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Noradrenergic mechanisms of arousal's bidirectional effects on episodic memory ☆

David Clewett [a,*], Michiko Sakaki [b], Shawn Nielsen [c], Giselle Petzinger [a,d], Mara Mather [a,c]

[a] Neuroscience Graduate Program, University of Southern California, USA
[b] School of Psychology and Clinical Language Sciences, University of Reading, UK
[c] Davis School of Gerontology, University of Southern California, USA
[d] Department of Neurology, University of Southern California, USA

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ABSTRACT

Arousal's selective effects on cognition go beyond the simple enhancement of emotional stimuli, sometimes enhancing and other times impairing processing of proximal neutral information. Past work shows that arousal impairs encoding of subsequent neutral stimuli regardless of their top-down priority via the engagement of β-adrenoreceptors. In contrast, retrograde amnesia induced by emotional arousal can flip to enhancement when preceding neutral items are prioritized in top-down attention. Whether β-adrenoreceptors also contribute to this retrograde memory enhancement of goal-relevant neutral stimuli is unclear. In this pharmacological study, we administered 40 mg of propranolol or 40 mg of placebo to healthy young adults to examine whether emotional arousal's bidirectional effects on declarative memory relies on β-adrenoreceptor activation. Following pill intake, participants completed an emotional oddball task in which they were asked to prioritize a neutral object appearing just before an emotional or neutral oddball image within a sequence of 7 neutral objects. Under placebo, emotional oddballs impaired memory for lower priority oddball+1 objects but had no effect on memory for high priority oddball−1 objects. Propranolol blocked this anterograde amnesic effect of arousal. Emotional oddballs also enhanced selective memory trade-offs significantly more in the placebo than drug condition, such that high priority oddball−1 objects were more likely to be remembered at the cost of their corresponding lower priority oddball+1 objects under arousal. Lastly, those who recalled more high priority oddball−1 objects preceding an emotional versus neutral oddball image showed greater increases in salivary alpha-amylase, a biomarker of noradrenergic system activation, across the task. Together these findings suggest that different noradrenergic mechanisms contribute to the anterograde and retrograde mnemonic effects of arousal on proximal neutral memoranda.

1. Introduction

Selectivity is at the core of efficient cognitive processing, helping us to prioritize significant information among competing sensory inputs. Years of research demonstrate that emotional experiences dominate this competition for limited mental resources to ensure behaviorally relevant/emotional events are preferentially processed and stored into long-term memory (Dolan, 2002; LaBar & Cabeza, 2006; McGaugh, 2000, 2013). However, this focus on the superiority of emotional memories has led to a blind spot in the emotion-cognition literature. In addition to enhancing processing of emotional stimuli, the effects of arousal also spill over to influence cognitive processing more broadly, sometimes enhancing and other times impairing processing of neutral information appearing just before or after something emotional (Mather & Sutherland, 2011).

One particularly striking example of how emotional arousal influences temporally adjacent neutral stimuli is provided by an oddball paradigm in which a perceptually deviant emotional image is embedded within a sequence of neutral stimuli. Whereas in some studies emotional stimuli enhance memory for preceding neutral items (Anderson, Wais, & Gabrieli, 2006; Knight & Mather, 2009), in other studies emotional stimuli impair memory for preceding neutral stimuli (Hurlemann et al., 2005;

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* Corresponding author at: New York University, 6 Washington Place, New York, NY 10003, USA.
E-mail address: clewett@usc.edu (D. Clewett).

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Hurlemann, Matusch, et al., 2007; Hurlemann, Wagner, et al., 2007; Strange, Hurlemann, & Dolan, 2003). To reconcile these discrepant findings, the *arousal-biased competition (ABC) model* posits that a momentary increase in arousal amplifies the effects of priority, such that memory of prioritized, important information is enhanced, whereas memory of lower priority information is impaired (Mather & Sutherland, 2011). Fundamentally, this framework builds upon the idea of biased competition in the brain whereby top-down goals or bottom-up perceptual salience help resolve competition among incoming sensory inputs (Beck & Kastner, 2009; Desimone & Duncan, 1995).

To test the ABC hypothesis explicitly, Sakaki, Fryer, and Mather (2014) manipulated priority in a visual oddball paradigm by altering the goal-relevance of neutral object images appearing just before (oddball−1 objects) or after (oddball+1 objects) an emotional versus neutral oddball image (Sakaki et al., 2014). As predicted, emotional arousal led to retrograde amnesia for oddball−1 objects when the oddball image was prioritized, whereas prioritizing the neutral oddball−1 image instead led to an emotion-induced retrograde memory enhancement for the object. In contrast, emotional arousal did not benefit memory of neutral oddball+1 objects prioritized in a top-down manner. These contrasting time-dependent effects of arousal suggest that emotion benefits on-going memory processing of already activated representations, but does not facilitate memory for ensuing items even when they are prioritized.

Emerging research lends credence to the idea that emotional arousal amplifies the effects of top-down priority in declarative memory for preceding information but not subsequent information. For instance, hearing a tone conditioned to shock enhances memory consolidation of preceding goal-relevant visual stimuli (Lee, Greening, & Mather, 2015). In addition, hearing an emotional sound immediately after seeing an object-scene pair leads to impaired memory for the less salient background scene (Ponzio & Mather, 2014). One oddball study demonstrated that increasing the amount of attention given to neutral items either by reducing the list length or having participants immediately recall versus not recall items at the end of each list, emotion enhanced long-term memory for preceding neutral images (Knight & Mather, 2009). On the other hand, emotion had a weaker effect on long-term memory of subsequent neutral items in the same study. Similarly, when items following oddball pictures are not prioritized by the task instructions, arousing oddballs tend to impair memory of subsequent neutral images (Hurlemann et al., 2005; Schmidt, 2002). Together these findings support the idea that emotional arousal strengthens consolidation of highly activated mental representations, while weakening memory of neutral representations that are either peripheral to the focus of attention or appear just afterward.

Although the ABC model helped reconcile puzzling findings about how arousal shapes cognitive selection processes, the neuromechanism by which arousal amplifies the effects of top-down priority in memory are poorly understood. It is widely recognized that norepinephrine (NE) released in the amygdala under emotional arousal contributes to the superiority of emotional events in attention and memory (Markovic, Anderson, & Todd, 2014; McGaugh, 2000, 2002; Strange & Dolan, 2004). In particular, numerous studies demonstrate that this NE- and amygdala-dependent enhancement of emotional memory relies on β-adrenergic receptor activation (Cahill, Prins, Weber, & McGaugh, 1994; McGaugh, 2013; Strange & Dolan, 2004).

By comparison, it has been less clear how β-adrenoreceptor activation influences memory for intrinsically non-arousing, neutral information. On the one hand, in addition to enhancing processing of emotional stimuli, β-adrenoreceptor activation mediates an emotion-induced retrograde amnesia of inconspicuous neutral stimuli (Hurlemann et al., 2005; Strange & Dolan, 2004; Strange et al., 2003), suggesting that these receptors can also account for the suppression of low-priority neutral information flanking something emotional. On the other hand, evidence in rodents demonstrates that increasing NE levels in the amygdala can enhance rather than impair memory consolidation of previously learned neutral objects, an effect that is blocked via the administration of the β-adrenoreceptor antagonist propranolol (Barsegyan, McGaugh, & Roozendaal, 2014; Roozendaal, Castello, Vedana, Barsegyan, & McGaugh, 2008). Thus it might not always be the case that β-adrenergic activation leads to emotion-induced memory impairments of neutral representations encoded beforehand.

Previous influential models of noradrenergic modulation of cognition fail to account for the full range of arousal-induced NE effects on memory processes, because they either focus on (1) the selective enhancement of emotionally or motivationally significant stimuli (Aston-Jones & Cohen, 2005; Markovic et al., 2014; McGaugh & Roozendaal, 2002) or (2) the impaired processing of neutral representations occurring before something unexpected and arousing (Bouret & Sara, 2005). To explain how NE mediates arousal's interaction with goal-directed attention, the *Glutamate Amplifies Noradrenergic Effects* (GANE) model proposes that the noradrenergic system amplifies the gain of prioritized information processing under arousal irrespective of how priority is instantiated (Mather, Clewett, Sakaki, & Harley, 2015). According to GANE, NE released under arousal modulates mental representations differently as a function of their activation strength, such that NE enhances prioritized inputs even further, while simultaneously suppressing noisy or weak inputs. This selective up-regulation of salient representations is achieved via positive local glutamate-NE feedback loops that generate sufficiently elevated levels of local NE to engage low-affinity β-adrenoreceptors; in turn, β-adrenoreceptor activation potentiates pre- and postsynaptic excitatory activity (Berridge & Waterhouse, 2003) and triggers synaptic plasticity processes that support memory consolidation (Marzo, Bai, & Otani, 2009; Salgado, Kohr, & Trevino, 2012; Treviño et al., 2012). At the same time, high glutamatergic activity representing strong inputs should also stimulate local GABAergic activity that inhibits weaker, competing representations (Brown, Walling, Milway, & Harley, 2005).

In summary, the GANE model shares the view of other theories positing that β-adrenoreceptor activation impairs processing of neutral or inconspicuous stimuli. However, the GANE model's novel prediction that β-adrenoreceptor activation also facilitates memory consolidation of goal-relevant neutral information has yet to be tested. Thus, the primary aims of this human pharmacological study were to test whether β-adrenoreceptor blockade: (1) abolishes emotion-induced retrograde memory enhancements for preceding goal-relevant stimuli (Sakaki et al., 2014), and (2) abolishes emotion-induced anterograde memory impairments for subsequent inconspicuous neutral stimuli (Hurlemann et al., 2005). We also aimed to determine whether overall noradrenergic system activation, as measured by changes in salivary alpha-amylase across an emotional task (Ditzen, Ehlert, & Nater, 2014), was associated with emotion's attention-dependent, bidirectional effects on nearby neutral information processing.

To test these hypotheses, we combined the emotional oddball paradigm used in Sakaki et al. (2014) with the administration of 40 mg of propranolol, a β-adrenoreceptor blocker. Our main hypothesis was that, under placebo, emotional oddball images would enhance memory of high priority oddball−1 objects, while impairing memory of less-attended oddball+1 objects. We predicted that β-adrenoreceptor blockade would attenuate this dichotomous influence of emotional oddballs on ongoing versus proactive mnemonic processes.