Neuropharmacological modulation of cognition

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Purpose of review

Problems relating to impulsivity, attention, and working memory occur in many neuropsychiatric disorders and represent important targets for pharmacological intervention. The purpose of this article is to review recent neuropharmacological manipulation studies in humans relating to these domains.

Recent findings

Serotonin manipulations in healthy volunteers did not affect response inhibition, a cognitive function implicated in impulsive symptoms of attention deficit hyperactivity disorder, trichotillomania, and substance abuse. Serotonin manipulations did affect performance on cognitive tests involving emotionally salient rewards and feedback, suggesting involvement of this neurochemical in affective aspects of impulsivity. Attentional deficits in attention deficit hyperactivity disorder and visuospatial neglect were ameliorated by noradrenergic drugs. Noradrenergic β-blockade suppressed the encoding of emotionally arousing unpleasant stimuli and reduced amygdala activation in healthy volunteers, with potential implications for posttraumatic stress disorder. Dopaminergic manipulations affected aspects of working memory in healthy volunteers and in patients with Parkinson's disease, with evidence for bidirectional effects depending on baseline performance.

Summary

Recent findings raise exciting prospects for modulating impulsivity, attention, and working memory in a variety of neuropsychiatric disorders. Future studies should use computerized cognitive assessment, measures of functional genetic polymorphisms, and neuroimaging techniques, in order to further elucidate the neurochemical substrates of cognition and optimize treatment approaches.

Keywords

arousal, dopamine, impulsivity, memory, noradrenaline, serotonin

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Abbreviations

ADHD attention deficit hyperactivity disorder
L-DOPA 3,4-dihydroxy-L-phenylalanine

1350-7540

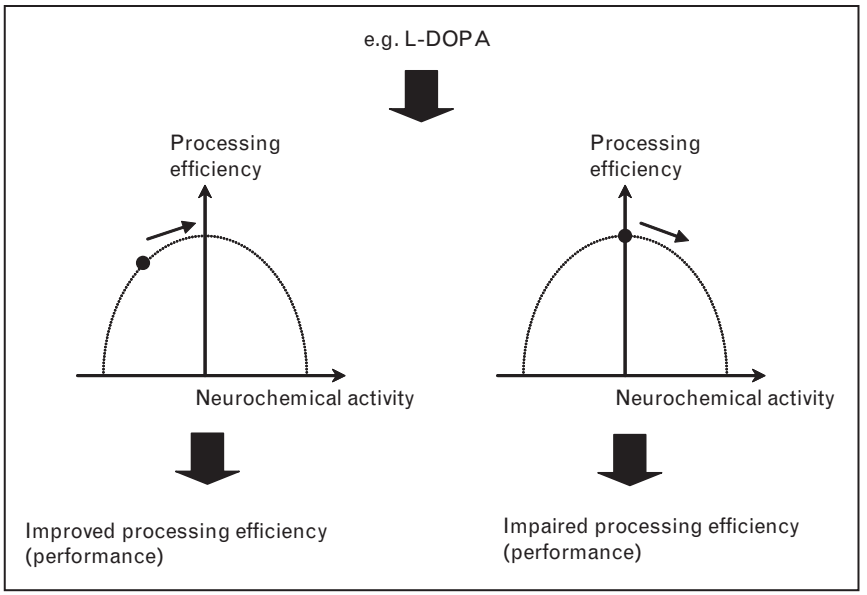
Introduction

The prefrontal cortex is critically involved in cognition and receives ascending input from various neuromodulatory systems [1]. Given the exquisite sensitivity of the prefrontal cortex to its chemical environment, pathologic disruption of these neuromodulatory systems can lead to profound cognitive deficits. Conditions associated with fronto-striatal dysfunction and cognitive deficits include stroke, Parkinson's disease, and attention deficit hyperactivity disorder (ADHD) [2,3]. Pharmacological interventions have the potential to ameliorate cognitive dysfunction in these disorders, and thereby to improve quality of life and everyday functioning. More than 100 neurotransmitters have been identified, but only some of these have been found to exert significant influences on cognition to date. Amongst these are the monoamines serotonin, noradrenaline, and dopamine [1,3], which form the focus of the present review.

Contemporary cognitive models have shifted away from the notion that neurochemicals exert a generalized influence on cognition, towards the view that this involvement may be to some extent dissociable. Since Emil Kraepelin's research into the effects of alcohol and other substances on simple reaction times in healthy volunteers [4•], increasingly specific drugs have been developed along with computerized methods of neuropsychological assessment [5–8]. Consequentially, substantial progress has been made in fractionating different components of cognition and in elucidating the underlying neurochemical and neural substrates of these processes. It is becoming increasingly evident furthermore that the effects of pharmacological manipulations are dependent upon baseline function. Evidence suggests that baseline neurochemical activity can determine not only the magnitude but also the direction of drugs effects on different cognitive domains, according to the inverted U model (Fig. 1) [9,10,11••,12••]. The aim of the present review is to highlight key recent neuropharmacological manipulations in humans relating to impulsivity, attention, and working memory. These domains have been

Figure 1 The inverted-U model of human cognition

Acute neuropharmacological potentiation (in this case of the dopaminergic system) improves (left) or impairs (right) different cognitive abilities as a function of baseline activity in neural regions sub-serving those domains. Baseline activity can be influenced by factors such as expression of functional genetic polymorphisms (e.g. catechol-O-methyltransferase, COMT), underlying neuropathology, and long-term medication.



classically linked to serotonin [13], noradrenaline [14], and dopamine [15] respectively, and are of particular importance in everyday life and in relation to cognitive deficits manifested across several prevalent neuropsychiatric disorders.

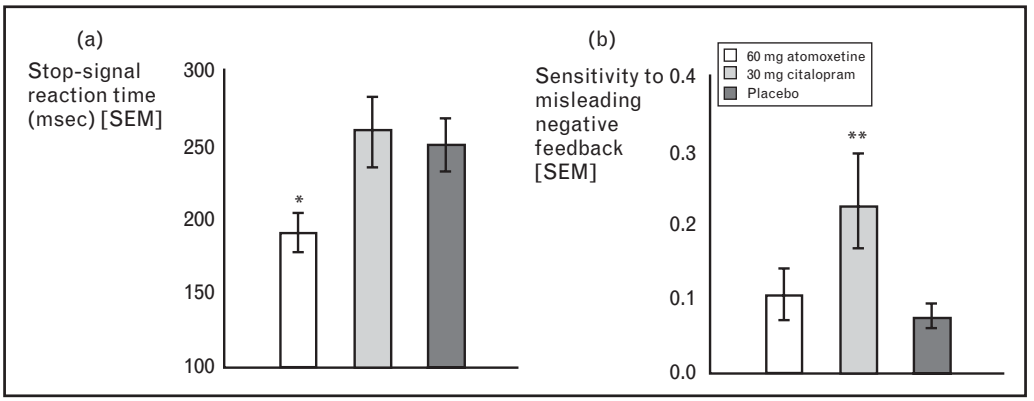
Impulsivity

Soubrié was among the first to suggest, some 20 years ago, that serotonin was critically involved in behavioural inhibition and thus impulsivity [13]. Certainly there is evidence that disruption of serotonergic pathways in animals can affect laboratory measures of impulsivity [16,17]. In humans, reduced levels of serotonin metabolites have been found in the cerebrospinal fluid of violent offenders and suicide victims [18–20]. Further, Tyano and colleagues [21•] recently confirmed correlations between low plasma serotonin levels and measures of violence and suicidal behaviour in suicide-attempters. From a neuropsychological perspective, several dissociable constructs relating to impulsivity have been proposed in the literature [22–24], and it is important to question whether serotonin manipulations affected these processes.

The term 'response inhibition' refers to the ability to inhibit or suppress simple motor responses that have been rendered prepotent [23], and deficits in this ability are implicated in impulsivity in several contexts. Impairment in this cognitive function is one of the most consistently reported neuropsychological deficits in patients with ADHD, which is regarded by many as an archetypal disorder of impulsivity [25•]. Multiple studies in patients with ADHD have identified beneficial effects of psychostimulant drugs on this ability (e.g. [26••]). Impairments in response inhibition were also recently identified in patients with trichotillomania, an atypical impulse control disorder characterized by excessive hair-pulling [27••]. Indeed, the magnitude of impaired response inhibition was found to correlate significantly with symptom severity. Monterosso and co-workers [28••] identified impaired response inhibition in abstinent methamphetamine abusers. It is unclear so far whether this finding suggests impaired impulse control as a 'risk factor' that predates substance abuse, or rather reflects neuropathological consequences of substance abuse.

Contrary to the classic hypothesis linking impulsivity primarily to serotonin, several neurochemical manipulations in healthy volunteers militate against involvement of serotonin in response inhibition. In a double-blind placebo-controlled design, Clark *et al.* found that depletion of brain serotonin (using the dietary amino-acid tryptophan depletion technique [29]) had no effect on response inhibition as indexed by the highly sensitive stop-signal reaction time (SSRT) task [30••], which had previously been shown to be dependent upon the integrity of the right inferior frontal gyrus [31]. Using a similar study design, neither a medium nor a higher dose of the serotonin 1A receptor agonist buspirone affected response inhibition in healthy volunteers [32]. Also, Chamberlain *et al.* [33••] found that administration of citalopram (a selective serotonin reuptake inhibitor) had no effect on response inhibition in healthy participants whereas atomoxetine (a selective noradrenaline reuptake inhibitor) improved this cognitive function (Fig. 2). It is interesting to note that there is little evidence to support the utility of serotonin based drugs

Figure 2 The effects of atomoxetine compared to citalopram on response inhibition and sensitivity to misleading negative feedback in healthy volunteers



(a) Response inhibition (stop-signal reaction times). (b) Sensitivity to misleading negative feedback. Inhibition of noradrenaline reuptake (atomoxetine) improved response inhibition with no effect on feedback learning, whereas inhibition of serotonin reuptake (citalopram) had no effect on response inhibition but increased sensitivity to misleading feedback. These findings implicate noradrenaline in simple motor impulsivity but suggest a role for serotonin in situations of emotional significance. $^{*}P < 0.05$, $^{**}P < 0.01$ versus placebo. Reprinted with permission [33••].

in the treatment of the core impulsive motor symptoms of ADHD [34], whereas atomoxetine and psychostimulants are effective, and exert their effects via noradrenergic or dopaminergic mechanisms [3,34,35].

As a consequence of these negative findings with regard to serotonin manipulations and response inhibition, it has been proposed that serotonin may be involved in other aspects of impulsivity, particularly when emotionally salient rewards or feedback are involved. In support of this proposal, Cools *et al.* [36••] found that serotonin depletion modulated reward-related speeding in healthy subjects, especially in those with high levels of self-reported impulsivity. The effects of serotonin depletion on reward-related speeding have also been reported to be dependent on the serotonin transporter polymorphism [37••]. Thus, tryptophan depletion abolished reward related speeding in people with the short-short (ss) genotype, but not in people with the long-long (ll) genotype, highlighting the evolving view that functional genetic polymorphisms in the central nervous system may dictate behavioural responses to neurochemical manipulations. Elsewhere, citalopram was found to increase sensitivity to misleading emotionally salient negative feedback in healthy volunteers, on a test of probabilistic learning (Fig. 2) [33••], again suggesting a role for serotonin in affective aspects of impulsivity.

Attention

Noradrenergic projections from the locus coeruleus to diffuse brain regions exert regulatory influences on attention, arousal, and vigilance [14,38–41], whereas there is a relative paucity of data implicating serotonin and dopamine in these processes [42]. Low to moderate levels of noradrenergic activity are thought to optimize prefrontal cortex function and maintain alertness, but higher levels (such as during times of extreme stress) may take the prefrontal cortex off line in favour of more automated 'flight/fight' responses [43•].

Problems with attention are integral to the diagnostic criteria for ADHD [44]. In a recent study by Llorente and co-workers [45••], significant correlations were reported between levels of urinary noradrenergic metabolites in children with ADHD and computerized measures of sustained attention. No significant correlations were found between urinary dopamine metabolites and sustained attention measures. Several studies have reported beneficial effects of psychostimulant medications on measures of attention in ADHD patients. For example, in an acute study Turner *et al.* [46•] showed that methylphenidate improved sustained attention as indexed by target sensitivity on the Cambridge Neuropshychological Test Automated Battery (CANTAB) Rapid Visual Information Processing (RVIP) test, using a within-subject double-blind design in adult patients. The RVIP test had previously been shown to be dependent upon a right lateralized fronto-parietal neural network [47]. Chronic treatment studies have also been undertaken, as exemplified by a recent study by Boonstra *et al.* [26••], who found that 3-week methylphenidate dosing improved attentiveness on a continuous performance test using a double-blind within-subject design in adult patients.

Another disorder involving attentional problems that may be amenable to pharmacological treatment is visual neglect syndrome, in which sufferers show impaired leftward exploration of space following right hemisphere stroke [48]. Malhotra and colleagues [49••] examined the effects of guanfacine (a noradrenergic agonist) on a computerized test of space exploration, in which patients had to locate target stimuli amongst distractors.

Guanfacine improved space exploration (target detection) in neglect patients with parietal/temporal lobe involvement but did not improve performance in a patient with dorsolateral prefrontal cortex involvement, suggesting that guanfacine's cognitive effects may be dependent upon the anatomical integrity of this latter region.

Heightened attention and arousal are strongly implicated in the development of posttraumatic stress disorder (PTSD), and patients with this condition show abnormal responses to noradrenergic pharmacological manipulations [50]. Noradrenergic potentiation with yohimbine induces panic attacks and flashbacks in people with PTSD, and drugs such as propranolol and clonidine (an $\alpha 2$ adrenoceptor agonist) may help to alleviate the symptoms of hyperarousal [50]. Various pharmacological studies in healthy volunteers support the existence of coupling between noradrenaline and the formation of memories for emotional events and stimuli, most likely through interactions with the amygdala and related medio-temporal structures [43•,51]. Thus β-blockade at the time of encoding can reduce later recall of emotionally salient events and stimuli [43•]. van Stegeren *et al.* [52••] demonstrated, using functional magnetic resonance imaging (fMRI) in healthy volunteers, that propranolol suppressed amygala activation during viewing of unpleasant stimuli.

Working memory

Working memory has been associated with dopaminergic neurotransmission, ever since the classic paper by Goldman-Rakic and co-workers [53] showing that regional dopamine depletion in the prefrontal cortex of rhesus monkey impaired spatial working memory. Many studies in animals and humans show that pharmacological manipulations of this system can affect working memory performance [15,54,55].

Gibbs and D'Esposito [56••] used an innovative event-related fMRI working memory paradigm, in order to investigate the effects of bromocriptine (a dopamine D2 receptor agonist) in healthy volunteers. Behaviourally, there was evidence that bromocriptine impaired performance accuracy in volunteers with high (but not low) baseline memory span (Reading Span test, conducted separately). Dopaminergic manipulation *per se* was associated with reduced brain activation during encoding but increased activity during recall/recognition. Mehta *et al.* [57] investigated the effects of methylphenidate on spatial working memory performance in conjunction with positron emission tomography, in healthy participants. Methylphenidate treatment was associated with improved spatial working memory performance and reductions in regional blood flow (i.e. improved processing efficiency) in the dorsolateral prefrontal cortex and other neural regions. Drug-induced improvements in spatial working memory performance were greater in subjects with lower baseline capacity [57].

Dopaminergic antagonists have also been shown to affect working memory processes. Mehta *et al.* [10] examined cognitive effects of the D2 receptor antagonist sulpiride in healthy participants, and found evidence for beneficial effects on a spatial working memory test sub-served by regions including the dorsolateral prefrontal cortex (significant for visit two only) [58]. Sulpiride, however, impaired other aspects of cognition such as performance on delayed-response and task set-switching paradigms. These findings collectively suggest not only that dopaminergic manipulations can impair or improve cognition depending on baseline performance, but also that the effects of such manipulations are highly dependent upon the precise components of working memory being examined.

Progressive dopaminergic depletion in Parkinson's disease has been linked to working memory impairments, and 3,4-dihydroxy-L-phenylalanine (L-DOPA) has been found to affect cognition in this patient group. Owen and colleagues [59] tested patients with Parkinson's disease using several different working memory tasks. Medicated patients with mild and severe symptoms showed impaired spatial working memory, whereas only patients with severe clinical symptoms showed additional impairments on verbal and visual working memory tests. Unmedicated patients were intact on these memory tasks. This relationship between the range of working memory domains affected in Parkinson's disease and the severity of illness may be consequential to pathological spatio-temporal progression of striatal dopamine depletion.

The contribution of L-DOPA to working memory performance in Parkinson's disease has been evaluated by Lewis *et al.* [60••], who examined 20 patients both on and off L-DOPA medication. It was found that whereas attentional set-shifting was impaired under both conditions, L-DOPA ameliorated a working memory deficit (manipulation measure) that was evident in the off drug condition. Thus, working memory deficits in Parkinson's disease appear to be psychologically specific and related to dopamine function. Consistent with findings in healthy participants, dopaminergic medications in Parkinson's disease likewise appear to improve some aspects of cognition whilst 'overdosing' and impairing others [12••,61], with likely clinical implications.

Conclusion

In this review, human pharmacological manipulations of impulsivity, attention, and working memory were discussed. While these domains have been classically linked with serotonin, noradrenaline, and dopamine, it

is important to bear in mind that there are likely to be important functional overlaps between these systems. Novel potential treatment directions suggested by the literature, such as the use of noradrenergic drugs to target impaired response inhibition in trichotillomania or attentional deficits in visuospatial neglect, should be evaluated in carefully controlled chronic studies.

Therapeutic possibilities exist for drugs acting on other neurochemical systems that were outside the scope of this review, such as acetylcholine and γ-aminobutyric acid [62,63]. Furthermore, functional genetic polymorphisms are likely to play important roles in determining baseline cognitive function and response to neuropharmacological manipulations, and this is a critical area for ongoing research [64,65]. Deployment of objective computerized tests and neuroimaging techniques in neuropsychiatric patient populations, along with genetic measures, will improve our understanding of cognition and its substrates. This will lead to improved algorithms for the treatment of cognitive deficits in neuropsychiatric disorders.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 633–634).

1 Robbins TW. Chemical neuromodulation of frontal-executive functions in humans and other animals. Exp Brain Res 2000; 133:130–138.

2 Rubia K, Smith AB, Brammer MJ, *et al.* Abnormal brain activation during inhibition and error detection in medication-naive adolescents with ADHD. Am J Psychiatry 2005; 162:1067–1075.

3 Biederman J. Attention-deficit/hyperactivity disorder: a selective overview. Biol Psychiatry 2005; 57:1215–1220.

4 • Müller U, Fletcher PC, Steinberg H. The origin of pharmacopsychology: Emil Kraepelin's experiments in Leipzig, Dorpat and Heidelberg (1882–1892). Psychopharmacology (Berl) 2006; 184:131–138.
A historical account of Emil Kraepelin's early neuropharmacological studies.

5 Sahakian BJ, Morris RG, Evenden JL, *et al.* A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. Brain 1988; 111 (Pt 3):695–718.

6 Owen AM, Downes JJ, Sahakian BJ, *et al.* Planning and spatial working memory following frontal lobe lesions in man. Neuropsychologia 1990; 28:1021–1034.

7 Owen AM, Roberts AC, Polkey CE, *et al.* Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. Neuropsychologia 1991; 29:993–1006.

8 Murphy FC, Sahakian BJ, Rubinstein JS, *et al.* Emotional bias and inhibitory control processes in mania and depression. Psychol Med 1999; 29:1307–1321.

9 Wilder J. Recent developments in the law of initial values. Exp Med Surg 1962; 20:126–131.

10 Mehta MA, Manes FF, Magnolfi G, *et al.* Impaired set-shifting and dissociable effects on tests of spatial working memory following the dopamine D2 receptor antagonist sulpiride in human volunteers. Psychopharmacology (Berl) 2004; 176 (3–4):331–342.

11 •• Arnsten AF, Li BM. Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. Biol Psychiatry 2005; 57:1377–1384.
This is an excellent review of the involvement of catecholamines in prefrontal cortex mediated cognitive abilities, showing key findings from the animal literature.

12 •• Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. Neurosci Biobehav Rev 2006; 30:1–23.
This is a comprehensive and well written review of the literature on Parkinson's disease, L-DOPA treatment, and cognitive functioning, in relation to the inverted 'U'.

13 Soubrié P. Reconciling the role of central serotonin neurons in human and animal behaviour. Behav Brain Res 1986; 9:319–364.

14 Robbins TW. Cortical noradrenaline, attention and arousal. Psychol Med 1984; 14:13–21.

15 Marsden CA. Dopamine: the rewarding years. Br J Pharmacol 2006; 147 (Suppl 1):S136–S144.

16 Mobini S, Chiang TJ, Ho MY, *et al.* Effects of central 5-hydroxytryptamine depletion on sensitivity to delayed and probabilistic reinforcement. Psychopharmacology (Berl) 2000; 152:390–397.

17 Winstanley CA, Eagle DM, Robbins TW. Behavioral models of impulsivity in relation to ADHD: Translation between clinical and preclinical studies. Clin Psychol Rev 2006; 26:379–395.

18 Asberg M, Traskman L, Thoren P. 5-HIAA in the cerebrospinal fluid. A biochemical suicide predictor? Arch Gen Psychiatry 1976; 33:1193–1197.

19 Linnoila M, Virkkunen M, Scheinin M, *et al.* Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. Life Sci 1983; 33:2609–2614.

20 Virkkunen M, Rawlings R, Tokola R, *et al.* CSF biochemistries, glucose metabolism, and diurnal activity rhythms in alcoholic, violent offenders, fire setters, and healthy volunteers. Arch Gen Psychiatry 1994; 51:20–27.

21 • Tyano S, Zalsman G, Ofek H, *et al.* Plasma serotonin levels and suicidal behavior in adolescents. Eur Neuropsychopharmacol 2006; 16:49–57.
This paper emphasizes the likely involvement of serotonin in emotionally salient aspects of impulsivity. Significant negative correlations were found between plasma serotonin levels and suicidal behaviour severity in suicidal inpatients.

22 Evenden JL. Varieties of impulsivity. Psychopharmacology (Berl) 1999; 146:348–361.

23 Aron AR, Fletcher PC, Bullmore ET, *et al.* Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nat Neurosci 2003; 6:115–116.

24 Clark L, Robbins TW, Ersche KD, *et al.* Reflection impulsivity in current and former substance users. Biol Psychiatry 2006; Jan 28 [Epub ahead of print]

25 • Lijffijt M, Kenemans JL, Verbaten MN, van Engeland H. A meta-analytic review of stopping performance in attention-deficit/hyperactivity disorder: deficient inhibitory motor control? J Abnorm Psychol 2005; 114:216–222.
This is a comprehensive meta-analysis of response inhibition findings in ADHD to date. Impaired response inhibition was found across studies, but was confounded in children (but not adults) by lengthened reaction times.

26 •• Boonstra AM, Kooij JJ, Oosterlaan J, *et al.* Does methylphenidate improve inhibition and other cognitive abilities in adults with childhood-onset ADHD? J Clin Exp Neuropsychol 2005; 27:278–298.
It is shown here that 3-week methylphenidate treatment improved aspects of sustained attention, objectively assessed, in adults with ADHD. Treatment also improved response inhibition, but only in participants with slow stop-signal reaction times beforehand.

27 •• Chamberlain SR, Fineberg NA, Blackwell AD, *et al.* Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. Am J Psychiatry 2006; 163:1282–1284.
This paper identifies severely impaired response inhibition, according to objective assessment with the stop-signal reaction time task, in un-medicated patients with trichotillomania (repetitive hair pulling). Patients with obsessive compulsive disorder were also impaired, but to a lesser degree. As stop-signal impairment correlated with trichotillomania symptom severity, this cognitive deficit represents an important target for novel pharmacological interventions.

28 •• Monterosso JR, Aron AR, Cordova X, *et al.* Deficits in response inhibition associated with chronic methamphetamine abuse. Drug Alcohol Depend 2005; 79:273–277.
In this study, chronic methamphetamine abusers (who were 5–7 days abstinent) showed impaired response inhibition, implicating problems in this domain either in the manifestation of, or in the consequences of, substance abuse.

29 Young SN. The use of diet and dietary components in the study of factors controlling affect in humans: a review. J Psychiatry Neurosci 1993; 18:235–244.

30 •• Clark L, Roiser JP, Cools R, *et al.* Stop signal response inhibition is not modulated by tryptophan depletion or serotonin transporter polymorphism in healthy volunteers: implications for the 5-HT theory of impulsivity. Psychopharmacology (Berl) 2005; 182:570–578.
Contrary to the classical link between serotonin and impulse control, it was shown that depletion of serotonin in healthy volunteers did not affect response inhibition.

31 Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. Trends Cogn Sci 2004; 8:170–177.

32 Chamberlain SR, Muller U, Blackwell AD, *et al.* Lack of deleterious effects of buspirone on cognition in healthy male volunteers. J Psychopharmacol (in press).

33 •• Chamberlain SR, Muller U, Blackwell AD, *et al.* Neurochemical modulation of response inhibition and probabilistic learning in humans. Science 2006; 311:861–863.
This paper reports a double-dissociation for the involvement of serotonin and noradrenaline in probabilistic learning and response inhibition, using citalopram and atomoxetine.

34 Biederman J, Spencer T, Wilens T. Evidence-based pharmacotherapy for attention-deficit hyperactivity disorder. Int J Neuropsychopharmacol 2004; 7:77–97.

35 Biederman J, Spencer T. Attention-deficit/hyperactivity disorder (ADHD) as a noradrenergic disorder. Biol Psychiatry 1999; 46:1234–1242.

36 •• Cools R, Blackwell A, Clark L, *et al.* Tryptophan depletion disrupts the motivational guidance of goal-directed behavior as a function of trait impulsivity. Neuropsychopharmacology 2005; 30:1362–1373.
In this paper, depletion of brain serotonin disrupted reward-related speeding on a task involving emotionally salient reward and feedback, as a function of self-reported impulsivity. This is consistent with serotonin playing a role in affective aspects of impulse control.

37 •• Roiser JP, Blackwell AD, Cools R, *et al.*, Serotonin transporter polymorphism mediates vulnerability to loss of incentive motivation following acute tryptophan depletion. Neuropsychopharmacology 2006; Mar 15 [Epub ahead of print].
In this healthy volunteer study, it was shown that tryptophan depletion affected reward-related speeding only in participants with the short-short (but not long-long) variant of the serotonin transporter gene, showing that neurochemical manipulations can be dependent upon functional genetic polymorphisms.

38 Foote SL, Aston-Jones G, Bloom FE. Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal. Proc Natl Acad Sci U S A 1980; 77:3033–3037.

39 Berridge CW, Arnsten AF, Foote SL. Noradrenergic modulation of cognitive function: clinical implications of anatomical, electrophysiological and behavioural studies in animal models. Psychol Med 1993; 23:557–564.

40 Smith A, Nutt D. Noradrenaline and attention lapses. Nature 1996; 380:291.

41 Aston-Jones G. Brain structures and receptors involved in alertness. Sleep Med 2005; 6 (Suppl 1):S3–S7.

42 Coull JT. Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology. Prog Neurobiol 1998; 55:343–361.

43 • Chamberlain SR, Muller U, Blackwell AD, *et al.* Noradrenergic modulation of working memory and emotional memory in humans. Psychopharmacology (Berl) 2006; Apr 27 [Epub ahead of print]
This is a tabulated review of the effects of noradrenergic manipulations on memory processes in healthy volunteers. Implications for posttraumatic stress disorder and other conditions are discussed.

44 Diagnostic and statistical manual of mental disorders IV (DSM-IV). Arlington: American Psychiatric Association; 1994.

45 •• Llorente AM, Voigt RG, Jensen CL, *et al.* Performance on a visual sustained attention and discrimination task is associated with urinary excretion of norepineprhine metabolite in children with attention-deficit/hyperactivity disorder (AD/HD). Clin Neuropsychol 2006; 20:133–144.
Preliminary findings reported in this paper support a particular role for noradrenaline rather than dopamine in mediating aspects of sustained attention.

46 • Turner DC, Blackwell AD, Dowson JH, *et al.* Neurocognitive effects of methylphenidate in adult attention-deficit/hyperactivity disorder. Psychopharmacology (Berl) 2005; 178:286–295.
This paper shows that acute methylphenidate improved aspects of cognition in adults with ADHD, including sustained attention.

47 Coull JT, Frith CD, Frackowiak RS, *et al.* A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory. Neuropsychologia 1996; 34:1085–1095.

48 Parton A, Coulthard E, Husain M. Neuropharmacological modulation of cognitive deficits after brain damage. Curr Opin Neurol 2005; 18:675–680.

49 •• Malhotra PA, Parton AD, Greenwood R, *et al.* Noradrenergic modulation of space exploration in visual neglect. Ann Neurol 2006; 59:186–190.
Noradrenergic drugs may be useful in the treatment of visuospatial neglect. It is shown here that guanfacine improved target detection in neglect patients with lesions not affecting the dorsolateral prefrontal cortex.

50 Southwick SM, Brenner JD, Rasmusson A, *et al.* Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. Biol Psychiatry 1999; 46:1192–1204.

51 McGaugh JL. The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu Rev Neurosci 2004; 27:1–28.

52 •• van Stegeren AH, Goekoop R, Everaerd W, *et al.* Noradrenaline mediates amygdala activation in men and women during encoding of emotional material. Neuroimage 2005; 24:898–909.
It is shown here that the β-blocker propranolol reduced neural responses to some types of emotionally salient stimuli. This suggests critical coupling between noradrenergic transmission and the amygdala (and associated regions), with implications for understanding and treating posttraumatic stress disorder.

53 Brozoski TJ, Brown RM, Rosvold HE, *et al.* Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. Science 1979; 205:929–932.

54 Robbins TW. Dopamine and cognition. Curr Opin Neurol 2003; 16 (Suppl 2):S1–S2.

55 Cools R, Robbins TW. Chemistry of the adaptive mind. Philos Transact A Math Phys Eng Sci 2004; 362:2871–2888.

56 •• Gibbs SE, D'Esposito M. A functional MRI study of the effects of bromocriptine, a dopamine receptor agonist, on component processes of working memory. Psychopharmacology (Berl) 2005; 180:644–653.
The authors present a prime example of how drug manipulations can be coupled with powerful neuroimaging cognitive paradigms. The authors used a novel fMRI test to investigate the effects of dopaminergic manipulation (in this case, using bromocriptine) on component processes of working memory. Behaviourally, there was evidence that participants with lower baseline memory span scores showed greater improvement on drug, consistent with the inverted 'U' model.

57 Mehta MA, Owen AM, Sahakian BJ, *et al.* Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. J Neurosci 2000; 20: RC65.

58 Owen AM, Morris RG, Sahakian BJ, *et al.* Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. Brain 1996; 119 (Pt 5):1597–1615.

59 Owen AM, Iddon JL, Hodges JR, *et al.* Spatial and nonspatial working memory at different stages of Parkinson's disease. Neuropsychologia 1997; 35:519–532.

60 •• Lewis SJ, Slabosz A, Robbins TW, *et al.* Dopaminergic basis for deficits in working memory but not attentional set-shifting in Parkinson's disease. Neuropsychologia 2005; 43:823–832.
In this paper, patients with Parkinson's disease were tested on and off L-DOPA medication. Treatment ameliorated working memory impairments but not attentional set-shifting impairments in these patients.

61 Swainson R, Rogers RD, Sahakian BJ, *et al.* Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. Neuropsychologia 2000; 38:596–612.

62 Sahakian B, Joyce E, Lishman WA. Cholinergic effects on constructional abilities and on mnemonic processes: a case report. Psychol Med 1987; 17:329–333.

63 Salmond CH, Chatfield DA, Menon DK, *et al.* Cognitive sequelae of head injury: involvement of basal forebrain and associated structures. Brain 2005; 128 (Pt 1):189–200.

64 Meyer-Lindenberg A, Nichols T, Callicott JH, *et al.* Impact of complex genetic variation in COMT on human brain function. Mol Psychiatry 2006; Jun 20 [Epub ahead of print].

65 Mattay VS, Goldberg TE, Fera F, *et al.* Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proc Natl Acad Sci U S A 2003; 100:6186–6191.