Neuropharmacological modulation of cognition
Samuel R. Chamberlaina,b, Ulrich Müllera,b, Trevor W. Robbinsb,c and Barbara J. Sahakiana,b

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

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
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**

Soubrie 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 psycho-stimulant 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.
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/flight’ 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 Neuropsychological 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 α2 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 amygdala 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).


A historical account of Emil Kraepelin's early neuropsychiological studies.


This is an excellent review of the involvement of catecholamines in prefrontal cortex mediated cognitive abilities, showing key findings from the animal literature.


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’.


19. Linnola M, Virkkunen M, Scheinin M, et al. Low cerebrospinal fluid 5-hydroxytryptamine levels and suicidal behavior in psychiatric 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.


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.


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.


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.


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.


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.


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.


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.


Llorente AM, Voigt RG, Jensen CL, et al. Performance on a visual sustained attention and discrimination task involving emotionally salient reward and feedback, as a function of self-regulated attention and discrimination task is associated with urinary excretion of norepinephrine metabolite in children with attention-deficit/hyperactivity disorder (ADHD). Neuropsychopharmacology 2006; Apr 27 [Epub ahead of print].

In this healthy volunteer study, it was shown that tryptophan depletion disrupted the motivational guidance of goal-directed behavior as a function of trait impulsivity. Neuropsychopharmacology 2005; 30:1362–1373.


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 neuromaging cognitive paradigms. The authors used a novel MRI 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.


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; 43:829–835. 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.


