Review

Noradrenergic modulation of cognition: Therapeutic implications

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Abstract

The noradrenaline (norepinephrine) system exerts profound influences on cognition via ascending projections to the forebrain, mostly originating from the locus coeruleus. This paper provides an overview of available infrahuman and healthy human studies, exploring the effects of specific noradrenergic manipulations on dissociable cognitive functions, including attention, working memory, cognitive flexibility, response inhibition and emotional memory. Remarkable parallels across species have been reported which may account for the mechanisms by which noradrenergic medications exert their beneficial effects in disorders such as depression and attention-deficit hyperactivity disorder (ADHD). The literature is discussed in relation to prevailing models of noradrenergic influences over cognition and novel therapeutic directions, including in relation to investigating the effects of noradrenergic manipulations on other disorders characterized by impulsivity, and dementias. Unanswered questions are also highlighted, along with key avenues for future research, both proof-of-concept and clinical.

Keywords

Noradrenaline, norepinephrine, cognition, working memory, emotional memory, inhibition, attention, translational, cognitive flexibility, Intra-Dimensional Extra-Dimensional, Intra-Dimensional / Extra-Dimensional, modulation, locus coeruleus

Introduction

More than one-hundred distinct neurochemicals have been identified in the human brain, but few of these have demonstrable influences over high-level cognitive functions (Robbins and Arnsten, 2009). These key 'neuromodulators' include serotonin, acetylcholine, dopamine and noradrenaline. Neuronal cell bodies for these systems are concentrated in the raphé nucleus, basal forebrain, ventral tegmentum/substantia nigra and locus coeruleus (LC) respectively (Dahlstroem and Fuxe, 1964). Despite the relatively discrete anatomical extent of these nuclei, they exert wide-spread influences over distributed cortical neural regions and associated cognitive functions, via ascending projections. Although there is differential innervation of cortical structures by such neuromodulators, there is likely to be important 'cross-talk' among these systems (Briand et al., 2007). The aim of this primer is to review the role of the noradrenaline system in cognition across species.

The LC is a cluster of noradrenaline-containing neurones (~14.5 mm length, 2.5 mm thickness in adult humans; Fernandes et al., 2012), located adjacent to the fourth ventricle in the brainstem. It contains a relatively small number of neurones – 1500 (per nucleus) in the rat, through to ~15,000 in humans (Berridge and Waterhouse, 2003). Despite its small size, the LC is responsible for most of the noradrenergic neurones projecting to the cortex (including cingulate), amygdala, thalamus, hypothalamus, hippocampus and cerebellum (Swanson and Hartman, 1975). Traditionally, it was believed that the basal ganglia were not innervated by the noradrenaline system: however, the shell of the nucleus accumbens may receive some non-LC noradrenergic innervation (Berridge et al., 1997; but see also Delfs et al., 1998). On account of its extensive forebrain projections, noradrenaline has been linked with a variety of functions including arousal, stress responses, anxiety, executive control and memory consolidation. In fact, an early theoretical proposal was that the LC functioned akin to the 'cognitive arm' of a central sympathetic ganglion (Amaral and Sinnamon 1977):

> Thus activation of the peripheral sympathetic nervous system prepares the animal physically for adaptive phasic responses to urgent stimuli, while parallel activation of the locus coeruleus increases attention and vigilance, preparing the animal cognitively for adaptive responses to such stimuli (Aston-Jones et al., 1991, p. 516).

This suggestion remains important in relation to modern models concerning the role of noradrenaline in cognition, which will be described later. It has been suggested that the relationship between arousal (or noradrenaline status) and cognition may operate according to the inverted-U Yerkes-Dodson principle (Yerkes and Dodson, 1908) such that, for a given cognitive function, there exists an 'optimal' level of activity to facilitate maximal behavioural performance (Robbins, 2000). Different cognitive

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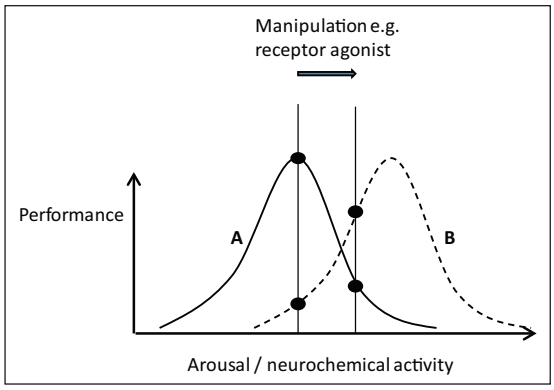

Figure 1. Inverted U model of cognitive function. The example shown considers two cognitive functions, (A) and (B), which exhibit different optimal set points, in terms of arousal/neurochemical activity. An increase in neurochemical activity (e.g. via administration of a receptor agonist) shifts cognitive function (A) beyond its optimal point, leading to behavioural impairment. In contrast, the manipulation shifts cognitive function (B) towards its optimal point, leading to behavioural improvement.

abilities are likely to operate with distinct optimal points, such that an increase in arousal/noradrenaline function may augment one function while impairing another (Figure 1). Through these actions, the brain is able to adapt flexibly to changes in the external environment and context.

In terms of synthesis, the noradrenaline and dopamine precursor pathways are intrinsically linked: tyrosine is hydroxylated to yield dihydroxyphenylalanine (DOPA) which is then decarboxylated to yield dopamine, which is then hydroxylated to yield noradrenaline (Axelrod, 1974). The noradrenaline (norepinephrine) transporter (NET) is the principal mechanism for terminating noradrenergic transmission in the central nervous system. The NET also exerts a dual role in the cortex, enabling reuptake not only of noradrenaline but also dopamine, due to the relative paucity of dopamine reuptake transporters therein (Bymaster et al., 2002; Stahl, 2003).

Adrenoceptors are membrane-bound, G-protein-coupled receptors found throughout the body as well as the brain and mediate a range of responses to the catecholamines adrenaline and noradrenaline (Robinson and Hudson, 2000). An initial distinction deriving from basic pharmacological studies on isolated tissues was drawn between alpha- and beta-receptors. A subsequent classification was between post-synaptic (alpha-1) and pre-synaptic (alpha-2) 'autoreceptors', originally with the latter positioned on sympathetic pre-synaptic nerve terminals and regulating (inhibiting) noradrenaline release. However, later it was found that pre-synaptic 'autoreceptors' were also present on the dendrites of noradrenergic cell bodies, for example in the LC where they played a role in regulating (reducing) cellular firing, as a consequence of the effects of released noradrenaline onto those somatic-dendritic autoreceptors. Moreover, pre-synaptic adrenoceptors may also be found on the terminals of other cells that do not use noradrenaline as their neurotransmitter. These 'heteroreceptors' may thus also play a part in regulating release of other neurotransmitters such as acetylcholine (Gilsbach and Hein, 2012).

Several pharmacological agents have been used in human research, which target specific components of the noradrenaline system (key examples are provided in Table 1). Many of these compounds have therapeutic uses in psychiatry and in medicine more broadly (Zhou, 2004).

Some drugs, such as clonidine, exert particularly potent agonistic effects at pre-synaptic alpha-2 receptors, leading to a net

Table 1. Key examples of pharmacological agents used to manipulate noradrenergic function in humans.

Drug (example of potential psychiatric indication)	Principal action	Approx. time to peak plasma level	Approx. half-life	Example psychiatric dose range
Atipamezole	Alpha-2a antagonist	1 h	2 h	n/a
Atomoxetine (ADHD)	Selective noradrenaline reuptake inhibitor (SNRI)	1–2 h	5 h	40–100 mg
Clonidine (ADHD; tics)	Alpha-2 receptor agonist	3–5 h	6–24 h	0.1–1.8 mg
Desipramine (depression)	Tricyclic (inhibits reuptake noradrenaline, also serotonin to lesser degree)	4–6 h	7–60 h	100–200 mg
Dexmedetomidine	Alpha-2 receptor agonist	0.5 h	2 h	n/a
Guanfacine (ADHD)	Alpha-2a receptor agonist	1–4 h	10–30 h	1–3 mg
Idazoxan	Alpha-2 receptor antagonist (& 5-HT_{1A} receptor agonist)	1 h	6 h	n/a
Lofexidine (withdrawal symptoms e.g. opioid related)	Alpha-2 receptor agonist	3 h	11 h	0.2–2.4 mg
Phenylephrine	Alpha-1 receptor agonist	0.25–1 h	1–2 h	n/a
Prazosin	Alpha-1 receptor antagonist	1.5 h	2 h	n/a
Propranolol (anxiety/panic)	Centrally active beta antagonist	1–2 h	3–6 h	5–640 mg
Reboxetine (depression)	Selective noradrenaline reuptake inhibitor (SNRI)	2 h	13 h	1–4(8) mg
Yohimbine	Alpha-2 receptor antagonist	0.15 h	0.5 h	n/a

ADHD: attention-deficit hyperactivity disorder; n/a: not applicable.

reduction of noradrenergic activity via actions at pre-synaptic receptors at both cell body and synaptic terminal. However, with increasing dose the net drug effect is a product of competing influences at pre- and post-synaptic receptors. This action is not quite as pronounced with other alpha-2 agonists such as guanfacine.

Further receptor classifications have been based on genetic as well as neuropharmacological evidence. For the alpha-1 adrenoceptor, there are three proposed subtypes, namely 1A, 1B and 1D; for the alpha-2 adrenoceptor, proposed subtypes are 2A (2D in humans), 2B and 2C; and for the beta-receptor family, the division is into beta-1, and beta-2 (and also atypical beta-3 and beta-4 subtypes, the latter being identified in cardiac tissue).

Phenylephrine and prazosin are active at all subtypes of alpha-1 receptors (with agonist and antagonist properties respectively) (Table 1). Alpha-1 subreceptor selective compounds suitable and shown safe for systemic use in humans have yet to be developed. Two experimental compounds used in non-human research are oxymetazoline (alpha-1a receptor agonist with additional partial 2a-receptor agonist effects) and WB4101 (alpha-1a antagonist). For the alpha-2 receptor subtypes, clonidine is a relatively general agonist, and yohimbine a general antagonist, whereas guanfacine is a selective agonist for the alpha-2A receptor subtype and atipamezole a relatively selective alpha-2A antagonist (Table 1). For the beta-receptor, the beta-2 subtype is relatively more sensitive to noradrenaline than adrenaline, and drugs such as clenbuterol and salbutamol are selective agonists (albeit they are mainly used in inspired rather than oral form to treat asthma and other respiratory disorders). Propranolol is an example of a general beta-receptor antagonist or 'beta blocker', and is widely used in oral form in humans (Table 1): sotalol is similar, but does not penetrate to the brain to any great extent.

Possible cerebral asymmetry in the functional role of noradrenaline

There has been some speculation about the functional role of noradrenaline based simply and solely on its neuroanatomical distribution. For example, this neurotransmitter is found in relatively high concentrations in the parietal (including somatosensory) cortex (Levitt et al., 1984; Morrison and Foote, 1986). Moreover, there are asymmetries in thalamic concentrations in both humans and rats (Oke et al., 1978, 1980). For humans the bias is to left pulvinar but to right somatosensory thalamic input areas: for rats it is to the left thalamus anteriorly and to the right posteriorly. Additionally, right-sided cerebral infarction causes much greater effects on noradrenaline concentrations versus left-sided infarction, especially when made in the frontal pole region (Robinson, 1979). These interesting, but somewhat disparate, findings of hemispheric asymmetries have led to suggestions regarding the possible role of cortical of NA in attention and arousal (Tucker and Williamson, 1984). For example, Posner and Petersen (1990) have proposed that the system is implicated in 'alerting', mediated preferentially by modulation of a proposed attentional system, located predominantly in the right cerebral cortex, consistent with the purported role of the right frontal cortex in sustained attention. However, in assessing these proposals, it is difficult to infer functionality from levels of neurotransmitter alone, especially in the absence of robust psychopharmacological evidence supporting this specific interaction.

Noradrenaline and cognition: Early lessons from Korsakoff's syndrome

One of the earliest pathological 'models' linking noradrenaline, the LC and specific cognitive abilities was that of Korsakoff's syndrome, a disorder first recognized by the Russian neurologist Sergei Korsakoff in the late nineteenth century. Korsakoff's syndrome is typically characterized by severe memory problems including anterograde and retrograde amnesia, along with confabulation and lack of insight. Memory problems extend also into domains of short-term and working memory, which may well reflect frontal lobe dysfunction. This disorder, due to thiamine deficiency, occurs in individuals with chronic alcohol use and malnutrition (Mair and McEntee, 1983) and is associated with lesions in neural regions known to be rich in noradrenaline neurons. Such lesions are visible using magnetic resonance imaging (MRI), and occur in the brainstem and periventricular structures primarily (Malamud and Skillicorn, 1956).

Crucially, it has been demonstrated that lumbar cerebrospinal fluid (CSF) levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), the major metabolite of noradrenaline, are greatly diminished in people with Korsakoff's syndrome (<80% of mean control values) (Mair et al., 1986); and that reduced levels of MHPG correlate significantly with the extent of short-term memory impairment in these individuals. Early work indicated that two-week treatment with the alpha-2 receptor agonist clonidine significantly ameliorated mnemonic and attentional (e.g. Stroop effect) deficits in such individuals (e.g. Figure 2) (Mair and McEntee, 1986; McEntee and Mair, 1980). It is possible that the generally opposite effects of the same dose of clonidine in healthy volunteers (see later) arise primarily from its pre-synaptic action, which may be absent or deficient in patients with Korsakoff's syndrome, thus unmasking a predominantly post-synaptic adrenoceptor action. Although subsequent clinical trials using noradrenergic agents in people with this disorder have not emerged, the Korsakoff's model of noradrenergic dysfunction serves to emphasise the role of this system in mnemonic processing, and also spurred several important lines of trans-species research (Mair et al., 1986).

Noradrenergic involvement in neuropsychiatric disorders

The noradrenaline system has been implicated across a variety of important neuropsychiatric disorders. Selective noradrenergic agents are not generally regarded as first-line treatments for depression. However, abnormalities of the noradrenaline system have long been implicated in the pathophysiology of the disorder and in the brain mechanisms by which various medications exert their beneficial effects on depressive symptoms (De Silva and Hanwella, 2012; Dell'Osso et al., 2011; Frazer, 2000). Several noradrenergic medications exhibit anti-depressant effects, notably atomoxetine (formerly tomoxetine), reboxetine and venlafaxine (Chouinard et al., 1984; Eyding et al., 2010; Zerbe et al., 1985). Tricyclic medications, particularly desipramine, have effects on the noradrenaline system and were amongst the classic treatment armamentarium for depression. These agents were largely superseded in clinical practice by medications with superior side effect and safety profiles (e.g. selective serotonin reuptake inhibitors (SSRIs)). Many patients with depression nonetheless do not respond to first-line treatments with serotonergic agents, leading

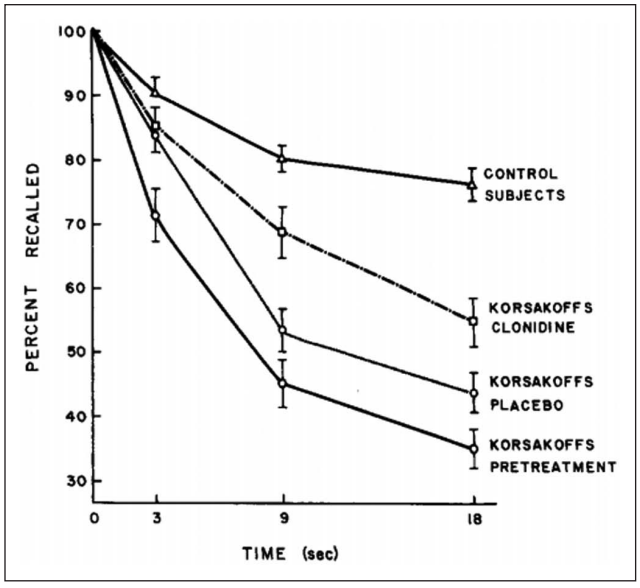

Figure 2. Performance on a short term memory task in people with Korsakoff's syndrome (an early model of noradrenergic dysfunction) versus controls. Patients showed profound mnemonic impairment, which was significantly ameliorated via clonidine administration as compared to placebo. Reprinted from Mair and McEntee (1983) with permission from Elsevier.

to consideration of noradrenergic agents as alternative treatments, or as candidate augmentation strategies. It is probable that certain depressive symptoms are more likely to respond to noradrenergic agents, especially problems relating to motor inactivity, inattention and lack of arousal (Dell'Osso et al., 2011). Clearly, understanding of the role of noradrenaline in cognition could be of considerable therapeutic importance given the wide prevalence of cognitive dysfunction in patients with depression, which likely impede quality of life and everyday function (Roiser et al., 2003). It is probable that such deficits, at least in some domains, persist despite serotonin-based treatments.

Though not considered in depth here, medications with noradrenergic effects are also critically important in the treatment of attention-deficit hyperactivity disorder (ADHD) (for detailed discussion see Del Campo et al., 2011). Cognitive problems are suggested by the diagnostic criteria for ADHD, which comprise symptoms of impulsivity, hyperactivity, and/or inattention (*Diagnostic and Statistical Manual Version Four Revised* (DSM-IV-TR), American Psychiatric Association, 2000). Furthermore, cognitive deficits have been demonstrated across salient domains with medium-large effect sizes in children and adults with ADHD, using objective translational tests (Chamberlain et al., 2011; Finke et al., 2011). First-line treatments for ADHD include stimulants (e.g. methylphenidate) which are thought to increase free levels not only of dopamine, but also of noradrenaline, by blocking reuptake and triggering release (Biederman, 2005). Also, more selective noradrenergic agents, atomoxetine and guanfacine, represent alternative treatment options for ADHD and are listed in international treatment guidelines (Seixas et al., 2012). The former medication blocks noradrenaline reuptake while the latter is an alpha-2 receptor agonist. Modafinil, a wake-promoting agent used for the treatment of narcolepsy, shows some efficacy in the treatment of ADHD (Greenhill et al., 2006; Wigal et al., 2006). Modafinil has been reported to improve cognitive functions such as response inhibition and working memory in healthy volunteers (Turner et al., 2003). The behavioural and cognitive effects of modafinil appear to be contingent, at least in part, on noradrenaline (Duteil et al., 1990; Winder-Rhodes et al., 2009). Novel candidate treatments for ADHD and related conditions may well emerge in future, with noradrenergic properties, particularly medications capable of blocking noradrenaline reuptake and activating alpha-2 receptors.

A role for noradrenergic dysfunction in the manifestation of disorders occurring at the other end of the age spectrum has also been posited (Marien et al., 2004). For example, Parkinson's disease has been associated with degeneration of noradrenaline neurones in the LC and cortex (Delaville et al., 2011; Vazey and Aston-Jones, 2012). In Alzheimer's disease, although cholinergic pathology and neuronal loss of the hippocampus and neocortex are regarded as amongst the primary phenomena, there is also progressive degeneration of the LC (Heneka et al., 2010). It remains to be seen whether these recent suggestions as to the role of noradrenaline in dementias can be translated into the application of noradrenergic agents therapeutically. One recent study has given some preliminary indication of possible efficacy; originally designed so as to test possible anti-depressant effects of atomoxetine in Parkinson's disease, none were actually found. However, there were post-hoc indications of significant improvements in global cognitive function and daytime sleepinesss that warrant further study (Weintraub et al., 2010). Due note will need to be given to the potential cardiovascular effects of noradrenergic medications, which may be expected to be potentially problematic in older individuals with medical co-morbidities.

Noradrenaline and dissociable cognitive functions across species

Here, we consider the role of noradrenaline in several cognitive domains, first describing key findings in animal models, and then providing a systematic review of noradrenergic manipulations conducted in humans. For the latter, published studies exploring the effects of noradrenergic manipulations on cognitive domains of interest in healthy volunteers were identified by (a) composing a list of selective noradrenergic agents deployed in humans, based on expert knowledge (Table 1); and (b) conducting PubMed searches based on each compound from this list plus the following search text: 'Attention' OR 'attentional' OR 'attention' OR 'memory' OR 'response inhibition' OR 'inhibitory control' OR 'stop-signal' OR 'SSRT' OR 'SST' OR 'Go/no-go' OR 'cognitive flexibility' OR 'set-shift' OR 'set-shifting' OR 'intra-dimensional extra-dimensional (IDED)' OR 'intra-dimensional / extra-dimensional (ID/ED)' OR 'reversal' or 'extradimensional' or 'extra-dimensional'. Individual papers were selected manually based on findings from the above search strategies, and by inspecting reference lists for these papers.

Attention. Although, to quote William James 'Everyone knows what attention is…' (James, 1890), a precise neuroscientific definition of 'attention' remains elusive. Certainly though, the

relationship between the noradrenergic system and attentional processes has been relatively well studied, in comparison to other cognitive domains. Attention can be considered in terms of space (e.g. attending to one spatial area rather than another) or for stimuli or objects (i.e. specific sensory attributes, independent of precise location); and in time (i.e. sustained attention, searching for stimuli in a given location over a time period). An alternative scheme for classifying attention has also been suggested, focusing on activation (alertness), selection, and control (Corbetta and Shulman, 2002). Attention, broadly defined, is dependent on a distributed fronto-parieto-thalamic network (Coull, 1998).

Based largely on microiontophoretic effects of noradrenaline reported in early animal studies, one (still prevailing) model is that the LC plays a key role in mediating changes in the 'signal-to-noise' ratio in terminal domains including the cortex and hippocampus (Everitt et al., 1990; Foote et al., 1980; Segal and Bloom, 1976). These studies indicated that alterations in signal-to-noise processing appeared largely driven by a suppression of background neural activity by noradrenaline, while acetylcholine appeared to enhance responses. Another suggestion, allied to this, is Easterbrook's hypothesis: namely that elevations of noradrenaline under arousing or stressful circumstances lead to a narrowing of attentional focus, in a re-formulation of the Yerkes-Dodson type hypothesis (Easterbrook, 1959).

Consistent with the above models, it was demonstrated that depletion of noradrenaline from the dorsal noradrenergic ascending bundle of the locus coerulerus in rats, using the catecholamine neurotoxin 6-hydroxydopamine, was associated with greater attention to contextual or spatial rather than local environmental cues, suggesting a re-allocation of spatial attention (Selden et al., 1990a, 1990b). Furthermore, depletion of LC-cortical noradrenaline in rats led to impaired attention (5-choice reaction time test, 5-CRT) specifically when visual targets were presented unpredictably in time, or when bursts of white noise occurred prior to target presentation (Carli et al., 1983; Cole and Robbins, 1992; Milstein et al., 2007). These latter studies, emphasizing a mediating role for noradrenaline in performance optimization when stimuli occur unpredictably and/or when background noise is evident, were followed up by pharmacological manipulations in rats. It was shown that an alpha-1 agonist improved monitoring of visual stimuli (vigilance) on the 5-CRT whereas the alpha-1 antagonist prazosin had the opposite effect (Puumala et al., 1997). Using three different attentional paradigms, it was also demonstrated that the alpha-2 agonist guanfacine improved attention and reduced distractibility in monkeys, albeit with more consistent effects in one monkey versus the other (O'Neill et al., 2000).

Inhibition of noradrenaline reuptake using atomoxetine has recently been shown to improve sustained attention (accuracy) on the 5-CRT in rats, but only when the paradigm was rendered more challenging by using variable inter-trial-intervals/unpredictable stimulus presentations (Robinson, 2012). Another study found that atomoxetine improved accuracy on a lateralised reaction-time task with long pre-stimulus preparatory times, but had the opposite effects when preparatory times were made brief (Jentsch et al., 2009). This result might conceivably have arisen from a capacity to enhance focused attention, thus more efficiently ignoring distractors during the delayed preparation time (but perhaps detrimentally so, at short preparation intervals).

Another prevailing suggestion in terms of noradrenaline models, is that the LC may exhibit two forms of firing: phasic and tonic. Electrophysiological single-unit recordings from LC cells during a sustained attention task in monkeys demonstrated that optimal task performance was associated with high phasic rates of LC firing whereas relatively poor performance corresponded to high tonic rates of firing (Aston-Jones et al., 1991; Rajkowski et al., 2004; Usher et al., 1999). Phasic firing occurred ~100 ms post-target and ~200 ms pre-response. It was suggested that the 'phasic' mode enables focused attention but that the 'tonic mode' of LC activity may facilitate task disengagement, theoretically to enable exploration of other salient aspects of the environment (Aston-Jones and Cohen, 2005).

Studies exploring the role of noradrenergic manipulations on attention in healthy humans are summarized in Table 2. As can be seen, there was evidence from multiple (though not all) studies that the alpha-2 agonist clonidine impaired sustained attention. For example, clonidine impaired performance on the rapid visual information processing task (RVIP) in one healthy volunteer study (Coull et al., 1995a) while another study reported that clonidine impaired attention during challenging trials on a task analogous to the animal 5-CRT (Jakala et al., 1999b). Findings from a follow-up study using RVIP in conjunction with functional magnetic resonance imaging (fMRI), indicated that clonidine reduced activation in the thalamus during an RVIP task-control state, perhaps indicative of effects on the default mode network during states of low arousal (Coull et al., 1997). There was also some evidence that clonidine impaired focused attention via a 'broadening of attentional focus', with subjects being more affected by distal distractors (Coull et al., 1995c).

Studies using sustained attention tasks with guanfacine generally reported no significant effect on attention (Coull et al., 2001; Jakala et al., 1999b; Kugler et al., 1980), albeit with some evidence from one healthy volunteer study for non-specific lengthening of reaction times (Kugler et al., 1980). One study found that noradrenaline reuptake inhibition with atomoxetine improved RVIP sustained attention (Crockett et al., 2010) while another did not (Chamberlain et al., 2006b).

Additional evidence supportive of effects of clonidine on aspects of attention comes from an important study using a two-choice reaction time task with and without distracting noise (Smith and Nutt, 1996). It was found that attention was significantly impaired by clonidine but only in the quiet condition: the deleterious effect of clonidine on attention was blocked by presentation of 'noise' and by concurrent administration of the alpha-2 antagonist idazoxan. Again, this may be suggestive that the effects of pharmacological manipulation of noradrenaline may depend on baseline arousal and context.

Event-related potentials (ERP) represent a useful paradigm employed in the investigation of attention and its neural substrates (see Herrmann and Knight, 2001). Some researchers have suggested that the frontal P300 (P3), an ERP measure, represents a marker of LC activity (e.g. see Nieuwenhuis et al., 2011; Pineda et al., 1989). For detailed discussion see (Nieuwenhuis and Jepma, 2011). In humans, there is evidence linking pupil diameter (another potential marker of LC activity) to P300 responses and performance on an auditory oddball task (Murphy et al., 2011). The P300 phenomenon is closely related to the motivational salience of an oddball occurrence, and supports a relationship between

Table 2. Effects of noradrenergic manipulations on attention (ATN) in healthy volunteers.

Author(s) and year	Drug(s) and dose(s) (mg)/ design	*n* (females) (per drug condition)/age (years)	Attentional task(s)	Effects of active drug manipulation (and comment)
(Kugler et al., 1980)	Clonidine 0.15 or guanfacine 1; then 2 h later, clonidine 0.3 or guanfacine 2/non-controlled	24 (0) (12)/~18–30	Five choice reaction-time test	Lengthening of reaction times with clonidine and guanfacine versus baseline (could be interpreted as ATN ↓). No control placebo arm.
(Clark et al., 1986)	Clonidine 0.1 or methylphenidate 50/cross-over, PLC	10 (0) (10)/18–30	Dichotic auditory attention task	ATN ↓ by clonidine (reduced target detection and discrimination).
(Brooks et al., 1988)	Atenolol 100 or metoprolol 200 or propranolol 160 (NB in divided daily doses over two-week period)/ parallel, PLC	32 (0) (8)/21–25	Simple auditory reaction test	ATN ↔
(Currie et al., 1988)	Propranolol 40 or 80 or 160; or atenolol 50 or 100; or oxazepam 15 /cross-over, PLC	12 (0) (12)/19–29	Continuous attention task (computerized); choice reaction-time test	ATN ↔ by beta receptor manipulation. (ATN ↓ by oxazepam).
(Clark et al., 1989)	Clonidine 0.2/cross-over, PLC	10 (0) (10)/18–30	Posner cueing paradigm	Clonidine ↓ behavioural cost of invalid cueing.
(Smith et al., 1992)	Idazoxan 120 (NB in divided daily doses for 22-days) /parallel, PLC	24 (0) (12)/18–45	Digit vigilance task; Broadbent focused attention and search test	Idazoxan shortened reaction times for stimuli presented in same location as previous ('compatible/repetition' trials; day 3 only; search task; ATN ↑).
(Mervaala et al., 1993)	Atipamezole 7.5# (alpha 2 antagonist)/no control, ERP	6 (0) (6)/26–41	Auditory event-related potentials	Atipamezole ↓frontal P300 amplitude. Non-controlled trial. ATN ↑↓
(Middleton et al., 1994)	Clonidine 0.09#/cross-over, PLC	16 (8) (16)/19–28	RVIP	Some evidence that ATN correlated significantly with cardiovascular parameters under clonidine conditions. Overall ATN effects not reported.
(Coull et al., 1995a)	Clonidine 0.12# or 0.20#; or diazepam 5 or 10/ mixed, PLC	88 (44) (12–16)/~22–25	RVIP; divided attention task	ATN ↓ by clonidine.
(Coull et al., 1995c)	Clonidine 0.2# or haloperidol 0.5 or diazepam 10 or low-tryptophan drink/parallel, PLC	56 (?) (12–16)/~20–30	Adapted Broadbent selective attention task; focused attention task; attentional search task	Some evidence that clonidine impaired performance when distractors located distal to target ('broadening of attentional focus'). (ATN ↓ generally by diazepam).
(Smith and Nutt, 1996)	Idazoxan 40 or clonidine 0.2 or both/parallel, PLC	74 (0) (?6)/18–35	Two-choice reaction time test with and without distracting noise	ATN ↓ by clonidine in quiet condition – effect reversed by idazoxan and noise.
(Coull et al., 1997)	Clonidine 0.1# or 0.12#/ mixed, PLC, ^{15}O water PET	25 (0) (12–13)/18–47	RVIP	ATN ↔. Some effects of clonidine in resting state: increase of thalamic rCBF after clonidine, non-specific across tasks.
(Shelley et al., 1997)	Clonidine 0.1 or droperidol 1/cross-over, PLC, ERP	10 (0) (10)/20–32	Multi-dimensional auditory selective attention task	ATN ↔ by clonidine; but increased processing negativity at irrelevant location. ATN ↓ by droperidol; also attenuation of processing negativity. Neither affected P3 amplitude.

Table 2. (Continued)

Author(s) and year	Drug(s) and dose(s) (mg)/ design	*n* (females) (per drug condition)/age (years)	Attentional task(s)	Effects of active drug manipulation (and comment)
(Jakala et al., 1999b)	Clonidine 0.04# or 0.16# or 0.4#; guanfacine 0.56# or 2.32#/cross-over, PLC	43 (15) (6–12)/23–35	Choice reaction-time test	ATN ↓ by higher dose clonidine at hardest task level. ATN ↔ by guanfacine.
(Middleton et al., 1999)	Clonidine 0.12#, idazoxan 40, clonidine 0.1# + idazoxan 40/mixed, PLC	48 (23) (16)/~20–30	RVIP	ATN ↓ (for second testing session: after clonidine alone; and clonidine with idazoxan).
(Coull et al., 2001)	Clonidine 0.2 or guanfacine 1, cross-over, PLC, fMRI	10 (5) (10)/18–45	Cueing attentional paradigm	ATN ↓ by clonidine (reduced alerting effect of warning cues); also attenuated task-related activity in left temporo-parietal junction, left insula, and right superior parietal cortex. ATN ↔ by guanfacine.
(Fu et al., 2001)	Clonidine 0.1, no control condition	6 (6) (6)/~20–40	Simple sustained attentional task, responding to directional arrows (left or right)	Clonidine ↑ rCBF bilaterally in insular cortices and ↓ in left angular gyrus and right superior prefrontal cortex.
(Coull et al., 2004)	Dexmedotomidine (alpha 2 agonist) or midazolam (titrated to sedative point, precise doses unclear), cross-over, PLC, fMRI	10 (5) (10)/21–37	Visual target detection task	ATN ↓ by dexmedotomidine and midazolam. White noise attenuated the deleterious effects of dexmedootomidine but not midazolam. Presentation of white noise during dexmedotomidine session enhanced left thalamic activity.
(Chamberlain et al., 2006b)	Atomoxetine 60 or citalopram 30/parallel, PLC	60 (0) (20)/20–35	RVIP	ATN ↔
(Nieuwenhuis et al., 2007)	Clonidine 0.15, parallel, PLC	32 (16) (16)/18–25	Attentional blink task, visual search task	ATN ↔ (except for slowing of overall response speed on visual search task with clonidine).
(De Martino et al., 2008)	Propranolol 20 or 40; or reboxetine 4; or nadolol 40/NB mixed design, three experiment study, PLC	96 (48) (~15)/~20–30	RSVP	Propranolol 40 mg impaired detection of T2 ('attentional blink') stimuli (ATN ↓); opposite effect with reboxetine (ATN ↑).
(Crockett et al., 2010)	Atomoxetine 60 mg or citalopram 30 mg/cross-over, PLC	30 (17) (30)/~20–30	RVIP	ATN ↑ by atomoxetine. Citalopram ↔
(Bodner et al., 2012)	Propranolol 40/cross-over, PLC	13 (4) (13)/18–25	AX-CPT	ATN ↔

AX-CPT: AX-continuous performance task; ERP: event-related potentials; fMRI: functional magnetic resonance imaging; PET: positron emission tomography; PLC: placebo-controlled; rCBF: regional cerebral blood flow; RSVP: rapid sequence of visual stimuli task; RVIP: rapid visual information processing task.
↑: improved; ↓: impaired; ↔: unchanged; ↓↑: mixed effects (as compared to placebo); #: dose estimate only, as administered based on body weight.

LC-NA activity and aspects of information processing/memory (as reviewed in Nieuwenhuis et al., 2005a). For example, it has been found that atipamezole, an alpha-2 antagonist, reduced frontal P300 amplitudes: however, this was a non-controlled study in relatively few subjects (Mervaala et al., 1993). Interestingly, while digit span improved with alpha-2 antagonism in this study (held to represent focused attention), word recognition (held to reflect divided attention) deteriorated.

It has been noted that the refractory firing period of LC cells corresponds to the 'attentional blink' phenomenon (Nieuwenhuis et al., 2005b) which refers to a transient impairment in the ability to detect the second of two signals presented rapidly in succession. During attentional blink, there is an absence of the P300 response that would ordinarily be observed (Vogel et al., 1998). Indeed, one study found that attentional blink performance was impaired specifically by central (as opposed to peripheral) beta-receptor antagonism (propranolol) irrespective of target valence, but that noradrenaline reuptake inhibition (reboxetine) improved attentional blink for emotionally-valenced stimuli (De Martino et al., 2008). Another study found that alpha-2 agonism with

clonidine had no notable effect on attentional blink (Nieuwenhuis et al., 2007), although some general task slowing was noted.

Clark et al. (1986) found that noradrenergic manipulation with clonidine impaired both focused and divided attention during dichotic listening experiments, suggesting deleterious effects of attention and/or occurrence of sedation. However, contrasting findings were reported in another study by Clark and co-workers (Clark et al., 1989) using the Posner paradigm (Posner, 1980) which examines the covert orienting of attention (the act of shifting attention to a location in space without deliberate eye movement to the given location). Clonidine diminished the behavioural cost of invalid cueing, without affecting valid cueing or response speed to a significant degree. This finding was interpreted in terms of a role for the noradrenergic system in enabling 'attentional disengagement'. Elsewhere, there was some evidence that alpha-2 antagonism with idazoxan enhanced attention to the location of preceding cues (compatible/repetition trials), at least, early in the treatment course (Smith et al., 1992), a finding somewhat complementary to the earlier clonidine result.

Although not strictly within the scope of the current review, studies have also explored effects of medications with less selective noradrenergic properties on attention. For example, it has been shown that the stimulant medication methylphenidate, and modafinil (a wake-promoting agent), enhanced perceptual processing speed during a visual attention capacity task in healthy volunteers, particularly in those with worse baseline function (Finke et al., 2010).

Overall, these findings support the notion that noradrenaline acts on aspects of attention that are functionally and neurally widespread, likely contingent on baseline arousal/stress and the balance between tonic and phasic firing of the LC. It is likely that LC activity is influenced by top-down processing via descending cortical projections, and by local mechanisms governing synaptic noradrenaline levels in terminal projection areas.

Working memory. Working memory can be defined as the ability to transiently store and manipulate salient information, in order to form and manipulate complex representations for the guidance of goal-directed behaviour (Baddeley, 1986, 1992). Meta-analysis indicates that working memory depends on a widespread bilateral fronto-parietal network (Rottschy et al., 2012). Apart from the aforementioned model of Korsakoff's syndrome implicating noradrenaline in aspects of memory in humans, there also exist tiers of evidence from the animal literature consistent with this proposition. Some of the earliest research used irreversible lesion techniques and identified deleterious effects of LC lesions on working memory in rats (e.g. Wenk et al., 1987). A classic body of literature also reported age-related reductions in noradrenaline function, and that these changes correlated significantly with the extent of working memory impairments, in rats and in mice (Leslie et al., 1985; Markowska et al., 1989). Furthermore, it was found that transplantation of LC cell tissue into the third ventricle of elderly rats improved aspects of working memory (Collier et al., 1988). Nonetheless, it is important to acknowledge that other systems – particularly dopamine – may be of greater influence in the instantiation of age-related working memory decline, and perhaps working memory in general (Luine et al., 1990).

Arnsten and colleagues have demonstrated across a number of studies that treatment with alpha-1 and alpha-2 agonists can affect working memory (spatial delayed response performance) in rhesus monkeys (Arnsten, 1997, 2009). For example, opposing effects on the firing of neurons involved in a working memory task have been demonstrated in vivo (see Figure 3). This line of approach is consistent with the view that moderate levels of noradrenaline facilitate prefrontal functions (especially working memory), but that, during times of extreme stress, high levels of noradrenaline may serve to take the prefrontal cortices 'off line' in favour of more automated flight/fight responses (including emotional memory, see below). Although not considered further here, it should be noted that complementary enhancing effects of noradrenaline and dopamine manipulations on prefrontal physiology during working memory have also been reported (see e.g. Robbins and Arnsten, 2009 for discussion). Gamo and colleagues (2010) explored the effects of noradrenaline reuptake inhibition using atomoxetine on working memory in monkeys, again using a delayed response task. Atomoxetine significantly improved working memory performance and this benefit was blocked by coadministration of idazoxan (Figure 4).

Findings from studies exploring effects of noradrenergic medications on working memory processes in healthy human volunteers are indicated in Table 3. The two studies using desipramine reported no effect on working memory itself, albeit one of these yielded uncontrolled evidence for improvement after treatment ended (Dimascio et al., 1964; Ross et al., 1984). No behavioural effects were seen with noradrenaline reuptake inhibition (reboxetine; atomoxetine – one trial with each) (Kerr et al., 1996; Marquand et al., 2011). Manipulations using beta-blockers yielded inconsistent effects (impairment, improvement and null in roughly equal measure).

The majority of clonidine studies identified deleterious effects on aspects of working memory (Coull et al., 1995b; Jakala et al., 1999a; Smith et al., 2003; Tiplady et al., 2005), with a minority showing no significant effect (Choi et al., 2006; Frith et al., 1985; Middleton et al., 1999). There was some evidence that co-administration of caffeine blocked the deleterious effect of clonidine (Smith et al., 2003), and that, contrary to what might be expected, concomitant administration of idazoxan with clonidine led to synergistic deleterious effects rather than opposing effects on working memory as well as on attentional set-shifting (see below and Middleton et al., 1999). Also, one study reported differential effects of clonidine on working memory depending on the precise task under study: spatial working memory was improved by high dose clonidine while visual working memory was impaired by low dose clonidine (Coull et al., 1995b).

Guanfacine also improved spatial working memory in one healthy volunteer study (Jakala et al., 1999a) but not in another study using the same paradigm (Müller et al., 2005a). Using fMRI, this time in conjunction with an 'N-back' style task, no behavioural effects of guanfacine were seen in healthy volunteers: however, improvements were seen in people with traumatic brain injury (McAllister et al., 2011). There were also some effects of guanfacine on neural activation in both groups, in regions not usually associated with working memory.

Viewed altogether, data from non-human primates are strongly suggestive that the noradrenaline system, particularly alpha receptors, play a role in working memory. However, findings in humans are less clear – the most consistent finding being that alpha-2 receptor agonism (presumably at inhibitory autoreceptors in the locus coeruleus) with clonidine led to working memory decrements.

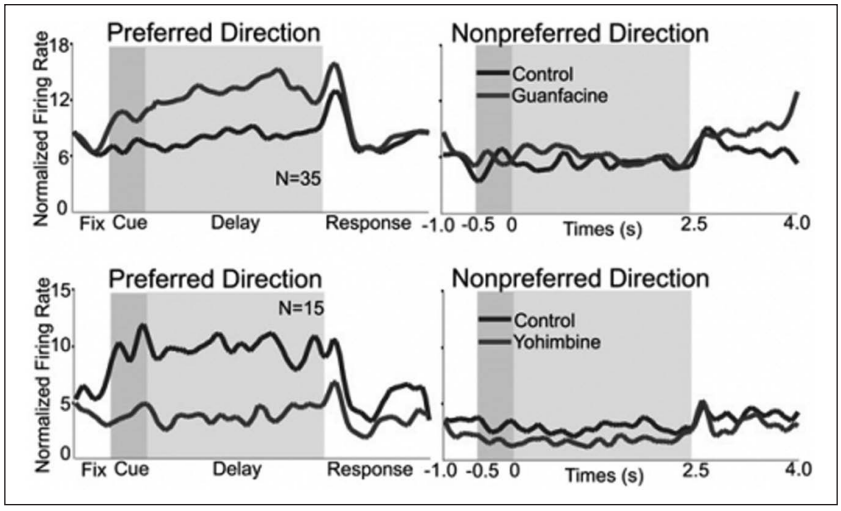

Figure 3. Summative effects of noradrenaline manipulations on spatial delay-related activity in populations of prefrontal cortex neurons in monkeys, during a working memory task. Alpha-2 receptor agonism using guanfacine enhanced firing of task-relevant neurons (top left) while alpha-2 receptor antagonism with yohimbine had the converse effect (bottom left). No such changes were seen with control neurons (top right, bottom right). N refers to the number of neurons studied. Figure adapted from Wang et al. (2007) and reprinted with permission from Elsevier.

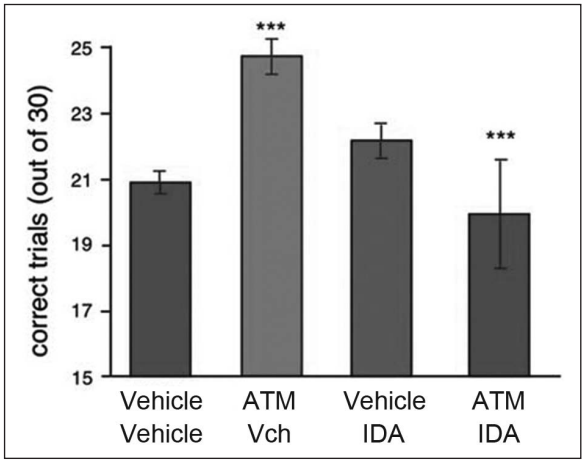

Figure 4. Effects of placebo, atomoxetine (ATM), idazoxan (IDA), and their combination on working memory performance in monkeys. Atomoxetine significantly improved working memory performance versus placebo while idazoxan reversed this improvement (***p<0.001). Idazoxan had no significant effect on working memory performance when given alone. Figure adapted from Gamo et al. (2010) and used with permission from Elsevier.

However, interpreting such decrements is often problematic in view of parallel effects of clonidine on attention and arousal.

Inhibitory response control. Response inhibition can broadly be defined as the suppression of pre-potent motor responses that are inappropriate to the task at hand (Chamberlain et al., 2006d; Robbins, 2012b). The ability has been operationalised by two main types of cognitive tasks: go/no-go tasks, and stop-signal tasks. The precise contribution of distinct neural regions to response inhibition, and whether 'response inhibition' is a discrete function remains under debate (Hampshire et al., 2010). However, it is generally accepted that performance on tasks of response inhibition (as defined above) is dependent on distributed neural circuitry including the inferior frontal gyrus, according to several tiers of evidence from human patients with frontal lesions, and from fMRI studies in healthy people (inter alia) (Aron et al., 2003, 2007). Data from animal studies implicate similar regions, although assuming homology of regions across species is potentially problematic (Eagle et al., 2008; Iversen and Mishkin, 1970). The nature of go/no-go and stop-signal tasks is subtly different, with the former emphasising action restraint when a response is needed from two or more options: and the latter requiring cancellation of an already-initiated response. Generally, stop-signal tasks are therefore believed to be potentially more sensitive to neurochemical manipulations and disorders characterised by impulsivity.

Importantly, it has been demonstrated that alpha-2 receptor blockade with yohimbine, infused over several days into the prefrontal cortices of two monkeys, impaired response inhibition (the ability to inhibit responses to no-go signals) (Ma et al., 2003). Following these findings through using a translational version of the stop-signal task, multiple studies have reported beneficial effects of noradrenaline reuptake inhibition (atomoxetine) on response inhibition in rats, with serotonin manipulations generally not impacting the primary inhibitory control measure on this paradigm (Bari et al., 2009; Eagle et al., 2008, 2009). More recently, it has been demonstrated that cortical infusion of atomoxetine improved stop-signal response inhibition in rats (Bari et al., 2011). Worth noting is that atomoxetine has been found likewise to reduce impulsive/premature responses on the aforeconsidered 5-CRT paradigm (Robinson, 2012; Robinson et al., 2008). Nonetheless, it may be that stop-signal tasks are particularly sensitive to noradrenergic manipulations, as opposed to other tests, which are impacted by selective serotonin and/or dopaminergic manipulations (Robbins, 2012b).

Studies examining the effects of noradrenergic manipulations on inhibitory control in healthy volunteers are listed in Table 4.

Table 3. Effects of noradrenergic manipulations on working memory (WM) in healthy volunteers (adapted in part from Chamberlain et al. (2006b) with permission from Springer.

Author(s) and year	Drug(s) and dose(s) (mg)/ Design	N (females) (per drug condition)/Age (years)	Working memory task(s)	Effects of active drug manipulation (and comment)
(Dimascio et al., 1964)	Desipramine 50 or 100 or 200; imipramine 50 or 100 or 200/ cross-over, PLC	7 (0) (7)/21–27	Serial addition	WM ↔ by desipramine. (addition speed measure impaired by high dose imipramine).
(Desai et al., 1983)	Oxprenolol (beta-blocker) 80, diazepam 5/parallel groups, PLC	44 (?) (5–12)/18–24	Running memory test	WM ↔ (after oxprenolol). (WM ↓↑ after diazepam; dependent on baseline anxiety).
(Ross et al., 1984)	Desipramine variable dose ~2 week/non-randomized, PLC	8 (5) (8)/20–25	Serial word learning	WM ↔ on desipramine. Some improvement after withdrawal. Uncontrolled design.
(Frith et al., 1985)	Clonidine 0.2/cross-over, PLC	8 (0) (8)/19–44	Digit span	WM ↔
(Frcka and Lader, 1988)	Propranolol 160 or atenolol 50/ long term (8 days)	12 (6) (12)/20–48	Word recall	WM ↓ (after propranolol).
(Brooks et al., 1988)	Atenolol 100 or metoprolol 200 or propranolol 160/parallel, PLC	32 (0) (8)/21–25	Digit span	WM ↑ by atenolol (backward digit span).
(Mervaala et al., 1993)	Atipamezole 7.5# (alpha 2 antagonist)/no control	6 (0) (6)/26–41	Digit span, Moss spatial recognition, Word recognition	Atipamezole ↑ digit span. Non-controlled trial.
(Coull et al., 1995b)	Clonidine 0.12# or 0.20#; diazepam 5 or 10/mixed, PLC	88 (44) (12–16)/~22–25	SWM, Visual working memory	SWM ↓↑ (low dose clonidine no effect; high dose improved SWM) Visual WM ↓↑ (low dose impaired; high dose no effect).
(Kerr et al., 1996)	Reboxetine 0.5 or 1 or 4; amitriptyline 25/cross-over, PLC (alcohol)	10 (0) (10)/18–40	Sternberg	WM ↔ (after reboxetine).
(Jakala et al., 1999a; Jakala et al., 1999c)	Clonidine 0.04# or 0.16# or 0.4#; guanfacine 0.56# or 2.32#/mixed, PLC	55 (15?) (6–12)/23–35	SWM	WM ↓↑ by clonidine (low and high doses impaired WM). WM ↑ by guanfacine.
(Middleton et al., 1999)	Clonidine 0.12#, idazoxan 40, clonidine 0.1# + idazoxan 40/ mixed, PLC	48 (23) (16)/~20–30	SWM	WM ↔ (after clonidine alone). WM ↓ (after combined idazoxan + clonidine).
(Swartz et al., 2000)	Guanfacine 2–3/parallel groups, no placebo control, ^{15}O water PET	19 (7) (13)/20–59 (+ 24 epilepsy patients)	Delayed matching to sample	Increase of dorsal prefrontal rCBF after guanfacine; behavioural results not reported.
(Smith et al., 2003)	Clonidine 0.2 or caffeine 120; or both/cross-over, PLC	24 (0) (6)/18–35	Repeated digits, word list	WM ↓ (after clonidine, reversed by caffeine); single-blind design.
(Veselis et al., 2004)	Dexmedetomidine propofol thiopental (various doses)/ parallel, PLC	83 (32) (~10)/not specified	Auditory continuous recognition test	WM ↔ (all subjects after dexmedetomidine) Small *n*.
(Müller et al., 2005a)	Guanfacine 1 or 2/parallel group, PLC	60 (0) (20)/20–39	SWM, digit span	WM ↔
(Müller et al., 2005b)	Propranolol 25 or atenolol 50/ mixed, PLC	24 (12) (16)/19–27	Manipulation task	WM ↓ (after propranolol, in low anxiety volunteers). WM ↔ (after atenolol).
(Swann et al., 2005)	Yohimbine 20 or 30 or 40/ cross-over, placebo first	9 (5) (9 + 8)/~23–37	Immediate and delayed memory task	WM ↔, more impulsive responses after yohimbine; small *n*.
(Tiplady et al., 2005)	Clonidine 0.15 or 0.3; temazepam 15 or 30/cross-over, PLC	15 (8) (15)/18–25	Sternberg, logical working memory, selective reminding	WM ↓ (after clonidine and temazepam, dose effects).
(Choi et al., 2006)	Clonidine 0.1 or ephedrine 25/ cross-over, PLC	18 (7) (18)/18–27	Rey-Osterrieth Complex Figures task	WM ↔
(Alexander et al., 2007)	Propranolol 40/cross-over, PLC	16 (8) (16)/~18–30	Rey-Osterrieth Complex Figures task	WM ↔ (including during Trier Stress test).

Table 3. (Continued)

Author(s) and year	Drug(s) and dose(s) (mg)/ Design	N (females) (per drug condition)/Age (years)	Working memory task(s)	Effects of active drug manipulation (and comment)
(Swartz et al., 2008)	Guanfacine 2–3/uncontrolled	10 (4) (10)/~20–40	Delayed matching-to-sample	WM ↑ post guanfacine. No control for practice effects.
(Campbell et al., 2008)	Propranolol 20 or 40 or 60, cross-over, PLC	72 (36) (72)/18–35	Rey-Osterrieth Complex Figures task; Digit span	WM ↔ for Rey-Osterrieth. WM ↑ with 40 mg for digit span forward and back.
(Winder-Rhodes et al., 2009)	Prazosin 3 or modafinil 300 mg or both/cross-over, PLC	12 (0) (12)/18–39	Digit span and digit ordering	WM ↔
(Oei et al., 2010)	Propranolol 80/parallel, PLC	54 (0) (27)/18–35	Sternberg	WM ↓ at low load WM ↑ at high load NB effect driven by propranolol blocking distinction between emotional and neutral distractors.
(McAllister et al., 2011)	Guanfacine 2/cross-over, PLC, fMRI	14 (8) (14)/~30–40	N-Back	WM ↔ Some effects of guanfacine on neural activation in regions not usually associated with WM performance.
(Marquand et al., 2011)	Atomoxetine 60/cross-over, PLC	50 (0) (50)/20–39	Delayed match-to-location WM task	WM ↔ behaviourally. Atomoxetine ↓ activity in WM network for rewarded trials

fMRI: functional magnetic resonance imaging; PAL: paired associates learning task; PET: positron emission tomography; PLC: placebo-controlled; rCBF: regional cerebral blood flow; Sternberg: Sternberg memory scanning task; SWM: Spatial working memory task.
↑: improved; ↓: impaired; ↔: unchanged; ↓↑:mixed effects (as compared to placebo); #: dose estimate only, as administered based on body weight.

Several studies showed significant effects of atomoxetine on stop-signal response inhibition. In work by Chamberlain and co-workers (2006b), beneficial effects on response inhibition were seen following atomoxetine, with serotonin reuptake inhibition (citalopram) having no effect on this task, but impacting probabilistic learning. In a follow-up fMRI study, it was found that atomoxetine improved response inhibition, and augmented activation in the right inferior frontal gyrus/insula during successful inhibition (Chamberlain et al., 2008). Although a fixed dose study, plasma levels of drug were recorded and the extent of right frontal activation covaried significantly with plasma levels of drug (Figure 5). This may be related to a recent finding of a significant association of a NET polymorphism with fMRI activity of the right inferior gyrus during successful performance of a stop-signal reaction time task (SSRT) task, in a large sample of adolescent volunteers (Whelan et al., 2012). In an fMRI study undertaken by Graf and colleagues using a go/no-go task, on the other hand, noradrenaline reuptake inhibition using a relatively large dose of atomoxetine significantly impaired inhibitory control (Graf et al., 2011). Drug-dependent increases in error signals were identified in the bilateral inferior frontal cortices and pre-supplementary motor area.

Another study reported no significant behavioural effect of atomoxetine on response inhibition in healthy volunteers versus placebo, while methylphenidate did improve this function significantly (Nandam et al., 2011). However, it is worth noting that mean performance under atomoxetine was numerically intermediate between placebo and methylphenidate: and that the statistical difference between methylphenidate and atomoxetine on response inhibition was of borderline significance (p=0.05). Crockett et al. (2010) using a go/no-go paradigm, found that atomoxetine significantly improved response inhibition in a cross-over design as compared to under the citalopram condition but, again, the comparison with the placebo condition did not attain statistical significance.

The few available healthy volunteer studies using guanfacine, prazosin or propranolol have yielded no significant effects of noradrenaline manipulation on response inhibition. In view of the limited number of healthy volunteer studies, and strong evidence from animal studies suggesting noradrenergic effects on response inhibition, clearly further research is needed in humans.

Cognitive flexibility

Cognitive flexibility can be considered as the ability to adapt behavioural strategies in the light of changing situational requirements and experience. Cognitive flexibility has been usefully fractionated into several distinct processes in the neuropsychological literature, where a distinction is made between reversal learning and set-shifting (Birrell and Brown, 2000; Dias et al., 1996; Owen et al., 1991). Reversal learning refers to the ability to switch responding from one stimulus to another, within the same stimulus dimension. In contrast, extra-dimensional set-shifting refers to the ability to inhibit and shift attention away from a previous relevant stimulus dimension, onto a different stimulus dimension that was previously irrelevant. These abilities are tapped by paradigms including the Wisconsin Card Sorting Test (WCST) and the Cambridge neuropsychological test automated battery (CANTAB) IDED task, the latter of which fractionates these and other aspects

Table 4. Effects of noradrenergic manipulations on inhibitory control (IC) in healthy volunteers.

Author(s) and year	Drug(s) and dose(s) (mg)/design	*n* (females) (per drug condition)/age (years)	Inhibitory control task	Effects of active drug manipulation (and comment)
(Müller et al., 2005a)	Guanfacine 1 or 2/ parallel, PLC	60 (0) (20)/20–39	SSRT	IC ↔ Some evidence for dose-dependent sedative effects of guanfacine.
(Chamberlain et al., 2006b)	Atomoxetine 60 or citalopram 30/parallel, PLC	60 (0) (20)/20–35	SSRT	IC ↑
(Chamberlain et al., 2008)	Atomoxetine 40/cross-over, PLC, fMRI	19 (0) (19)/19–46	SSRT	IC ↑; plus right frontal activation ↑ by atomoxetine during successful inhibition; plasma drug levels correlated significantly with right frontal activation.
(Winder-Rhodes et al., 2009)	Prazosin 3 or modafinil 300 mg or both/cross-over, PLC	12 (0) (12)/18–39	SSRT	IC ↔
(Crockett et al., 2010)	Atomoxetine 60 mg OR citalopram 30 mg/ cross-over, PLC	30 (17) (30)/~20–30	Go/No-Go	Some evidence IC ↑ by atomoxetine (significantly better than under citalopram, but not versus placebo).
(Graf et al., 2011)	Atomoxetine 80/cross-over, PLC, fMRI	12 (0) (12)/~20–35	Combined Go/No-Go-Eriksen Flanker Paradigm	IC ↓; drug-dependent increase of error signal (incorrect minus correct No-Go trials) in bilateral inferior frontal cortices and pre-supplementary motor area.
(Nandam et al., 2011)	Atomoxetine 60/cross-over, PLC	24 (0) (24)/18–35	SSRT	IC ↔ in terms of statistical significance. However, effect size atomoxetine versus placebo medium (0.32); IC under atomoxetine numerically intermediate between methylphenidate and placebo.
(Hester et al., 2012)	Atomoxetine 60/cross-over, PLC, fMRI	27 (0) (27)/18–35	Error awareness task	IC ↔ No effect of methylphenidate or citalopram on IC also.

fMRI: functional magnetic resonance imaging; PLC: placebo-controlled; SSRT: stop-signal reaction time task.
↑: improved; ↓: impaired; ↔: unchanged; ↓↑:mixed effects (as compared to placebo); #: dose estimate only, as administered based on body weight.

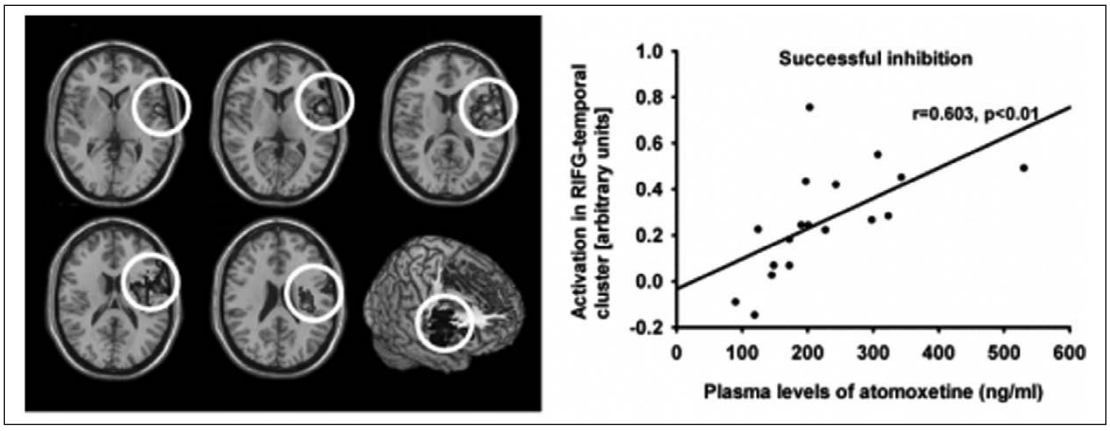

Figure 5. Atomoxetine increased brain activation during inhibitory control in the right inferior frontal gyrus. Left panel: representative slices with regions encircled for clarity). Right panel: right frontal activation during successful response inhibition correlated significantly with plasma levels of drug. Figure adapted from Chamberlain et al. (2008) and used with permission from Elsevier.

of set-learning and flexibility over a total of nine task stages. Remarkable functional homology across species has been shown for cognitive flexibility, as indicated in Figure 6. While reversal learning appears to be primarily under the neuromodulatory control of serotonin, set-shifting appears less contingent on serotonin and more demonstrably dependent on noradrenaline (and dopamine) (Robbins, 2012b).

Using an attentional set-shifting paradigm in rodents, it was found that lesions of the dorsal noradrenergic bundle selectively impaired extra-dimensional set-shifting (Tait et al., 2007). Consistent

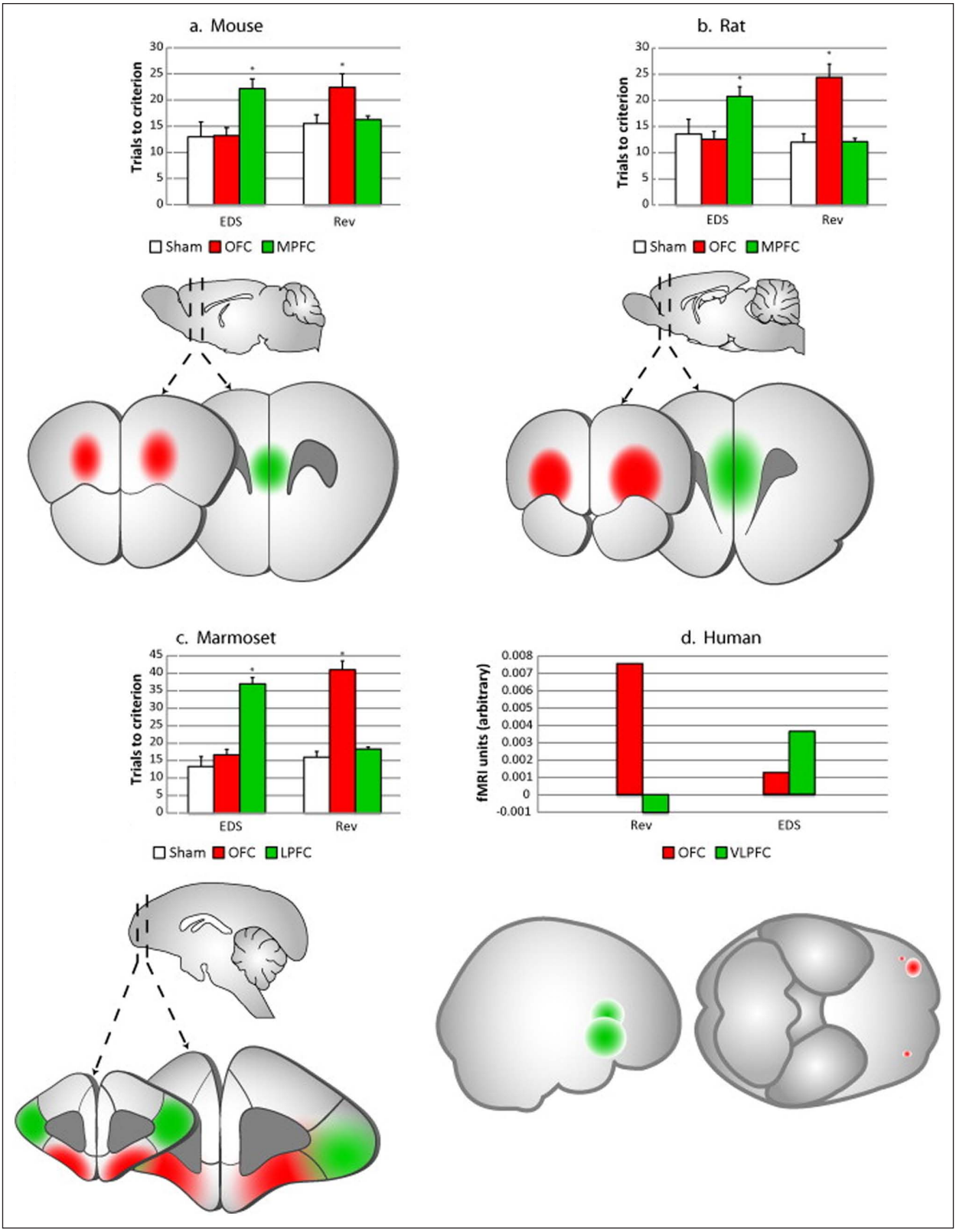

Figure 6. Remarkable functional homology across species has been demonstrated using set-shifting tests. Lesions to the orbitofrontal cortices (OFC) impair reversal learning in (a) mice, (b) rats and (c) marmosets: while (d) in humans, reversal learning activates the equivalent regions. Lesions to the medial/lateral prefrontal (MPFC/LPFC/VLPFC) regions impair set-shifting across species (a)–(c), with the lateral prefrontal cortices also activating during set-shifting in humans (d). This figure is adapted from Keeler and Robbins (2011) and used with permission from Elsevier. Original data are from Birrell and Brown, 2000; Bissonette et al., 2008; Dias et al., 1996; Hampshire and Owen, 2006; McAlonan and Brown, 2003.

Table 5. Effects of noradrenergic manipulations on cognitive flexibility (CF) in healthy volunteers.

Author(s) and year	Drug(s) and dose(s) (mg)/design	*n* (females) (per drug condition) /age (years)	Cognitive flexibility task	Results and comment
(Coull et al., 1995a)	Clonidine 0.12# or 0.20#; or diazepam 5 or 10 /mixed, PLC	88 (44) (12–16)/ ~22–25	CANTAB IDED	CF ↔
(Beversdorf et al., 1999)	Propranolol 40 or ephedrine 25/cross-over, PLC	18 (9) (18)/18–37	Shape re-arrangement task, anagram task	CF ↔ (although performance on propranolol for anagram task significantly better than on ephedrine in best problem solvers)
(Jakala et al., 1999a; Jakala et al., 1999c)	Clonidine 0.04# or 0.4#; or guanfacine 0.56# or 2.32#/ Mixed, PLC	55 (15?) (6–12) / 23–35	CANTAB IDED	CF ↔ (Some evidence of slower responses for ED shift stage under clonidine 0.4)
(Rogers et al., 1999)	Clonidine 0.1 or methylphenidate 40 or tryptophan depletion, parallel, PLC	79 (24) (8–16)/~18–30	3D IDED	CF ↔ by clonidine. (Some mixed effects with methylphenidate and tryptophan depletion)
(Beversdorf et al., 2002)	Propranolol 40 or nadolol 50, cross-over, PLC	18 (9) (18)/22–27	Anagrams task	CF ↔ (although performance on propranolol significantly better than on nadolol)
(Silver et al., 2004)	Propranolol 40/cross-over, PLC	21 (10) (~21)/~22–26	Anagrams task	CF ↑
(Müller et al., 2005a)	Guanfacine 1 or 2/ parallel, PLC	60 (0) (20)/20–39	3D IDED	CF ↔ Some evidence for dose-dependent sedative effects of guanfacine.
(Choi et al., 2006)	Clonidine 0.1 (or ephedrine 25)/cross-over, PLC	18 (7) (18)/18–27	Anagrams task, compound RAT	CF ↔
(Alexander et al., 2007)	Propranolol 40/cross-over, PLC	16 (8) (16)/~18–30	Anagram task, compound RAT	CF ↑ (both tasks) in subjects exposed to Trier Stress Test (behavioural impairment resulting from stressor was blocked by propranolol)
(Campbell et al., 2008)	Propranolol 20 or 40 or 60, cross-over, PLC	72 (36) (72)/18–35	Anagram task (all sessions); WCST, compound RAT (40 mg and placebo sessions only)	CF ↑ on Anagrams task at 40 mg Some evidence for CF ↑ on RAT in subjects with worse non-drug performance given 40 mg CF ↔ for WCST

PLC: placebo-controlled; Cambridge neuropsychological test automated battery (CANTAB) RAT: remote associates test; WCST: Wisconsin card sorting test.
↑: improved; ↓: impaired; ↔: unchanged; ↓↑:mixed effects (as compared to placebo); #: dose estimate only, as administered based on body weight.

with a role for noradrenaline in cognitive flexibilty, chronic alpha-2 receptor antagonism with idazoxan impaired set-shifting (Rowe et al., 1996) while chronic treatment with desipramine improved performance (Lapiz et al., 2007). Further, atipamezole (an alpha-2 receptor antagonist, which may increase noradrenergic activity via actions at autoreceptors in the LC) improved attentional set-shifting (Lapiz and Morilak, 2006): and this effect was blocked by infusion of alpha-1 receptor antagonist into the medial prefrontal cortex. Atomoxetine enhanced set-shifting in rats that had been depleted of noradrenaline, while high doses in healthy rats impaired set-shifting (Newman et al., 2008). In adolescent rats, low doses of atomoxetine facilitated attentional set-shifting (Cain et al., 2011). Cumulatively, the evidence from rodents concords with a role for noradrenaline in modulating set-shifting, probably operating according to a Yerkes-Dodson inverted U-shaped function with improvements at low doses and deficits at higher ones.

Turning to studies conducted in healthy human volunteers, noradrenergic manipulations using medications such as clonidine, guanfacine and beta-blockers (propranolol, nadolol) generally had no detectable effects on cognitive flexibility as indexed by set-shifting paradigms in several studies (Table 5). However, the sample size per treatment arm for these set-shift studies varied from 6–20 subjects and so some studies may have been underpowered. One study combining the alpha-2 agonist clonidine and the alpha-2 antagonist idaxozan, far from finding a mutual antagonism of effects, actually demonstrated considerable synergy in producing deficits, selectively in ED-shifting, presumably dependent on disruption of noradrenergic function, but the precise mechanism remaining unclear (Middleton et al., 1999).

Evidence from several, but not all, studies showed that anagram task performance was improved by 40 mg propranolol, although this did not appear to generalize to lower (20 mg) or higher (60 mg) treatment conditions for the one study that included different doses. The beneficial effect of propranolol 40 mg on anagram task performance was also found under situations of stress (the Trier Stress test) in that medication blocked the detriment in performance that would otherwise have been expected.

Why might the infra-human data differ from human findings so far, with respect to attentional set-shifting? It is possible that ceiling effects could have contributed in the human studies, these being relatively easy tasks for healthy individuals. It is noteworthy that only high dose atomoxetine was found to impair set-shifting in a rat study while lower doses had no (positive or negative) effects, in contrast to positive effects reported with low dose in rats with central noradrenergic depletion (Newman et al., 2008). Thus, it may be that effects of noradrenaline manipulations on set-shifting would be more pronounced in humans with pre-existing pathology (e.g. Parkinson's disease). Another consideration is that extra-dimensional set-shifting is prone to practice effects, which could impact the ability to detect drug effects in within-subject designs: it may be worth employing a task-switching design which measures rapid shifting of task rules in a pre-trained performance mode, rather than using new learning.

Emotional memory. Effects of noradrenaline manipulations on emotional learning and memory have been extensively studied in both experimental animals and healthy human volunteers (Table 6). Overall, there is considerable agreement across species in conclusions about the role of NA in emotional memory, focusing especially on its role in the amygdala.

Table 6. Effects of noradrenergic manipulations on emotional memory (EM) in healthy volunteers (adapted in part from Chamberlain et al. (2006b) with permission from Springer).

Author(s) and year	Drug(s) and dose(s) (mg) /design	*n* (females) (per drug condition) /age (years)	Emotional memory task	Effects of active drug manipulation (and comment)
(Cahill et al., 1994; Cahill and Van Stegeren, 2003)	Propranolol 40/parallel groups, PLC	36 (19) (8–11)/27.4±4.6	Emotional slide story	EM ↓; small sample sizes
(Cahill and Van Stegeren, 2003; Van Stegeren et al., 1998)	Propranolol 40 or nadolol 40/parallel groups, PLC	75 (52) (10–15)/22.6±0.8	Emotional slide story	EM ↓ (after propranolol) EM ↔ (after nadolol)
(O'Carroll et al., 1999a)	Propranolol 40 or nadolol 40/parallel groups, PLC	36 (30) (12)/21.4±2.5	Emotional slide story	EM ↔ (after both propranolol and nadolol)
(O'Carroll et al., 1999b)	Yohimbine 20 or metoprolol 50/parallel groups, PLC	36 (18) (12)/~18–31	Emotional slide story	EM ↑ (after yohimbine) EM ↓ (after metoprolol)
(Reist et al., 2001)	Propranolol 40/parallel groups, PLC	21 (0) (5–6)/~35–65 (+ 17 PTSD patients)	Emotional slide story	EM ↓, similar effect in controls and patients; small sample sizes
(O'Carroll and Papps, 2003; Papps et al., 2002)	Reboxetine 4 or 8/ parallel groups, PLC	36 (10) (12)/~18–25	Emotional slide story	EM ↓ (dose-dependent); inverted U effect?
(Southwick et al., 2002)	Yohimbine 32# /parallel groups, PLC	30 (9) (14–16)/32.4±10.9	Emotional slide story	EM ↔, correlation with plasma MHPG levels; drug administration 5 min after slide presentation
(Van Stegeren et al., 2002)	Propranolol 40/parallel groups, PLC	60 (46) (15)/~18–22	Emotional slide story	EM ↔
(Cahill and Alkire, 2003)	Epinephrine 9.6 or 19.2/ parallel groups, PLC	42 (20) (?)/21.9±0.7	Emotionally valenced slides	EM ↑ (only primacy recall, slide 1–3); drug administration after slide presentation
(Harmer et al., 2003)	Reboxetine 4/parallel groups, PLC	24 (12) (12)/20–47	Emotionally valenced word list	EM ↑ (no negative bias)
(Strange et al., 2003)	Propranolol 40/parallel groups, PLC	24 (12) (12)/19–32	Emotionally valenced word list	EM ↓ (after propranolol)
(Grillon et al., 2004)	Propranolol 40/parallel groups, PLC	30 (?) (15)/29±2.8	Cued feared conditioning	EM ↔, emotional arousal ↓
(Harmer et al., 2004)	Reboxetine 8 (per day) or citalopram 20 (per day)/parallel groups, PLC, (7 days)	42 (21) (14)/25.0±4.2	Emotionally valenced word list	EM ↑ (after both drugs, increased memory for positive stimuli)
(Maheu et al., 2004; Maheu et al., 2005)	Propranolol 40 or 80; or metyrapone 2 x 750/ parallel groups, PLC	64 (0) (11–14)/19–36	Emotional slide story	EM ↓ (after high dose of propranolol, but not after low dose or metyrapone)

(Continued)

Table 6. (Continued)

Author(s) and year	Drug(s) and dose(s) (mg) /design	*n* (females) (per drug condition) /age (years)	Emotional memory task	Effects of active drug manipulation (and comment)
(Pryor et al., 2004)	Dexmedetomidine or thiopental or propofol/ parallel groups, PLC	83 (32) (10 dex.; variable)/18–50	Emotionally valenced slides	EM ↔ (dexmedetomidine) but small N for group
(Strange and Dolan, 2004)	Propranolol 40/parallel groups, PLC, fMRI	24 (12) (12)/20–39	Emotionally valenced word list	EM ↓ (after propranolol), reduced retrieval activation of amygdala/hippocampus
(Hurlemann et al., 2005)	Propranolol 40 or reboxetine 4/parallel, PLC	54 (27) (18)/20–30	Emotional oddball memory test	Propranolol ↓ short-term emotional recall; reboxetine ↑ short-term emotional recall especially for positive stimuli
(Moor et al., 2005; Schachinger et al., 2001)	Norepinephrine – nitroprusside sodium, epinephrine – esmolol followed by placebo/ cross-over	24 (0) (24)/~22–28	Emotionally valenced slides	EM ↑ (after norepinephrine); single blind design
(Van Stegeren et al., 2005); (Van Stegeren et al., 2007)	Propranolol 80/ cross-over, PLC, fMRI	28/30 (15) (14/15)/18–28	Emotionally valenced slides	EM ↓, less amygdala activation
(Miskowiak et al., 2007)	Reboxetine 4/parallel, PLC, fMRI	24 (10) (12), 23–38	Neural responses during categorization and recognition of self-referent personality words	No effect on neural response during categorization. Reboxetine ↓ activation in fronto-parietal network during subsequent correct recognition of positive target words and ↑ speed to recognize positive versus neutral words (↑ EM)
(De Quervain et al., 2007)	Propranolol 40 (or cortisone 25; or both together)/mixed cross-over, PLC	42 (21) (14), ~20–29	Recall of previously viewed emotionally valenced noun words	Propranolol alone EM ↔. Propranolol blocked impaired retrieval of high-arousal words resulting from cortisone administration.
(Hurlemann et al., 2007)	Reboxetine 4 with hydrocortisone 30/ parallel, PLC	57 (29) (18), 20–29	Emotional oddball memory test	Reboxetine ↑ magnitude and duration of emotion-induced retrograde amnesia, synergistic effects with hydrocortisone
(Schwabe et al., 2009)	Propranolol 40/cross-over, PLC	44 (0) (44), 19–33	Free recall of previously viewed emotionally valenced words	Propranolol reduced stress-induced memory enhancement for emotional verbal material (EM ↓)
(Tollenaar et al., 2009)	Propranolol 80/parallel, PLC	85 (0) (~26), 18–35	Personalised scripts for previous negative disturbing life event. Emotionally valenced words	EM ↔
(Kindt et al., 2009)	Propranolol 40/parallel, PLC	60 (43) (20)/18–28	Differential fear-conditioning procedure	EM ↓ by propranolol given before memory reactivation
(Van Stegeren et al., 2010)	Yohimbine 20/parallel, PLC, fMRI	48 (0) (12), 18–39	Presentation of emotionally valenced pictures during fMRI. Recall test one week later.	No significant effect of yohimbine alone on brain activation during picture viewing (some synergistic effects when given with cortisol). EM ↔ at one week recall
(Weymar et al., 2010)	Propranolol 80/parallel, PLC, ERPs	46 (0) (23)/19–31	Emotionally valenced pictures	Propranolol at encoding ↓ old/ new difference of mean ERP amplitudes for subsequent recall of unpleasant stimuli

Table 6. (Continued)

Author(s) and year	Drug(s) and dose(s) (mg) /design	*n* (females) (per drug condition) /age (years)	Emotional memory task	Effects of active drug manipulation (and comment)
(Kroes et al., 2010)	Propranolol 40/parallel, PLC	24 (12) (12)/19–34	Declarative memory test for emotional items (nouns)	Propranolol at retrieval ↓ declarative memory enhancement for emotional items (EM ↓)
(Soeter and Kindt, 2010)	Propranolol 40/parallel, PLC	50 (45) (25)/18–46	Differential fear-conditioning procedure	Propranolol given prior to memory reactivation ↓ startle fear response subsequentially (EM ↓) – this effect persisted at 1 month follow-up
(Soeter and Kindt, 2011a)	Propranolol 40/ uncontrolled	40 (29) (40)/18–32	Differential fear-conditioning procedure	Startle fear response ↓ to reactivated fear association and category-related information, with propranolol
(Soeter and Kindt, 2011b)	Yohimbine 20/parallel, PLC	30 (20) (15)/18–29	Differential fear-conditioning procedure	Formation of associative fear EM traces ↑ with yohimbine
(Groch et al., 2011)	Clonidine 0.1/cross-over, PLC	15 (0) (15), 19–28	Infusion during sleep following learning of emotional and neural stories/ pictures	Retention of story content words + pictures ↔ Clonidine ↓ superiority of emotional versus neutral memory for temporal order
(Kukolja et al., 2011)	Reboxetine 4 or hydrocortisone 30/ parallel, PLC, fMRI	51 (29) (~12), ~20–30	Encoding of emotional and neutral stimuli	Reboxetine ↑ hippocampal responses to emotional versus neutral stimuli; opposite effect with hydrocortisone
(Sevenster et al., 2012)	Propranolol 40/parallel, PLC	60 (41) (20)/18–30	Reactivation of previously fear-conditioned memory (e.g. spider pictures)	Startle fear response ↓ (EM ↓) with propranolol when outcome of retrieval cue not fully predictable
(Schwabe et al., 2012)	Propranolol 40/parallel, PLC, fMRI	52 (26) (13) /18–30	Reactivation procedure for recall of emotional pictures (and neutral pictures)	EM ↓ when propranolol given at retrieval. Propranolol did not affect fMRI during reactivation.
(Bos et al., 2012)	Propranolol 40/parallel, PLC	30 (20) (15)/~18–25	Differential fear-conditioning procedure	Propranolol impaired extinction learning i.e. ↑ EM strength
(Soeter and Kindt, 2012)	Yohimbine 20/parallel, PLC	40 (30) (20)/18–26	Differential fear-conditioning procedure	Yohimbine impaired extinction learning, i.e. ↑ EM strength
(Papadatou-Pastou et al., 2012)	Reboxetine 4/parallel, PLC, fMRI	24 (10) (12)/23–38	Emotional autobiographical memory retrieval	EM ↑ with reboxetine (increased speed of autobiographical memory retrieval). Reboxetine increased activation during processing of negative memories & reduced activation during positive memory retrieval in left frontal lobe and right superior temporal gyrus.

↑: improved; ↓: impaired; ↔: unchanged; ↓↑:mixed effects (as compared to placebo). PLC: placebo-controlled; #: dose estimate only, as administered based on body weight. ERP: event-related potentials; fMRI: functional magnetic resonance imaging; rCBF: regional cerebral blood flow.

Classical findings focused on observations that manipulations resulting in reduced NA activity (such as blockade of synthesis) impaired one-trial passive avoidance retention measures of aversive memory consolidation (Fernandez-Tome et al., 1979; Rainbow et al., 1976; Randt et al., 1971; Stein et al., 1975). Gallagher and colleagues (1977) found that intra-amygdaloid propranolol had similar effects, which were reversed by noradrenaline, thereby implicating beta receptors in aspects of emotional memory. It was later confirmed that intra-amygdaloid NA itself boosted aversive learning at low doses, whilst impairing it at higher doses (Ellis and Kesner, 1983; Liang et al., 1986, 1990).

Subsequent findings have built up an impressive body of evidence that locus coeruleal NA modulates aversive learning in the amygdala, often interacting with central influences of peripherally circulating hormones or neuropeptides (Cahill and McGaugh, 1996). These findings inspired the original attempts to study effects of NA beta receptor blockade through propranolol on emotional memory in human volunteers (e.g. Cahill et al., 1994). It has been noted that there appear to be opposing effects of manipulation of noradrenergic agonists on emotional and working memory, alpha-1 agonists tending to impair working memory at doses facilitating emotional learning in rats, and alpha-2 and beta receptor agents having opposite effects (Arnsten, 2000). Once again, this is strongly reminiscent of a Yerkes-Dodson formulation with performance of certain tasks being enhanced at doses of the adrenoceptor agonist that impair performance in others: presumably because the underlying processes are mediated by distinct neural systems with different levels of noradrenergic activity for optimal performance.

A parallel literature has found that profound (>95%) depletion from the forebrain effected by 6-hydroxydopamine lesions of the dorsal noradrenergic bundle impaired learning rather than performance (e.g. induced by motivational effects) deficits of a conditioned suppression procedure in rats (Cole and Robbins, 1987). Further studies confirmed that whereas discrete cue conditioning tended to be impaired, contextual learning was largely unaffected or even boosted, suggesting a hypothetical broadening of attention which would resolve the theoretical competition between discrete cues and context in favour of the latter (Selden et al., 1990b).

Effects of noradrenergic medications on emotional memory in humans have been reviewed in-depth elsewhere (Chamberlain et al., 2006c; Van Stegeren, 2008). The majority of the human studies used beta-blockers (mainly propranolol) but also, less commonly, reboxetine and yohimbine (the latter being an alpha-2 antagonist with additional effects at serotonin receptors) (Millan et al., 2000). Generally, the bulk of studies to examine the issue found that propranolol, given at encoding and/or retrieval, reduced recall for emotionally salient material. Furthermore, propranolol reduced learning processes relating to fear. Most propranolol studies used a dose of 40 mg and did not examine dose-dependency via a multiple-dosing regimen, or quantification of plasma levels.

Yohimbine increased fear conditioning in two studies (Soeter and Kindt, 2011b, 2012) and augmented recall of an unpleasant story/slide-show (O'Carroll et al., 1999b). Two other studies reported no significant effects of yohimbine on aspects of emotional memory (Southwick et al., 2002; Van Stegeren et al., 2010). Manipulations using reboxetine generally found significant influences on emotional memory, with augmenting effects on the recall of positive material/stimuli (over short and longer time frames: see Table 6). These findings are clearly of importance in relation to understanding the likely mechanisms of anti-depressant treatment, and may well relate to early effects of such medications on emotional 'bias', which are outside the scope of the current review (Harmer, 2012).

Summary: therapeutic implications and future research directions

On the basis of the extant data covered here, it is clear that noradrenaline is a key neurotransmitter, with its widely ramifying projection pathways, perhaps unsurprisingly, heavily implicated across multiple cognitive domains including both executive and non-executive functions encompassing attention, working memory, response inhibition, cognitive flexibility and emotional memory. The majority of these domains have benefited from study using translational paradigms across species. Nonetheless, it is to be acknowledged that the influence of the noradrenaline system over these domains may be related: for example, possible relationships of 'working memory' to 'working attention' have been suggested (Robbins, 2012a). An over-arching model of the role of noradrenaline in cognition, e.g. in terms of attentional processing, remains tentative at this stage. Also, effects of medication are likely to be contingent on baseline stress/arousal and, potentially, influenced by genetic polymorphisms in genes coding for components of the noradrenergic system (alpha- and beta-receptors; NET) (Barnett et al., 2011; Blanchard et al., 2011; Bonisch and Bruss, 2006; Greene et al., 2009). Given the above evidence from infrahuman and healthy volunteer studies implicating noradrenaline in the modulation of various cognitive functions, it is vital to consider the clinical implications of these findings, in relation to both pre-existing and novel therapeutic directions.

Despite the relatively widespread use of medications such as reboxetine and other elective noradrenaline reuptake inhibitors (SNRIs) in the treatment of depression (albeit usually as second-line, and/or as augmentation strategies), relatively little is known regarding the objective cognitive effects of noradrenergic treatments in this clinical arena. For example, preliminary data from one study (an eight-week double-blind placebo-controlled trial) indicated that reboxetine treatment was associated with significant improvements in sustained attention over time in individuals with depression, but that paroxetine and placebo were not (Ferguson et al., 2003). In view of the cognitive dysfunction often reported in depression (Roiser et al., 2003), more research is clearly needed to elucidate noradrenergic effects on cognition therein. The exception to this is the considerable progress that has been made, largely outside the scope of the current review, in relation to effects of SNRIs on emotional processing (Harmer, 2012; Harmer et al., 2009). In addition to the issue of cognitive effects of noradrenergic drugs on depression, it would also be valuable to consider whether targeting noradrenergic agents on depressed individuals with particular cognitive dysfunction likely to involve the noradrenergic system (e.g. relating to inattention or reduced arousal) may be of clinical utility, as has been posited may be the case (Stahl, 2003). The same is also evident in relation to other potential therapeutic arenas outlines below.

Given that medications with demonstrable efficacy in the treatment of cardinal symptoms of ADHD exert pronounced noradrenergic effects (Del Campo et al., 2011), one can consider whether other neuropsychiatric disorders characterized by

behavioural impulsivity may benefit from clinical trials using selective noradrenergic agents.

For example, noradrenergic agents may be of utility in the treatment of cognitive dysfunction associated with substance dependence, which is often associated with impairment across a range of cognitive domains, including response inhibition (Ersche and Sahakian, 2007). Indeed, rather than just representing a consequence of theorised toxic effects of drug use on the brain, recent data implicate impaired response inhibition as a vulnerability marker, also occurring in 'at risk' relatives without dependence (Ersche et al., 2012). This raises the prospect of targeting a cognitive problem directly involved in the pathogenesis and evolution of substance dependence over time. To our knowledge, effects of noradrenergic agents on cognition have not been studied in substance dependence. However, there have been a handful of clinical trials, not using cognitive measures, exploring effects of atomoxetine on symptoms in people with co-morbid ADHD and substance dependence.

In a 12-week open label study in people with ADHD and cocaine dependence, it was reported that ADHD symptoms significantly improved but that outcome measures relating to cocaine use did not, albeit there was a high drop-out rate across treatment arms (Levin et al., 2009). In a 12-week double-blind placebo-controlled trial of atomoxetine in ADHD plus alcohol dependence, cumulative heavy drinking days were significantly reduced by active treatment, but other measures of substance misuse were inconclusive (Wilens et al., 2008). Finally, in a small double-blind placebo-controlled pilot study in people with cocaine dependence, atomoxetine was given daily for 3–5 days prior to completion of experimental sessions involving administration of intranasal cocaine (Stoops et al., 2008). There was some suggestion that atomoxetine dose-dependently reduced subject ratings of 'willingness to take cocaine again', albeit these graphical trends did not obtain statistical significance, perhaps not surprising in view of the small sample size and thereby limited statistical power. Further investigation of the effects of noradrenergic agents on symptoms of substance dependence, as well as cognitive functioning and safety parameters, would be of interest. A recent preclinical study has shown that atomoxetine remarkably reduces both cocaine-seeking and heroin-seeking behaviour in rats under a second order schedule of reinforcement of intravenous drug self-administration, maintained in part by cues associated with the drugs (Economidou et al., 2011). Intriguingly, however, atmoxetine has no effect once these drugs have been self-administered. This suggests that a possible niche for the use of atomoxetine would be in treatment-seeking drug abusers who are striving to resist drug craving. Such an action would be consonant with the action of atomoxetine to modulate laboratory tasks of self-control such as the stop-signal task. Another issue worth mentioning in relation to substance dependence is that of withdrawal symptoms and their treatment. Lofexidine is used in the treatment of opioid withdrawal and the absence of cognitive studies in healthy volunteers using this agent is surprising. The single available study in opioid dependent individuals receiving methadone was suggestive of detrimental effects of lofexidine on a mathematical task versus placebo (Schroeder et al., 2007).

Several other conditions besides ADHD and substance dependence are associated with cognitive problems including pronounced response inhibition deficits, notably pathological grooming disorders (trichotillomania, pathological skin-picking) and pathological gambling (Chamberlain et al., 2006a; Odlaug et al., 2010, 2011). Of interest here is that 10-week treatment with atomoxetine, as part of a double-blind placebo-controlled trial, significantly improved symptoms of binge eating disorder (McElroy et al., 2007). Clearly caution is warranted, but findings in this review highlight the need for further clinical trials, particularly those also employing cognitive measures, across other – arguably more neglected – disorders associated with impulsivity.

Lastly, in terms of therapeutic directions, we wish to highlight the need to study effects of noradrenergic compounds at the other end of the age span from ADHD: namely, to evaluate possible beneficial effects on cognition in older individuals with disorders associated with cognitive dysfunction, such as Alzheimer's disease and Parkinson's disease (Vazey and Aston-Jones, 2012). Safety parameters and side effects will of course merit close scrutiny, in view of the frequent medical co-morbidities occurring in such individuals.

Turning now to elucidation of precise mechanisms, examination of brain activation during salient cognitive probes, in conjunction with pharmacological manipulation (pharmacofMRI) has yielded important theoretical and clinical insights into the role of the noradrenergic system in cognition. However, what ideally is needed is a method of more directly studying the status of the noradrenaline system and its components in vivo, particularly given practical difficulties in using standard imaging techniques to accurately visualize the small structure of the LC. Since the 1980s, some progress has been made in terms of developing radioligands capable of binding to central nervous system (CNS) receptors in vivo (Kegeles and Mann, 1997). When used in conjunction with positron emission tomography (PET) and/or single-photon emission computed tomography (SPECT), these radioligands can be used to assess neurotransmitters at baseline, and in response to pharmacological challenges (Del Campo et al., 2011). Radioligands capable of targeting specific noradrenergic components have only recently begun to emerge, due to a relative paucity of suitable tracers, non-specific binding of putative ligands, and other factors (Ding and Fowler, 2005).

Future research should seek to glean new insights into the noradrenergic modulation of cognition, by coupling radioligand-PET with objective cognitive assessment, and pharmacological manipulation. With time, it is hoped that novel subreceptor specific compounds will be developed for safe application in humans, to enable more precise fractionation of noradrenergic influences over cognition, with potential therapeutic implications. It will also be important to consider stratifying subjects in pharmacological manipulation studies as a function of polymorphisms in components of the noradrenergic system, such as the dopamine beta-hydroxylase and NET genes. This may help to resolve some of the inconsistencies in the extant human literature concerning direction and magnitude of effects. Also, we would recommend collecting plasma drug levels for individuals where possible, since thereby 'dose dependent' effects can be pragmatically explored even within the context of proof-of-concept single-dose study designs.

Acknowledgements

This paper should not be used to guide drug doses or prescribing; please refer to country specific prescribing guidelines such as the British National Formulary (UK) for these purposes.

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Conflict of interest

Dr Chamberlain consults for Cambridge Cognition and P1Vital; and has received speaker fees for industry symposia from Lilly. Dr Robbins consults for Cambridge Cognition, Lilly, Lundbeck, and GlaxoSmithKline. Dr Robbins has received research grants from Lilly, GlaxoSmithKline and Lundbeck.

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