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REVIEW

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Noradrenergic modulation of working memory and emotional memory in humans

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Abstract *Rationale:* Noradrenaline (NA) is implicated in arousal. Working memory is dependent upon prefrontal cortex, and moderate levels of NA are thought to facilitate working memory whereas higher levels during extreme stress may impair working memory and engage more posterior cortical and sub-cortical circuitry. The NA system also influences emotional memory via modulation of the amygdalae and related mediotemporal structures. NA dysfunction and abnormalities in arousal-dependent memory functions are evident in a variety of neuropsychiatric illnesses. *Objectives:* The authors provide a concise overview of pharmacological studies that have investigated effects of selective NA manipulations on working memory and emotional memory functions in healthy human volunteers. *Materials and methods:* Selection of relevant peer-reviewed publications was based on a PubMed search. *Results:* Studies to date indicate that: (1) the beta-blocker propranolol impaired working and emotional memory, (2) clonidine frequently impaired working memory, and (3) reboxetine, a selective noradrenaline reuptake inhibitor, enhanced emotional memory for positive material. *Conclusions:* Improved understanding of coupling between NA, cortico-subcortical circuitry and human mnemonic functions will suggest novel therapeutic directions for the treatment of neuropsychiatric conditions, such as attention deficit hyperactivity disorder and post-traumatic stress disorder. Future research directions are discussed in relation to neuroimaging techniques, functional central nervous system polymorphisms and study designs.

Keywords Noradrenaline · Norepinephrine · Memory · Cognition · Impulsivity · Emotion · Prefrontal

Abbreviations ADHD: Attention deficit hyperactivity disorder · fMRI: Functional magnetic resonance imaging · NA: Noradrenaline · PAL: Paired associates learning · PET: Positron emission tomography · PFC: Prefrontal cortex · PTSD: Post-traumatic stress disorder · SNRI: Selective noradrenaline reuptake inhibitor · SSRI: Selective serotonin reuptake inhibitor · SWM: Spatial working memory · WM: Working memory

Introduction

Ascending noradrenergic (NA) projections from the locus coeruleus to higher cortical regions are implicated in arousal and responses to acute stress and are thought to modulate cognitive functions dependent upon prefrontal cortex and associated circuitry (Aston-Jones et al. 1999; Usher et al. 1999; Robbins 2000, 2005). Moderate levels of NA may act to enhance prefrontal cortex (PFC) control of behaviour including (short-term) working memory, but higher levels of NA during extreme stress may act as a chemical switch to take PFC off-line in favour of more posterior cortical and sub-cortical processes (Arnsten and Robbins 2002). In animal studies, moderate levels of NA enhance working memory whereas higher levels impair this function (Arnsten and Li 2005), and these findings appear attributable to dissociable effects at alpha-2a and alpha-1 adrenoceptors, respectively (Arnsten et al. 1988; Rama et al. 1996; Tanila et al. 1996; Franowicz et al. 2002; Arnsten and Li 2005). Emotional (long-term) memory, which is distinct from working memory, refers to the

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formation, consolidation and retrieval of memories formed during times of heightened arousal or stress. Multiple studies implicate a pivotal role for the amygdalae in emotional memory, with mediotemporal structures being critical for conditioned fear learning and fearful responses in animals (LaBar and LeDoux 1996; Kilpatrick and Cahill 2003; McGaugh 2004). Augmentation of NA transmission (especially the beta-adrenergic system) in animals by systemic drug administration and local drug infusion into the amygdalae has been shown to enhance emotional memory, and such effects have been shown to be reversed by beta-blockade (McGaugh 2000, 2004; Roozendaal 2002; Phelps and LeDoux 2005).

Since Kraepelin's early pharmacological experiments in healthy volunteers using recreational and sedative drugs (Müller et al. 2006), increasingly sophisticated neuropsychological tasks and neurotransmitter-specific pharmacological agents have been developed for human use. Attempts to improve understanding of the role of NA in human working and emotional memory, and effects of NA agents, are of significant theoretical and clinical importance. NA drugs are used in the treatment of neuropsychiatric illnesses associated with PFC dysfunction and cognitive abnormalities, including attention deficit hyperactivity disorder (ADHD) (Arnsten and Li 2005) and depression (Harmer et al. 2003b; Chamberlain and Sahakian 2005). Noradrenergic (NA) transmission systems are also implicated in excessive emotional memory for traumatic events in post-traumatic stress disorder (PTSD) (Southwick et al. 1999, 2002; Nutt 2000; Giles 2005; Stone 2005). To characterise what is known of NA-mediated control of working and emotional memory in humans, we present a concise overview of available pharmacological studies conducted in healthy volunteers to date. We highlight limitations in the existing body of literature and promising new research directions.

Materials and methods

To systematically search for studies in healthy volunteers using pharmacological manipulation with noradrenergic drugs and neuropsychological testing of memory functions, we (a) composed a list of selective noradrenergic drugs that have or can be used in humans (described in Table 1), (b) conducted a PubMed search using the string: "memory AND (noradrenaline OR atomoxetine OR dexmedetomidine OR clonidine OR epinephrine OR guanfacine OR idazoxan OR lofexidine OR norepinephrine OR prazosin OR propranolol OR reboxetine OR yohimbine)", (c) selected studies investigating emotional long-term memory or working (short-term) memory in healthy volunteers after inspection of titles and abstracts and (d) complemented the search by manually cross-checking the reference lists of selected papers.

Results

Effects of NA manipulations on working memory

The results from studies investigating the effects of NA drugs on working memory are presented in Table 2, where it can be seen that a variety of cognitive paradigms was employed. Examples include the spatial working memory (SWM) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB), which assesses ability of volunteers to locate hidden tokens behind boxes using strategy (http://www.camcog.com), verbal tests of digit span and digit manipulation–see, e.g., (Müller et al. 2005a) and the Sternberg test (recognition probe for previously memorised digit or letter sequences) (Sternberg 1969).

Table 1 Descriptions for key NA pharmacologic agents

Drug	Pharmacological profile	Approximate $t_{max}/t_{1/2}$	Psychiatric dose range	Sample reference
Atomoxetine	Selective noradrenaline reuptake inhibitor (SNRI)	1–2/5 h	40–100 mg	(Bymaster et al. 2002)
Clonidine	Alpha2 noradrenaline receptor (adrenoceptor) agonist	3–5/6–24 h	0.1–1.8 mg	(Jakala et al. 1999a)
Dexmedetomidine	Alpha2 noradrenaline receptor (adrenoceptor) agonist	0.5 h/2 h	n/a	(Aho et al. 1993; Dutta et al. 2000)
Guanfacine	Alpha2 noradrenaline receptor (adrenoceptor) agonist (more selective than clonidine)	1–4/10–30 h	1–3 mg	(Jakala et al. 1999a)
Idazoxan	Alpha2 noradrenaline receptor (adrenoceptor) antagonist + 5-HT_{1A} receptor agonist	1/6 h	n/a	(Middleton et al. 1999)
Lofexidine	Alpha2 noradrenaline receptor (adrenoceptor) agonist	3/11 h	0.2–2.4 mg	(Midgley et al. 1982)
Prazosin	Alpha1 noradrenaline receptor (adrenoceptor) antagonist	1.5/2 h	n/a	(Sawaki et al. 2003)
Propranolol	centrally active beta noradrenaline receptor antagonist (beta-blocker)	1–2/3–6 h	5–640 mg	(Müller et al. 2005b)
Reboxetine	Selective noradrenaline reuptake inhibitor (SNRI)	2/13 h	1–4(8) mg	(Harmer et al. 2003b)
Yohimbine	Alpha2 noradrenaline receptor (adrenoceptor) blocker	0.15/0.5 h	n/a	(Swann et al. 2005)

Table 2 Effects of noradrenergic drugs on working memory in healthy volunteers

Author(s) and year	Drug(s) and dose(s) [mg]/design	*N* (females) [per drug condition]/Age [years]	Working memory task(s)	Results (and comment)
(Desai et al. 1983)	Oxprenolol 80, diazepam 5/ Parallel groups, PLC	44 (?) [5–12]/ 18–24	Running memory test	WM ↔ (after oxprenolol); WM ↓↑ (after diazepam; dependent on baseline anxiety)
(Frith et al. 1985)	Clonidine 0.2 (i.v.)/ Cross-over, PLC	8 (0) [8]/ 19–44	Digit span, PAL	WM ↓ (PAL); WM ↔ (other tasks)
(Frcka and Lader 1988)	Propranolol 160, atenolol 50/ Long term (8 days)	12 (6) [12]/ 20–48	Digit symbol task, word list	WM ↓ (after propranolol)
(Coull et al. 1995a–c)	Clonidine 0.12/0.20[a], diazepam 5/10/ Mixed, PLC	88 (44) [12–16]/ ~22–25	PAL, RVIP, SWM (8), 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 0.5/1/4, amitriptyline 25/ Cross-over, PLC (alcohol)	10 (0) [10]/ 18–40	Sternberg	WM ↔ (after reboxetine)
(Coull et al. 1997)	Clonidine 0.1/0.12[a]/ Mixed, PLC, ^{15}O water PET	25 (0) [12–13]/ 18–47	PAL, RVIP	WM ↔; increase of thalamic rCBF after clonidine
(Jakala et al. 1999a,b)	Clonidine 0.04/0.16/0.4[a], Guanfacine 0.56/2.32[a]/ Mixed, PLC	55 (15?) [6–12]/ 23–35	PAL, SWM (8)	WM ↓↑ (after clonidine low and high doses impaired WM; medium dose no effect) WM ↑ (after guan-facine); small sample sizes
(Middleton et al. 1999)	Clonidine 0.12[a] (i.v.), idazoxan 40, clonidine 0.12[a] (i.v.) + Idazoxan 40/ Mixed, PLC	48 (23) [16]/ ~20–30	SWM (8), RVIP	WM ↓ (after combined idazoxan + clonidine) WM ↔ (after clonidine alone)
(Swartz et al. 2000)	Guanfacine/ 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
(Rammsayer et al. 2001)	Reboxetine 2/4/ Cross-over, PLC	24 (0) [24]/ 20–38	Duration estimation	WM-related ↑ after lower dose; trend towards ↑ after higher dose
(Smith et al. 2003)	Clonidine 0.2, caffeine 120 clonidine 0.2 + caffeine 120/ 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 [infusion to steady state]	83 (32) [10 for dex/placebo]/ not specified	Auditory continuous recognition test	WM ↔ (all subjects after dexmedetomidine); small *N*
(Müller et al. 2005a)	Guanfacine 1/2/ Parallel groups, PLC	60 (0) [20]/ 20–39	SWM (12), digit span	WM ↔ (↓)
(Müller et al. 2005b)	Propranolol 25, atenolol 50/ Mixed, PLC	24 (12) [16]/ 19–27	Manipulation task	WM ↓ (after propranolol, in low-anxiety volunteers), WM ↔ (after atenolol)

Table2 (continued)

Author(s) and year	Drug(s) and dose(s) [mg]/design	*N* (females) [per drug condition]/Age [years]	Working memory task(s)	Results (and comment)
(Swann et al. 2005)	Yohimbine 20/30 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* + confounded by practice effects
(Tiplady et al. 2005)	Clonidine 0.15+0.3, temazepam 15+30/ Cross-over, PLC	15 (8) [15]/ 18–25	Sternberg, logical working memory, selective reminding	WM ↓ (after clonidine and temazepam, dose effects)

PAL Paired associates learning task, *PLC* placebo-controlled, *rCBF* regional cerebral blood flow, *Sternberg* Sternberg memory scanning task, *SWM (n)* CANTAB spatial working memory task (max. number of boxes), ↑/↓/↔/↓↑ improved/impaired/unchanged/mixed effects (as compared to placebo)
[a]Individual doses, recalculated per 80 kg body weight

Propranolol impaired working memory across multiple studies (Frcka and Lader 1988; Müller et al. 2005b), but other beta-blockers including oxprenolol and atenolol generally did not (Desai et al. 1983; Frcka and Lader 1988; Müller et al. 2005b). In comparison to these other beta-blockers, propranolol is relatively lipophilic and, thus, able to penetrate the blood–brain barrier, suggesting that central blockade may be necessary for modulatory effects on working memory (though this does not rule out a possible role for peripheral system) (Müller et al. 2005b). Impairing effects of propranolol on working memory were found to be dependent upon baseline anxiety, with more significant effects in volunteers with low-state anxiety (Müller et al. 2005b). With regard to alpha-2-adrenoceptor agonists, all studies using clonidine found impairing effects on working memory at one or more doses, but evidence for dose-dependent effects was not very consistent. In one study, lower and higher doses of clonidine (0.04 and 0.4 mg) impaired working memory but an intermediate dose (0.16 mg) had no effect (Jakala et al. 1999a). In another, the deleterious effects of clonidine were more marked at a higher compared to a lower dose (0.30 vs 0.15 mg) (Tiplady et al. 2005). In another investigation, Coull et al. (1995b) found that 0.12 mg clonidine had no effect on spatial working memory but impaired visual working memory, whereas 0.20 mg improved spatial working memory with no effect on visual working memory. It is important to compare these findings to those of guanfacine, a more selective alpha-2-adrenoceptor agonist. Guanfacine improved working memory in one study (0.56- and 2.32-mg doses) (Jakala et al. 1999a). Yet, in a more recent study using similar cognitive tests (CANTAB SWM), no significant effects were noted after doses of 1and 2 mg (and there was indeed a trend towards impairment on digit span, which was thought to be attributable to sedative effects of the drug) (Müller et al. 2005a). Another alpha-2-adrenoceptor agonist, dexmedetomidine, was found to have no significant effects on working memory overall, albeit this study used a small sample size (Veselis et al. 2004). The alpha-2-receptor blocker yohimbine appeared not to affect working memory per se but was found to increase a measure of impulsivity in that it led to increased numbers of inappropriate motor responses to non-target stimuli on a continuous performance test (Swann et al. 2005). For selective noradrenaline reuptake inhibitors (SNRIs), one study found no effects of reboxetine (0.5/1/4 mg) on a Sternberg test (Kerr et al. 1996), whereas another found that reboxetine (2 mg) improved temporal discrimination in the range of seconds, which is thought to reflect working memory and PFC function (Rammsayer et al. 2001).

In summary, propranolol (but not other beta-blockers with more limited central activity) was found to impair working memory across several studies, and clonidine impaired working memory in most studies. The single study using yohimbine found no evidence for general effects on working memory, and findings for guanfacine and SNRIs were inconsistent.

Effects of NA manipulations on long-term emotional memory

Studies using NA drugs to manipulate emotional memory functions in healthy volunteers are summarised in Table 3. Subjects typically viewed a short slide show accompanied by a descriptive narrative, after receiving medication or placebo in a double-blind and parallel group design. Slides between conditions remained the same, and emotional arousal was manipulated by varying the narrative. For example, in the neutral condition, a typical narrative related to watching a practice disaster drill, with actors and fake badly scarred legs; in the arousal version, the narrative instead explained that this was an actual disaster, indicating that the badly scarred legs were real (van Stegeren et al. 1998). Arousing effects were assessed in terms of self-rating scales and physiological recordings. At a later date, the volunteers returned to undertake a surprise test of memory for the original story. Recall and recognition memory for the emotional and neutral segments of the original story were quantified. Problems with this paradigm include the limited number of critical items and the lack of parallel versions. As indicated in Table 3, some studies (e.g. van Stegeren et al. 2005) used other paradigms designed to overcome these limitations, including presentation of emotional and neutral pictures from the International Affective Picture System (IAPS) (Lang and Bradley 1997) or sets of emotionally valenced words.

In initial studies by Cahill et al. (1994), pre-encoding administration of propranolol (designed to maximise beta-adrenergic blockade at the time of initial viewing of slides) reduced recognition and recall for the emotional component of the story in the arousal condition after 1 week. These findings have been replicated in most subsequent studies (van Stegeren et al. 1998; Reist et al. 2001; Maheu et al. 2004; van Stegeren et al. 2005) but not all (O'Carroll et al. 1999a). It has been suggested that emotional arousal enhances memory for central story information in men and peripheral details in women, which has been attributed to differential hemispheric amygdala specialisation between the sexes (see Cahill and van Stegeren 2003, for discussion). van Stegeren et al. (2002) have also examined whether beta-blockade *after* the stage of encoding has any effect on later emotional recall. They found no evidence to support a role for NA after encoding or later at retrieval. No effects of peripheral beta-blockade or correlations between blood pressure decrease and emotional memory functions have been observed in studies with hydrophilic substances like atenolol or nadolol that do not cross the blood–brain barrier (van Stegeren et al. 1998; O'Carroll et al. 1999a). Few studies were identified that had examined effects of alpha adrenoceptor antagonists and agonists on emotional memory (Table 3). Administration of 20 mg yohimbine increased emotional memory in one study (O'Carroll et al. 1999b). Another study found no effect of (intravenous) yohimbine on emotional memory, but the dose was administered after slide presentation (Southwick et al. 2002). The single study using dexmedetomidine found no effects on emotional memory albeit with a restricted sample size per group (Pryor et al. 2004).

Recent studies have used both positively and negatively valenced emotional material to explore the effects of NA drugs on emotional memory. Harmer et al. (2004) examined emotional memory for agreeable vs disagreeable personality characteristic words after a 7-day course of reboxetine (SNRI) (4 mg) (NB both encoding and retrieval were undertaken at end-of-study). Words were matched for frequency, meaningfulness and length. The treated group showed increased recall of positive personality characteristic words in particular compared to the placebo group, suggesting that NA manipulations can show differential effects depending upon the valence of stimuli.

Some studies were identified that had coupled NA manipulations with neuroimaging techniques. In one study using functional magnetic resonance imaging (fMRI), successful encoding of emotionally aversive nouns was found to engage the left amygdala, and this effect was abolished by administration of propranolol (Strange and Dolan 2004). Recognition of emotional noun words was found to engage the left hippocampus, but this effect was absent when beta-adrenergic blockade was used at the time of initial encoding. In another study, volunteers undertook fMRI while viewing affective pictures from the IAPS (van Stegeren et al. 2005). Viewing neutral pictures did not increase amygdala activation relative to baseline whereas viewing emotional pictures did. The increased activation after certain emotional stimuli was reduced in participants who had received 80 mg propranolol. These neuroimaging findings are consistent with an important role for NA-mediated modulation of amygdalae at the level of encoding, in particular, and possibly also during consolidation.

In summary, beta-blockade at the time of encoding of emotional stimuli with propranolol (but not other beta-blockers with more limited central actions) was found to reduce later recall (i.e. to reduce emotional memory) across the majority of studies. There was evidence from a single study that yohimbine increased emotional memory (O'Carroll et al. 1999b). Reboxetine (7-day treatment) increased emotional memory for positively valenced stimuli (Harmer et al. 2004). Neuroimaging evidence supported NA interactions with the amygdalae in emotional memory, especially at the encoding stage (Strange and Dolan 2004; van Stegeren et al. 2005).

Discussion

Working memory refers to the short-term storage and manipulation of items in memory and is thought to be dependent upon the PFC (Baddeley 1986; Arnsten and Li 2005). Emotional memory refers to formation, consolidation, and long-term retrieval of memories formed during times of stress and is thought to be dependent upon the amygdalae and related mediotemporal structures (Cahill et al. 1994; van Stegeren et al. 1998, 2005; Cahill 2003; Strange and Dolan 2004). Both working and emotional memory are arousal-linked cognitive functions that are

Table 3 Effects of noradrenergic drugs on emotional memory in healthy volunteers

Author(s) and year	Drug(s) and dose(s) [mg]/design	*N* (females) [per drug condition]/age [years]	Emotional memory task	Results 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
(van Stegeren et al. 1998; Cahill and van Stegeren 2003)	Propranolol 40, 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, 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, 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
(Papps et al. 2002; O'Carroll and Papps 2003)	Reboxetine 4/8/ Parallel groups, PLC	36 (10) [12]/ ~18–25	Emotional slide story	EM ↓ (dose-dependent); inverted U effect?
(Southwick et al. 2002)	Yohimbine 32* (i.v.)/ 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 9.6/19.2 (i.v.)/ 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. 2003b)	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), citalopram 20 (per day)/ Parallel groups, PLC, long term (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, 2005)	Propranolol 40/80, metyrapone 2×750/ 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)
(Pryor et al. 2004)	Dexmedetomidine thiopental propofol/ Parallel groups, PLC	83 (32) [10 dex.; variable]/ 18–50	Emotionally valenced slides	EM ↔ (dexmedetomidine) but small N for group

Table3 (continued)

Author(s) and year	Drug(s) and dose(s) [mg]/design	*N* (females) [per drug condition]/age [years]	Emotional memory task	Results and comment
(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
(Schachinger et al. 2001; Moor et al. 2005)	Norepinephrine–nitroprusside sodium (i.v.), epinephrine–esmolol (i.v.) followed by placebo/ Cross-over	24 (0) [24]/ ~22–28	Emotionally valenced slides	EM ↑ (after norepinephrine); single blind design
(van Stegeren et al. 2005)	Propranolol 80/ Cross-over, PLC, fMRI	28/30 (15) [14/15]/ 18–28	Emotionally valenced slides	EM ↓, less amygdale activation

*Approximation

important in everyday life and in understanding neuropsychiatric disorders. In this paper, we reviewed studies examining the effects of NA drugs on working and emotional memory in healthy human volunteers. The centrally and peripherally acting beta-blocker propanonol generally impaired working memory and reduced memory for emotional events/stimuli, and this was one of the most consistent findings in the literature. From a clinical perspective, these data suggest that the beta-adrenergic system represents a putative target for the treatment of PTSD (Southwick et al. 1999; Giles 2005; van Stegeren 2005). Neuroimaging evidence supports direct involvement of NA–amygdala coupling at the level of encoding, whereas the importance of this region during consolidation and retrieval remains disputed (Moor et al. 2005; van Stegeren et al. 2005). The alpha-2-adrenoceptor agonist clonidine generally impaired working memory, but findings with the more selective agent guanfacine were inconsistent, and the effects of these drugs on emotional memory could not be evaluated due to a paucity of studies. Effects of acute NA potentiation with reboxetine were inconsistent for working memory (Kerr et al. 1996; Rammsayer et al. 2001), while reboxetine was shown to increase emotional memory for positively valenced stimuli in one study (Harmer et al. 2004) and to enhance priming effects of emotional stimuli in another as a function of valence (Hurlemann et al. 2005). Thus, while NA is clearly implicated in emotional memory, differential effects have been reported as a function of stimulus valence and this remains an important area of investigation. In addition to effects on emotional long-term memory and priming, facilitating effects of reboxetine and atomoxetine on motor memory (learning of finger movement sequences) have been demonstrated that might also be arousal-dependent (Plewnia et al. 2004; Foster et al. 2006).

In reviewing the available studies, several methodological issues were identified. Many studies employed single drug doses, yet there is growing evidence that neurotransmitter systems may operate according to inverted-U functions, whereby too little or too much neurotransmitter can impair a given cognitive function in an optimal system (Cools and Robbins 2004). Therefore, it will be important in future works to clarify more precisely the effects of different drug doses. In this review, we focused on studies using selective NA agents rather than catecholaminergic drugs such as levodopa or methylphenidate that preferentially act on dopaminergic mechanisms. Nonetheless, NA drugs (Table 1) may exert secondary effects on other neurotransmitter systems, making it difficult to attribute behavioural effects explicitly to NA actions. One useful way to address this issue in future work would be to include drugs (or dietary amino acid manipulations) acting principally on other neurochemical systems as comparisons (Chamberlain et al. 2006b).

Another issue was that of possible ceiling effects on neuropsychological tasks, which can arise from reliance on high-functioning university students. Recruitment using community-orientated adverts or posters in places of work may be of greater utility. It is also possible to select

batteries of tests especially designed to avoid ceiling effects in high-functioning groups. With regard to sample sizes, *N*=15 per group was commonplace (Tables 2 and 3, range 6–24). Restricted sample sizes limit power to detect effects of medication, making it difficult to interpret negative findings.

Many studies used a placebo-controlled double-blind approach, which is the best practice. The issue of within-subject (crossover) vs between-subject (parallel groups) pharmacological designs is difficult, with advantages and disadvantages to both. On the one hand, within-subject designs help to control for subject variability but can lead to critical problems with interpretation due to practice effects on neuropsychological tests; on the other hand, between-subject designs increase the possibility for variability between groups but eliminates the practice effect (as long as de novo volunteers with no prior exposure to the tasks are included). One method of addressing the potential issue of practice effects in within-subject designs is to train participants up to a certain level of baseline performance during a practice or screening session. However, the parallel groups design is especially recommended for studies with 'single use', highly strategy-dependent paradigms and designs with surprise stress or emotional challenge.

Studies frequently employed visual analogue scales to assess subjective effects, including sedative effects and emotional changes after drug administration. Inclusion of salivary cortisol measures (for example using the convenient Sarstedt Salivette TM collection system) or other measures of HPA axis function may be useful to exclude baseline group differences and to help characterise interplay between situational anxiety, stress, NA transmission and HPA axis function (Harmer et al. 2003a; Schule et al. 2004; Chamberlain and Sahakian 2005; Tse and Bond 2005). Another relevant recent development is that of salivary sampling for alpha-amylase, an indicator of sympathetic activity and/or NA activation (Rohleder et al. 2004; van Stegeren et al. 2006). Employing such a technique in future NA studies will be of great importance.

Several promising techniques are emerging in the field of neuropsychopharmacology, which will help to elucidate more precisely the role of NA in cognition and coupling with components of neural circuitry. Increasingly selective NA drugs are being developed, and it is becoming possible to use agonist/antagonist drug designs (O'Carroll et al. 1999a; Bullmore et al. 2003; Hurlemann et al. 2005). Positron emission tomography (PET) and functional magnetic resonance imaging have enabled visualisation of neural correlates of working and emotional memory processes in health and in the context of neuropsychiatric illnesses (Callicott and Weinberger 1999; Canli et al. 2000; Cahill 2003; Racine et al. 2005; van Stegeren et al. 2005). Pharmacological fMRI will facilitate detection of neuromodulatory effects of NA agents on components of cortico-subcortical circuitry in a way that has not previously been possible (Gibbs and D'Esposito 2005a,b). Pure behavioural studies will continue to be important, as the behavioural sensitivity of cognitive tasks is frequently (and necessarily) sacrificed when adapting tasks for the scanner (e.g. see Fletcher et al. 1998). With the advent of pharmacogenetics, future work should also investigate effects of functional polymorphisms in genes known to modulate NA actions (Diaz-Asper et al. 2006; Neumeister et al. 2006).

In all, well-designed human psychopharmacological studies are difficult to perform but are essential to our understanding of the role of NA in human cognition, especially when viewed alongside studies in experimental animals. Greater understanding of the precise control of working and emotional memory in humans has important implications in the context of everyday human cognition and in the manifestation and treatment of neuropsychiatric disorders. While NA is clearly implicated in working memory and emotional memory, examination of the role of NA on other cognitive processes, such as attention (Smith and Nutt 1996), response inhibition (Chamberlain et al. 2006a–c) and affective processing (Harmer et al. 2003b; Chamberlain and Sahakian 2004; Erickson et al. 2005), may help to clarify the interplay between these cognitive domains and memory and facilitate the development of increasingly sophisticated neurobiological models and candidate treatments for neuropsychiatric illnesses.

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