Norepinephrine effects on the encoding and consolidation of emotional memory: improving synergy between animal and human studies

Running title: Norepinephrine effects on encoding and consolidation

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Abstract

Noradrenergic activity is important for emotional enhancement of memory. Although findings from both animal and human research provide extensive support for this general conclusion, there are some important, but often ignored, differences between these research lines. Whereas animal experiments mostly employ pharmacological manipulations in the post-learning phase to investigate the effects of sustained noradrenergic activation on the consolidation of long-term memory, neuroimaging studies in humans typically focus on much more dynamic changes in noradrenergic activity during the actual encoding of information. In this paper we discuss the possibility that these two types of noradrenergic effects interact in enhancing memory for emotionally arousing experiences, and explain how elucidating this mechanism might improve synergy between animal and human research.

Introduction

Extensive evidence indicates that noradrenergic activity is enhanced by emotionally arousing training conditions [1]. The hypothesis that norepinephrine plays a role in learning and memory emerged more than four decades ago when Kety [2] suggested that adrenergic catecholamines, such as epinephrine or norepinephrine, released by certain emotional states may serve "to reinforce and consolidate new and significant sensory patterns in the neocortex." The initial experiments investigating this general hypothesis examined the effects of systemic administration of adrenergic drugs on learning and memory [3]. The findings of Gold and van Buskirk [4] were among the first to suggest the involvement of central norepinephrine in memory. Many subsequent studies in rodents provided extensive support for the hypothesis that norepinephrine or a β-adrenoceptor agonist infused into the basolateral amygdala (BLA) or other brain regions such as the hippocampus or prefrontal cortex enhances long-term memory of emotionally arousing training experiences [1,5,6]. Human research generally supports the conclusions of animal studies indicating that an activation of the noradrenergic system is associated with better memory and that this influence involves the amygdala [7,8].

There are, however, some important but frequently overlooked methodological differences between the animal and human studies. Whereas most animal research has used post-learning pharmacological manipulations to induce sustained changes in noradrenergic activity during the consolidation phase of memory, human neuroimaging studies typically focus on much more dynamic, i.e., phasic, changes in noradrenergic activity during the actual encoding of emotional experiences into memory. While phasic noradrenergic signaling is centrally mediated through rapid increases in firing rates of locus coeruleus neurons [9], sustained noradrenergic activity after

encoding, at least partially, involves activation of peripheral adrenal stress hormone release: Both epinephrine [10] and glucocorticoids [11] trigger a tonic increase in noradrenergic activity in the amygdala. Such peripheral stress hormone effects on sustained noradrenergic activity might not only be produced as a result of tonic activation of noradrenergic neurons in the locus coeruleus [12] but also involve the activation of noradrenergic cell groups in the nucleus of the solitary tract [10] or an indirect stimulation of norepinephrine levels by inhibiting norepinephrine-reuptake mechanisms [13]. In this paper, we will argue that these phasic and sustained increases in noradrenergic activity might interact in enhancing memory for emotionally arousing experiences. The specific and phasic noradrenergic activation during memory encoding might make these memory traces amenable to the memory-enhancing effects of a more sustained noradrenergic activation in the post-learning consolidation phase. Notably, this sustained post-learning noradrenergic activity may also have no, or even opposite, effects when not preceded by phasic noradrenergic signaling during encoding.

Norepinephrine actions on memory consolidation

Animal studies have provided extensive evidence that noradrenergic activation, arising from catecholaminergic cell bodies in the locus coeruleus and the nucleus of the solitary tract, is critically involved in memory consolidation [14]. For example, norepinephrine or β-adrenoceptor agonists administered into the BLA immediately after an emotionally arousing training experience induce dose-dependent enhancement of memory consolidation [15-21]. Similar norepinephrine infusions into the hippocampus, entorhinal cortex or posterior parietal cortex enhance memory consolidation for inhibitory avoidance training when given even up to 6 hours after training

[22,23]. Conversely, post-training infusions of β-adrenoceptor antagonists impair retention and block the memory-enhancing effects of co-administered norepinephrine [19,20]. In addition to β-adrenoceptor influences, α_1-adrenoceptor agonist infusions into the BLA after training also enhance memory consolidation [24]. The α_1-adrenoceptor-induced memory enhancement most likely involves an interaction with β-adrenoceptors, as post-training intra-BLA infusions of a β-adrenoceptor antagonist block the memory enhancement produced by activation of α_1-adrenoceptors [25]. Undoubtedly, there are many other influences on memory consolidation provided by adrenomedullary and adrenocortical stress hormones, other neurotransmitter systems as well as local circuit neurons. Although memory modulation can be achieved by manipulation of any of these components, there are many interactions between the noradrenergic system and these neuromodulatory influences [14]. For example, drugs and hormones that enhance memory consolidation potentiate training-induced increases in norepinephrine levels in the amygdala whereas drugs that impair consolidation decrease amygdala norepinephrine levels [10,11]. Moreover, an attenuation of noradrenergic activity with a β-adrenoceptor antagonist administered into the BLA blocks the memory-modulatory influences of post-learning stress hormone or neurotransmitter administration [26,27].

Most pharmacological studies have used targeted administrations of norepinephrine or noradrenergic agents into relevant brain regions [14]. As these infusions are given mostly after the training experience, the norepinephrine likely induces a prolonged increase in noradrenergic activity during the consolidation phase of memory processing. In support of this view, *in vivo* microdialysis studies showed that noradrenergic activity in the amygdala is elevated for approximately 2 hours after an aversive learning experience [28] (Figure 1). Further and

importantly, in rats given inhibitory avoidance training, the magnitude of training-induced increases in amygdala norepinephrine levels assessed after the training correlates very highly with the rats' subsequent long-term retention performance, providing additional evidence that relatively long-lasting elevations in noradrenergic activity after the actual learning experience might be required to induce enhancement of memory consolidation. Such noradrenergic enhancement of amygdala activity modulates the consolidation of memory for many kinds of emotionally arousing training experiences [29]. Consistent with this evidence, post-training noradrenergic manipulation of BLA activity can influence neuroplasticity and information storage processes in other brain regions known to be involved in memory processing, including the hippocampus, caudate nucleus and insular cortex [1,14,30].

Human research demonstrated that systemic administration of the noradrenergic stimulant yohimbine before learning enhances memory [8]. Conversely, blocking the effects of endogenous norepinephrine using pre-learning administration of the β-adrenoceptor antagonist propranolol results in impaired memory for emotionally arousing events [7]. Such noradrenergic effects are centrally mediated, as the β-adrenoceptor blocker nadolol, which cannot cross the blood-brain barrier, does not have the same effect as propranolol [31]. Studies involving noradrenergic manipulations before encoding, however, cannot dissociate effects on encoding from effects on consolidation. Findings converge, however, with studies using post-learning exposure to psychosocial [32,33], physiological [34-37], and negatively emotionally arousing [38] stressors, which are also associated (albeit not uniquely) with sustained noradrenergic activity. Most direct evidence for noradrenergic involvement in memory consolidation comes from studies showing similar memory-enhancing effects following post-learning administration of yohimbine [39] and

epinephrine [40].

Norepinephrine actions on memory encoding

While pharmacological work in rodents mainly focused on the role of norepinephrine in enhancing the consolidation of memories, it is evident that norepinephrine must also play an important role during memory encoding. A large body of research implicates noradrenergic activation by the locus coeruleus in regulating attention, and thus in regulating sensory intake that is to be encoded. Work in monkeys has shown that locus coeruleus neurons exhibit two distinct modes of activity [9]. *Tonic* discharge rates of locus coeruleus neurons are positively associated with levels of arousal, and peak in states of stress [12]. By contrast, *phasic* locus coeruleus activity is related to levels of arousal in an inverted U-shaped fashion, with most efficient signaling at moderate levels of arousal [9]. These brief neuromodulatory signals are thought to send "interrupt" signals to currently active functional networks [41], resulting in disengagement from current attentional sets [9], rapid rearrangement of functional networks [42], and a reorienting of attention toward salient environmental information [43]. In humans, phasic norepinephrine has been linked to electrophysiological correlates of sensory processing [44], and to allocation of attention to both emotional and neutral stimuli [45]. Noradrenergic activity has furthermore been associated with activation of the "salience" network [46]. This network, which was delineated using measures of intrinsic functional connectivity in humans, integrates various neurocognitive functions relevant to processing salient stimuli, including attentional reorienting, homeostatic regulation, and interoception [47]. It is anchored in dorsal anterior cingulate cortex and anterior insula, but also involves the amygdala [47,48].

Human research using functional neuroimaging, which is particularly suited to study phasic activity in response to stimuli, has therefore focused on the amygdala during processing and encoding of emotional stimuli in humans. Amygdala activity during encoding, measured using PET, predicts memory for emotionally arousing experiences [49,50]. With BOLD-fMRI, such associations between amygdala activity and subsequent memory were extended to phasic, trial-by-trial, variation in success of emotional memory formation [51-53]. Connectivity between amygdala and hippocampus increases during encoding [54] and predicts subsequent memory [55]. Enhanced mnemonic activity in hippocampus for emotional stimuli furthermore depends on the integrity of the amygdala [56].

While neuroimaging studies into the amygdala cannot establish noradrenergic involvement, pharmacological studies have provided more direct evidence for the key role of norepinephrine in facilitating the amygdala's role during memory formation. For instance, ß-adrenoceptor blockade using propranolol during encoding reduces both the emotional memory enhancement effect [7] and the amygdala response to emotional material [57,58], although it may also reduce neutral memory [59]. Enhancing noradrenergic activity using the selective norepinephrine-reuptake inhibitor reboxetine has the opposite effect of increasing the amygdala responsiveness [60]. The fact that these effects are specific to relevant brain regions makes it unlikely that they are caused by cardiovascular artefacts. Finally, carriers of a common functional deletion in the gene coding for the presynaptic α_{2b}-adrenoceptor (*ADRA2B*), who have elevated norepinephrine levels, exhibit stronger amygdala responses to aversive stimuli [61], stronger increases in phasic amygdala responses during stress [62], and stronger enhancement of emotional memory [63]. Thus, there is abundant evidence demonstrating that (correlates of) phasic noradrenergic activity

and amygdala activity predict enhanced memory formation for emotional material in humans.

Interactions between noradrenergic actions during encoding and consolidation

Up until recently, encoding and consolidation processes have been studied in relative isolation, largely along the lines of human versus animal research, respectively. The reason for this is that research in animals has often relied on targeted pharmacological manipulations in the post-learning consolidation phase which are too invasive to employ in humans. Contrariwise, the non-invasive techniques available in humans are more suited to study mnemonic processes during encoding, because most conventional methods for human functional neuroimaging are developed for detecting time-locked, evoked neuronal activity. Human functional neuroimaging cannot be easily applied to latent, temporally unpredictable neural processes such as those that may occur during consolidation. Therefore, research into encoding and consolidation processes has not yet been optimally integrated, leaving important open questions regarding the relationship between these two processes. Are they simply *additive*, with more activity in either leading to better memory, or could it be that they *interact*: Can activity at encoding determine the fate of a memory during the consolidation phase? Before turning to this question, we will first describe recent interdisciplinary attempts at connecting encoding and consolidation processes in animal and human work.

The first attempts at connecting encoding and consolidation processes have been made in rodent electrophysiology. These studies have shown increased synchronization of neuronal oscillations between amygdala and hippocampus, for instance, during acquisition and expression of conditioned fear [64], but also after immobilization stress [65], both of which are experiences

that likely trigger sympathetic and noradrenergic arousal [66]. Importantly, amygdala-hippocampal, but also amygdala-medial prefrontal, theta synchronization is increased during sleep after similarly arousing experiences, and this increase predicts memory one day later [67]. Although no studies to date have explicitly linked these effects to noradrenergic activity, arousing experiences due to reward or novelty furthermore strengthen spontaneous reactivation ("replay") of waking patterns of hippocampal activity during post-learning awake rest periods [68,69]. Note that both "offline" rest periods after learning and sleep are seen as critical periods for memory consolidation. In conclusion, it appears that neural circuits underlying encoding and consolidation at least partly overlap.

Following this logic, recent work using functional neuroimaging in humans has attempted to capture the same phenomena in humans by investigating post-learning reactivations of encoding patterns of neuronal activity within, and connectivity between, the regions implicated in rodent work. Early studies demonstrated that hippocampal-neocortical connectivity indeed persists during rest following encoding of neutral memories [70,71]. Persistence of this connectivity [70] as well as persistence of hippocampal [72] and entorhinal [73] activity patterns during post-encoding rest was furthermore linked to subsequent memory recall. For emotional memories, it was shown that enhanced amygdala-hippocampal connectivity persists during a waking period (in the range of approximately 0-30 minutes) after fear learning, and predicts long-term expression of fear [74]. Furthermore, fear learning enhances hippocampally driven spontaneous reactivation of patterns of activity in neocortical representational regions within the ventral visual stream, showing that recently acquired memory representations reactivate spontaneously during post-encoding rest when associated with emotionally arousing events through fear conditioning

[75]. Note that, although a direct link with norepinephrine remains to be shown, these reactivations occur within a time frame that falls within the period during which noradrenergic activity remains elevated following arousing footshocks in rodents (see Figure 1).

A critical open question is what the nature is of the relationship between phasic noradrenergic activity during encoding and sustained activity during consolidation. Several studies have provided converging evidence for the notion that the memory-modulatory effects of sustained post-learning noradrenergic activity depend on phasic noradrenergic activity during encoding. Animal studies typically employ emotionally arousing training conditions and consistently find memory-enhancing effects of post-learning noradrenergic activation (see section on memory consolidation above), but human studies that have applied experimental stress induction procedures after memory encoding have shown a selective enhancement of consolidation for information that was arousing during encoding [32,34-37] (but see [33]). A recent study showed that stronger cortisol reactivity to post-learning stress induction was associated with stronger subsequent memory effects in amygdala and hippocampus [76], which suggests that post-learning elevation of stress hormones makes memories more dependent on phasic activity in medial temporal lobe structures during encoding. Beneficial effects of post-learning manipulations have also been reported with systemic administration of epinephrine [40] and hydrocortisone [77,78]. It appears that such post-learning manipulations are only effective within a limited time window [38], which roughly corresponds with the time window in which "replay"-like effects were found [74,75]. Notably, beneficial effects of post-learning manipulations on retention of emotionally arousing material reported in the human literature are often accompanied by a numerical decrease for neutral material studied within the same context

[34,35,40,78]. Such a selective mnemonic impairment for neutral material is particularly evident in the E-1 paradigm, in which memory for neutral items is impaired when directly followed by an emotionally arousing oddball [79], but only when non-salient (i.e., task-irrelevant) [80]. One explanation for such dual post-learning effects of norepinephrine was recently proposed by Mather et al. [81], who argue that such effects are due to bidirectional local interactions of norepinephrine with glutamatergic activity in brain regions involved in representing the items.

Converging evidence from neuropsychological and rodent studies, however, point toward another explanation, namely that the amygdala continues to play a critical role in both the enhancement of consolidation of emotionally arousing information as well as the impairment of the consolidation of neutral information after post-learning arousal. For instance, patients with Urbach-Wiethe disease (UWD), which causes progressive calcification particularly of the BLA [82], not only fail to show a normal emotional enhancement effect [83], but also lack the selective impairment for neutral stimuli preceding emotionally arousing oddballs in E-1 paradigms [79]. This effect cannot simply be explained by general impairment of noradrenergic signaling, as UWD patients appear to exhibit normal arousal responses to, for instance, unconditioned stimuli [84,85]. Furthermore, rodent work shows that infusion of the β-adrenoceptor agonist clenbuterol into the BLA triggers a long-term increase in excitability of hippocampal neurons, but only when administered after an emotionally arousing inhibitory avoidance experience. Critically, clenbuterol infusion has an *opposite* effect in home-cage control animals which did not undergo the arousing training experience [30]. Noradrenergic activity in the amygdala during memory encoding also appears to determine the direction of the effect of post-learning administration of stress hormones on memory. For instance, the synthetic glucocorticoid dexamethasone, which

increases norepinephrine levels in brain [11], administered post-training enhances long-term memory for inhibitory avoidance training in rats with intact noradrenergic signaling in the BLA, but has an opposite effect when noradrenergic signaling in the BLA during training is blocked using a β-adrenoceptor antagonist [27]. Figure 2 summarizes the model of how the effect of post-learning stress exposure and associated *sustained* increases in noradrenergic activity on memory consolidation might interact with *phasic* noradrenergic activity in the amygdala during memory encoding.

Conclusions and future directions

In conclusion, a critical analysis of the extant literature on the effects of norepinephrine on memory shows a divide between animal research, which has mainly investigated the consolidation phase, and human research, which has traditionally focused on encoding processes. As we outlined, a synergy of these two research lines is beginning to emerge. This is important particularly because noradrenergic effects on encoding and consolidation are not *additive* but *interactive*: Noradrenergic signaling during encoding determines the *direction* of noradrenergic effects during consolidation. Furthermore, we have argued that the amygdala, as a "nexus" within distinct large-scale neural networks [86], plays a critical role in both phases. Future research should leverage the strengths of both human and animal research: The ability of human functional neuroimaging to map interactions within large-scale neural systems and the ability to employ invasive novel technologies such as optogenetics in rodents. A synergy of these two fields will help us in understanding the neural mechanisms underlying the mnemonic consequences of emotional experiences.

Acknowledgments

BR is supported by a Topfund grant from Radboud University and EJH is supported by a grant from the European Research Council (ERC-2015-CoG 682591).

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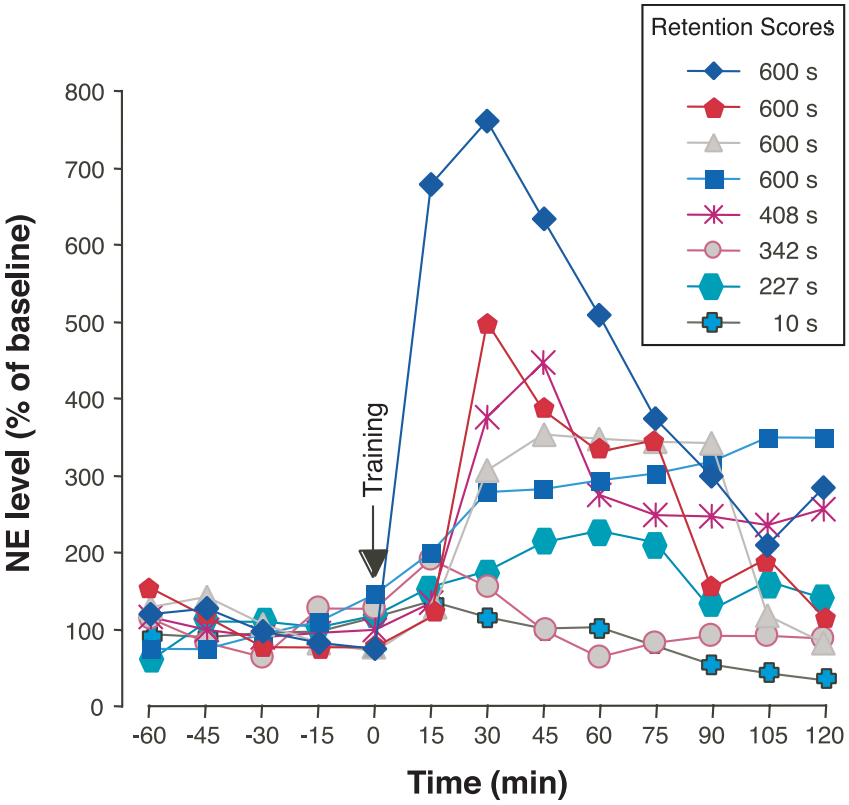
Figure Legends

Figure 1

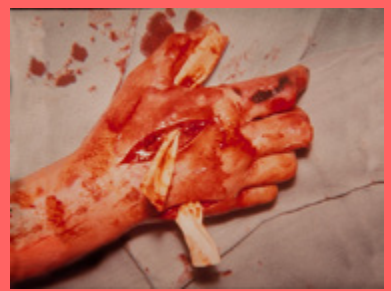
Norepinephrine levels in the amygdala are elevated for 2 hours after footshock stimulation during inhibitory avoidance training and correlate with 24-hour retention performance. Percent of baseline norepinephrine following inhibitory avoidance training is graphed for each individual rat. The key notes retention latencies 24 hours after the training session (maximum latency = 600 seconds). Longer retention latencies are interpreted as indicating better memory. Correlation values for the first five post-training samples varied from +0.75 to +0.92. Adapted from McIntyre et al. [28].

Figure 2

Interaction between phasic noradrenergic signaling during encoding and sustained noradrenergic activity during memory consolidation. This figure illustrates the core proposal of this paper that sustained noradrenergic activity during consolidation enhances memory for events that were associated with phasic noradrenergic signaling during encoding, but may impair memory for events that were not preceded by phasic noradrenergic signaling during encoding. Both the phasic and sustained noradrenergic effects depend on the amygdala.


Retention Scores
600 s
600 s
600 s
600 s
408 s
342 s
227 s
10 s
NE level (% of baseline)
800
700
600
500
400
300
200
100
0
Training
-60
-45
-30
-15
0
15
30
45
60
75
90
105
120
Time (min)

Phasic NE Amygdala



No phasic NE Amygdala

Enhanced Memory

Post-learning Stress & Sustained NE

Impaired Memory

Encoding

Consolidation