *et al*. 2006). Specifically, evidence indicates that these patients are substantially impaired in a wide range of neuropsychological task performances (Heinrichs & Zakzanis, 1998; Reichenberg & Harvey, 2007), and these impairments often impede everyday function and quality of life for many patients (Morein-Zamir *et al*. 2007). PCEs may prove beneficial as an add-on to antipsychotic medication, as it has been suggested that, in patients with schizophrenia, even small improvements in cognitive functions, such as enhancing the ability to adapt efficiently to new situations and to plan effectively, could help them make the transition to independent living (Altamura & Glick, 2010;

Davison & Keefe, 1995). Enhancing patients' cognition will not only improve their quality of life, but will also enable them to access jobs and integrate with society. In consequence, governments are relieved from the cost burden of ongoing care for these patients (Nicholl *et al*. 2010). In keeping with this, we have shown that PCE drugs improve cognitive performance in patients with schizophrenia (Barnett *et al*. 2010), and that modafinil (Provigil®), a wake-promoting drug licensed for narcolepsy, can improve cognitive flexibility as measured by extra-dimensional attentional set-shifting in patients with chronic schizophrenia (Turner *et al*. 2004*a*). Recently, modafinil has been shown to enhance some aspects of social cognition such as emotional facial recognition in patients with first episode of psychosis (Scoriels *et al*. 2010). However, many of the studies cited above are acute proof of concept studies and therefore one must be cautious about inferred long-term clinical significance, which still requires confirmation in experimental studies.

Nevertheless, children with ADHD can benefit from PCEs. ADHD is a heritable and disabling disorder characterized by core cognitive and behavioural symptoms of impulsivity, hyperactivity, and inattention. It is the most prevalent neuropsychiatric childhood disorder which affects around 3–7% of children worldwide (APA, 2000; Polanczyk *et al*. 2007). Structural abnormalities in fronto-striato-circuitry (Durston *et al*. 2003) and dysfunction in catecholamine neurotransmission, specifically in NA and DA pathways in the prefrontal cortex (PFC) have been implicated in ADHD (Yang *et al*. 2007). This leads to inefficient information processing and hypo-activation in the frontal lobes (Stahl, 2008). As a result, ADHD patients have significant impairments in performing working memory (WM) and executive function tasks (Biederman *et al*. 2007; Chamberlain *et al*. 2007; Dowson *et al*. 2004). However, if these impairments are not treated early, they can lead to significant negative life events such as drop out from education, job dismissal, criminal activities, substance abuse, and driving accidents (Barkley, 2006). PCEs such as methylphenidate (Ritalin®) (Dodds *et al*. 2008), selective NA reuptake inhibitor (SNRI) atomoxetine (Strattera®) (Chamberlain *et al*. 2007; Donnelly *et al*. 2009) and modafinil (Turner *et al*. 2003), increase DA and NA levels in the PFC (Mehta *et al*. 2004; Stahl, 2009; Wilens, 2006) and alleviate cognitive impairments in ADHD patients (DeVito *et al*. 2008; Turner *et al*. 2004*b*). Indeed, studies in our laboratory that use double-blind placebo-controlled designs showed that methylphenidate improves WM, cognitive flexibility, attention and response inhibition in both children and adults with ADHD (DeVito *et al*. 2008; Turner *et al*. 2004*b*). For example, DeVito *et al*. (2008) used the Cambridge Gambling Task, a test of decision making and risk taking, and showed that a single 0.5 mg/kg dose of methylphenidate reduced large bets on this task in ADHD boys, who performed similarly to healthy boys without medication. In consequence, PCEs can effectively improve core symptoms, abnormal behaviours, self-esteem, cognition, social and family function in ADHD patients (Sahakian & Morein-Zamir, 2007). However, methylphenidate is successful in treating only about 60–70% of ADHD children, meaning that 30% of patients with ADHD either do not respond to treatment or the drug causes adverse side-effects, such as headache, stomach pain, loss of appetite, trouble sleeping, dizziness and nausea, which precludes the use of methylphenidate. Atomoxetine may be a more acceptable treatment due to its low abuse liability and minimal adverse side-effects (Heil *et al*. 2002). Still, unlike methylphenidate which improves spatial WM (SWM), sustained attention, and response time in ADHD patients and healthy volunteers (Elliott *et al*. 1997; Turner *et al*. 2004*b*), atomoxetine only improves response inhibition possibly due to its selective NA modulation (Chamberlain *et al.* 2006, 2007), and is likely to be less effective in treating the range of cognitive deficits associated with ADHD. Therefore, there is a need for medication with improved efficacy and reduced side-effects for ADHD.

Furthermore, studies employing the same methodology show that modafinil also significantly improves short-term memory span, visual memory, spatial planning, and stop-signal motor inhibition in ADHD adults (Turner *et al*. 2004*b*). These improvements are consistent with randomized, double-blind placebo-controlled clinical trials with modafinil that demonstrate symptom reduction in ADHD children and adolescents (Biederman *et al.* 2005, 2006; Greenhill *et al*. 2006; Swanson *et al*. 2006). Hence, in psychiatry ethics, developing novel PCEs that improve the wellbeing and quality of life for these patients meets the 'right to receive effective treatment that would offer them a reasonable opportunity to improve their mental condition' (Bloch & Green, 2008, p. 490).

Pharmacogenomics

Another important argument for developing novel PCEs relates to the rise of pharmacogenomics and individualized medicine that aim to combat neuropsychiatric and neurodegenerative diseases. Pharmacogenomics is the discipline behind how genes

influence the body's response to drugs. There is growing evidence that key gene variants can change activity within specific neuronal circuits and, as a result, influence particular cognitive-affective phenomena. For example, the catecholamine-*O*-methyltrasferase (COMT) gene has been shown to affect responses to COMT inhibitors and to predict WM performance whereas the $Val^{108/158}$ polymorphism exerts a significant effect on enzyme activity and affects DA-regulated PFC activity during WM tasks, and also modifies the effect of dopaminergic drugs (e.g. the COMT enzyme inhibitor tolcapone) in the PFC (Diaz-Asper *et al*. 2008; Goldberg *et al.* 2003). Similarly, the therapeutic response in AD appears to be genotype-specific, with APOE-4/4 carriers being the worst responders to conventional treatments (Cacabelos, 2005). However, although behavioural phenotypes and action of PCEs are generally complex (Diaz-Asper *et al*. 2006), both reflecting the action of multiple genes and neurotransmitters respectively, it is possible that using pharmacogenomics to develop targeted PCEs for particular subgroups and individual responsiveness will lead to greater efficacy and reduced side-effects.

PCEs improve cognition in healthy individuals

PCEs also improve cognition in non-sleep-deprived healthy adults. For example, Turner *et al*. (2003) showed that a single oral dose of modafinil (100 mg or 200 mg) significantly improved performance on tests of digit span, visual pattern recognition memory, spatial planning, and stop signal reaction time (SSRT) task, or response inhibition, in healthy volunteers. Modafinil also improved the response time in tests of decision making, delayed matching to sample, and spatial planning (Müller *et al*. 2004). More recently, it improved accuracy in an attention-shifting task, without reaction time trade-off (Marchant *et al*. 2009), especially when participants' resources were most challenged. Consistent with this, Müller *et al*. (2004) demonstrated that modafinil significantly reduced error rates in a long-delay visuo-spatial task and manipulation conditions, without speed-accuracy trade-off.

Similarly, an acute dose of atomoxetine can improve response inhibition in healthy adults. Chamberlain *et al*. (2009) used functional magnetic resonance imaging and examined the brain mechanism by which atomoxetine exerts its cognitive enhancing effects in healthy volunteers. They found that atomoxetine led to increased activation in the right inferior frontal gyrus (RIFG) when participants attempted to inhibit their responses in the SSRT task. The RIFG has previously been shown to be activated during inhibitory motor control (Aron *et al*. 2003). It is thought that atomoxetine improves response inhibition via noradrenergic mechanisms. In contrast, methylphenidate has been shown to enhance SWM performance in healthy adults (Elliott *et al*. 1997). In a study employing sophisticated neuropsychological tests and brain-imaging measures (see Supplementary online material), Mehta *et al*. (2000) showed that methylphenidate improves both performance and efficiency in the SWM neural network, which includes the dorsolateral PFC and posterior parietal cortex in healthy volunteers (Owen *et al*. 1996). These areas have been significantly associated with WM and executive functions (Robbins *et al*. 2000). Moreover, studies using positron emission tomography and contrasting [^{11}C]raclopride binding, with the participants either on or off methylphenidate, have further indicated that methylphenidate influences dopaminergic function, particularly in the striatum (Wang *et al*. 1999). Other DA agonists improve WM and performance of executive tasks in healthy individuals (Mehta & Riedel, 2006; Roesch-Ely *et al*. 2005). There is evidence for enhancement of other forms of memory by PCEs. For example, evidence from healthy volunteers show that ampakine CX516 and ChEIs also lead to moderate improvements in recall and short-term memory (Wezenberg *et al*. 2007). In particular, pilots who took donepezil just before learning specific manoeuvres in a flight simulator outperformed a control group on tests of performance conducted 1 month later (Yesavage *et al*. 2002). However, the mechanism of action for improvement in attention, memory and executive function of PCEs still remains to be determined in many cases. For example, to exert its cognitive enhancing effects, modafinil has been shown to elevate numerous neurotransmitters including NA, DA and glutamate (Minzenberg & Carter, 2008; Volkow *et al*. 2009).

Neurotransmitter modulation of cognition

Evidently, as these improvements relate to neurotransmitter modulation and function (Iversen *et al*. 2009), the effects of some PCEs might follow the Yerkes–Dodson law, which explains the relationship between arousal and performance. This principle might be translated to several neurotransmitter systems where cognitive function often follows an inverted U-shaped curve, with deviations from the optimal level in either direction producing sub-optimal performance (Robbins & Sahakian, 1979; Robinson & Sahakian, 2009). For instance, low levels of

NA release engage α_2-adrenergic receptors and improve executive function whereas higher levels of NA release engage α_1-adrenergic receptors which cause significant stress in humans and animals (Arnsten, 2000; Finlay *et al*. 1995) and impair prefrontal functionality (Ramos & Arnsten, 2007). A similar U-inverted relationship is evidenced between DA and WM function (Vijayraghavan *et al*. 2007) as both marked increases and decreases of DA in the PFC have been associated with sub-optimal performance (Cools *et al*. 2003; Iversen, 2001, p. 31). Consistent with this hypothesis, methylphenidate improves cognitive performance in individuals with greater impairment (Konrad *et al*. 2004; Mehta *et al*. 2000) while guanfacine (Tenex®), an α_2-adrenergic receptor agonist, has beneficial effects on WM and attentional functions in patients with ADHD, but does not improve WM or executive functions in healthy male volunteers (Müller *et al*. 2005). Thus, the effects of pharmacological substances on cognition are complex as cognition is a multifaceted construct encompassing numerous mental functions including both cold cognition (such as attention, planning, problem solving, and response inhibition) and hot cognition (such as risky decision making; Roiser *et al*. 2006). For instance, PCEs may further modulate important human virtues such as creativity. A recent study by Farah *et al*. (2009) showed that the mixed amphetamine salts, adderall, licensed for the treatment of ADHD, enhanced performance on convergent tasks of creativity for lower-performing individuals and either impaired or did not change it for higher-performing individuals. These results on improvement and impairment on higher cognitive function with PCEs raises the issue of what we mean by a general term 'enhancement'. As healthy adults fall into a wide spectrum of normality, some individuals may be improved by a PCE drug while others remain unchanged or are even impaired (Randall *et al*. 2005; Robbins & Sahakian, 1979). Furthermore, there is as yet no robust empirical research to demonstrate that PCEs have effects on divergent thinking in healthy people.

Lifestyle use of PCEs by healthy individuals

The above results demonstrate the potential of PCEs to enhance certain cognitive domains in healthy adults. Therefore, attitudes towards their use by the general population need to be considered. In the next section, we focus our discussion on current and future trends of the use of PCEs by healthy people.

In the past few years there has been an unprecedented rise in the use of PCEs among healthy individuals for cognitive enhancement. Cognitive enhancement can be defined as the amplification or extension of core capacities of the mind through improvement or augmentation of internal and external information processing systems (Bostrom & Roache, unpublished data). Healthy university students (Desantis & Hane, 2010) and academics (Sahakian & Morein-Zamir, 2007) have been using PCEs to improve their cognitive function. More specifically, students are taking PCEs to improve academic performance (Rabiner *et al*. 2009) and are framing their actions as both physically harmless and morally acceptable (Desantis & Hane, 2010). For example, in the USA, 16% of college students (Babcock & Byrne, 2000) and 8% of undergraduates reported having illicitly obtained and used prescription stimulants (Hall *et al*. 2005; Lord *et al*. 2009; Teter *et al*. 2005). Furthermore, a 2005 survey by the US National Institute on Drug Abuse (NIDA, 2005) found that 2.5% of 13- to 14-yr-olds, 3.4% of 15- to 16-yr-olds and 5.1% of 17- to 18-yr-olds abused methylphenidate. In 2009, the figures for these groups were 1.8%, 3.6% and 2.1%, respectively (NIDA, 2009). Presumably, these young people are obtaining stimulant drugs from others who have prescriptions or purchasing them via the internet or street dealers.

Currently, the global market share of modafinil is more than US$700 million per year (Norman & Berger, 2008). Consistent with Greely's (2006) claim, that healthy physicians on call, students and academics are increasingly using PCEs to enhance cognitive abilities, it is estimated that around 90% of modafinil is predominantly used off-label by healthy, non-sleep-deprived individuals (Baranski *et al*. 2004; Vastag, 2004). In contrast, beta-blockers that are prescribed to reduce anxiety in clinical patients have been used by musicians to dampen physiological tremors in order to improve their performances on stage (Tindal, 2004).

In the UK, a newspaper survey of 1000 students showed that 1 in 10 were taking prescription drugs for cognitive enhancement (Lennard, 2009). In England, prescription rates of stimulants have been rising steadily from 220000 in 1998 to 418300 in 2004 (Niyadurupola, 2008). In 2008, the journal *Nature* conducted a poll about the use of PCEs by healthy academics, in which 1400 scientists from 60 different countries responded (Maher, 2008). One in five respondents used drugs for cognitive enhancement, with 52% of them obtaining the drug by prescription, while 34% obtained the drug via the internet and 14% through their pharmacy. The most popular drug was methylphenidate, with 62% of users; 44% reported taking modafinil mainly to improve concentration,

and 15% reported taking beta-blockers for anxiety. Of all respondents, 96% thought that people with neuropsychiatric disorders should be given cognitive enhancing drugs. In contrast, 86% of respondents thought that healthy children under the age of 16 yr should be restricted from taking PCE drugs.

Although some of these data were not rigorously collected, they nonetheless suggest the increased use of PCEs among healthy individuals. Their widespread use is not surprising given that small percentage increments in performance can lead to significant improvements in functional outcome. Indeed, a 10% improvement in memory score could lead to an improvement in an A-level grade or degree class (Academy of Medical Sciences, 2008, p. 150).

Neuroethical issues in cognitive enhancement

Nevertheless, the increase in lifestyle use of PCEs by healthy people raises numerous ethical issues that inform the growing field of neuroethics. Neuroethics is the study of the ethical, legal and social questions that arise when scientific findings about the brain are carried into medical practice, legal interpretations and health and social policy (Marcus, 2002). As such, modifying our inherent self, character and individuality through PCE drugs has important implications for society. For these reasons, their lifestyle use has prompted a significant interest both in the media and the public (Coveney *et al*. 2009; Stix, 2009). There is a concern that PCEs will threaten our notion of personhood and will dampen essential characteristics of what it means to be human (Farah *et al*. 2004; President's Council on Bioethics, 2003).

As a consequence, enhancing the brain and higher cognitive processes demands strong ethical considerations and a practical policy framework. To address this, we have argued elsewhere that before PCE drugs are prescribed to healthy people, their long-term safety, side-effects and their effectiveness must be tested to provide important facts necessary for further decision making about their regulation (Sahakian & Morein-Zamir, 2010). Moreover, we have engaged with the media about the need to establish regulations for the use of PCE drugs by healthy people (Mohamed & Sahakian, 2010). In Nature, we emphasized the need to ensure their safe use by healthy people (Greely *et al*. 2008) while in Science we advocated that ethical considerations in regard to societal issues associated with the use of PCEs by healthy people should be part of neuroethical training within university neuroscience programmes (Sahakian & Morein-Zamir, 2009).

But, what are the advantages and disadvantages of healthy people using PCEs? Since PCEs improve those with low cognitive performance (Robbins & Sahakian, 1979), it might be possible to mitigate the adverse environmental effects, such as poverty, on the brain and cognition through their use. This might contribute to removing disparity in society. It may also be that some 'healthy' people actually have undiagnosed attentional or other problems and are actually self-medicating with drugs such as ritalin. Furthermore, even healthy adults, who normally function well, are not always performing optimally due to sleep deprivation, jet lag or other stressors, and some might need to perform at their best possible level on every occasion (e.g. surgeons, air traffic controllers). In addition, PCEs might enable us to perform better in other competitive or life threatening situations. For instance, psychostimulants have been employed to boost cognition in soldiers in combat (Caldwell *et al*. 2000; Moran *et al*. 2007; Russo *et al*. 2008). PCEs have also been demonstrated to improve performance in shift workers (Ballon & Feifel, 2006), pilots (Caldwell, 2001) and school pupils with ADHD (Trout *et al*. 2007). Recently, the US Defence Advanced Research Project Agency (DARPA, 2007) introduced the Augmented Cognition Programme to enhance soldiers' memory and cognition through technology when under conditions of interrupted sleep and stress. However, if proven to be safe, PCEs may be preferred for cost-effectiveness when compared to other methods of enhancement such as expensive technology.

In contrast, the disadvantages of using PCEs include the potential harms and long-term side-effects that they might have in healthy people, particularly in adolescents where the brain is still in development. There are strong safety concerns, especially in the absence of informative data, for healthy individuals as the risk of adverse side-effects might outweigh the beneficial effects of PCE drugs. The abuse liability of some of the PCEs such as methylphenidate is also a concern. A recent study showed that modafinil blocked DA transporters and increased DA in the caudate, putamen and nucleus accumbens in healthy human brain (Volkow *et al*. 2009), which are areas in a network known to be involved in drug-seeking behaviour and addiction (Volkow & Li, 2004). This indicates the need for awareness about the risks involved in PCE use among healthy people and shows that a full ethical consideration of their use is required. To date, there have been no randomized psychopharmacological trials investigating the long-term effects of PCE drugs on healthy people.

There is still a further safety concern about the risks of purchasing substances advertised as PCEs over the internet (Forman *et al.* 2006*a*, *b*). As these drugs are not prescribed by a qualified doctor, they might not be suitable for some people. For instance, contra-indications of atomoxetine and modafinil include heart problems and hepatic impairments (British National Formulary, 2010). Additionally, if one is taking other medication there might be serious drug–drug interactions which could be dangerous in some cases.

With regard to personal autonomy, there are ethical concerns about healthy people being coerced or even forced into using a PCE. Society might force people to take psychoactive agents in order to perform better or to be in a particular mental state. For example, authorities in the USA ordered a mentally ill inmate in criminal proceedings to take psychotropic medication to improve his competence to stand trial and be executed (Boire & Ruiz-Sierra, 2003; Randall, 2004). There is also a considerable potential for indirect coercion resulting from a highly demanding 24/7 society where people feel compelled to take PCEs in order to meet social or workplace demands. Healthy people may resort to self-medication for inadequate sleep or over-exertion at work. For example, 33% of respondents in Maher's (2008) poll indicated that they would feel pressure to give PCE drugs to their children if other children at school were taking them. However, the use of PCEs to enhance cognition is one solution to improving the individual and society. Indeed, we have argued elsewhere that there are other methods of boosting cognition, including education and exercise (Sahakian & Morein-Zamir, 2010). For instance, physical exercise can improve learning and memory (Creer *et al*. 2010; Hillman *et al*. 2008). Through these non-pharmacological means we might be able to effectively and safely enhance cognition and well-being in society.

Another argument against their use is that they might further exacerbate the ever-growing disparity and inequality in society, especially if only the wealthy can access them. Equally, is it morally justified to use PCEs during exams, and does it give the user unfair advantage over those who are equally capable but not cognitively enhanced with drugs? Many universities as yet have no formal policy about the use of PCEs during exams. If PCEs become easily accessible in the future, will society consider their use as cheating or will they equate them to having a caffeine boost from coffee? Is it possible that once PCE drugs are widely available we might run the risk of becoming a homogeneous society? Could our perception of ourselves change from being human to being mechanistic beings with a modicum of emotion? Are we going to be over-enhanced only to be plagued by unwanted memories? Will using PCEs outdate important human virtues such as hard work and reflection and make us unable to take credit for our minds' achievements?

The advantages and disadvantages of using PCEs have to be evaluated carefully. With regards to fairness, enhancing cognition might lead to dramatic social benefits by reducing natural inequality and promoting social justice (Savulescu, 2006). This is because increasing cognitive ability on an individual level could have dramatic and positive effects on society and the economy as a whole (Bostrom, 2008). For instance, a 3% population-wide increase in IQ would reduce poverty rates by 25% (Weiss, 1998), and would lead to an annual economic gain of US$165–195 billion and up to 1.5% GDP growth (Salkever, 2005; Schwartz, 1994).

Public engagement in neuroscience

However, if healthy people take PCEs to gain a competitive edge but fail to see any difference in the long-term or notice possible impairments observed in high-functioning adults (Mattay *et al*. 2003) it could spark controversy and outcry in the public. Hence, determining who can use PCEs and under what circumstances involves complex decision making and ethical judgements. Thus, how neuroscientific discoveries impact on society has given rise to an enormous interest in the field of neuroethics, including the foundation of the Neuroethics Society (http://www.neuroethicssociety.org) which advocates further research on ethical questions that are yet to be answered. For instance, what are the possible long-term harms of using PCE drugs in healthy people, particularly in the developing brain? What are the implications of developments in pharmacogenomics? Without formal regulation of their use, healthy people can purchase PCEs via the internet, with all the inherent dangers in doing so. How would such easy access affect widespread use of these drugs by healthy young and elderly people and also impact on society? How would we, as neuropsychopharmacologists, react if we discover that our colleagues or our children's friends are taking PCEs? How should governments react? These questions in neuropsychopharmacology and neuroethics merit further rigorous research. They also clearly indicate the need to engage in discussion with the public about the social and ethical implications of the use of PCEs by healthy individuals

(Morein-Zamir & Sahakian, 2009; Ringach, 2009). For this to happen, neuropsychopharmacologists need to integrate experimental results within a neuroethical framework. In order to do this, they need to innovatively work together with social scientists, philosophers, and ethicists (Morein-Zamir & Sahakian, 2009; Sahakian & Morein-Zamir, 2009, 2010). This increases neuroscientists' role and responsibility in society (Farah *et al*. 2004) and puts them in a leading position to engage policy makers and a broad group of stakeholders, including the general public. This will ensure that technological advances in neuroscience are put to maximal benefit and minimal harm.

Conclusions

PCEs have the potential to ameliorate cognitive dysfunction and to provide important clinical benefits for patients. Further development of more effective PCEs with fewer side-effects, in addition to neuroprotective agents for patients with neurodegenerative diseases such as AD, is clearly worthy of pursuit. Pharmacogenomics will make it possible to target individuals with safe and effective drugs. PCEs can also improve cognitive function such as memory and attention in healthy individuals. However, their long-term cognitive enhancing potential as well as their side-effects in healthy people needs to be rigorously determined. Currently, the unprecedented rise of PCE use among the healthy raises numerous ethical issues. Scientists need to work together with social scientists, philosophers, ethicists, policy makers, and teachers to actively discuss the ethical consequences of PCE usage. This will ensure maximal benefit and minimal harm in the advances in neuroscience. Finally, the use of PCEs to enhance cognition is one solution to improving the individual and society. However, this does not preclude other means of enhancing cognition such as education and exercise (Beddington *et al*. 2008; Sahakian *et al*. 2010).

Note

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Statement of Interest

B.J.S. consults for Cambridge Cognition Ltd. She has consulted for Novartis, Shire, GlaxoSmithKline, Lilly and Boehringer-Ingelheim. She has also received honoraria for Grand Rounds in Psychiatry at Massachusetts General Hospital (CME credits) (Boston, 27 April 2007) and for speaking at the International Conference on Cognitive Dysfunction in Schizophrenia and Mood Disorders: clinical aspects, mechanisms and therapy (Brescia, 17–19 January 2007). She was on the Medical Research Council Neurosciences and Mental Health Board (2010) and on the Science Co-ordination Team for the Foresight Project on Mental Capital and Wellbeing, 2008 (Office of Science, The Department of Innovation, Universities and Skills). She is currently on Panel LS5 for the European Research Council. As an Associate Editor, she also receives an honorarium from the journal *Psychological Medicine*.

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