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# Two Routes to Incidental Memory under Arousal: Dopamine and Norepinephrine

John Thorp,[1] David Clewett,[2] and Monika Riegel[1,3]

[1]Department of Psychology, Columbia University, New York, New York 10027, [2]Department of Psychology, New York University, New York, New York 10003, and [3]Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw 02-092, Poland

Review of Hauser et al.

Because we cannot remember everything we experience, our memory systems must be able to flexibly determine which information to store for future use. Characterizing the neural systems that underlie this selectivity is therefore critical to understanding human memory function. The release of neuromodulators, such as dopamine and norepinephrine, plays a fundamental role in prioritizing processing of important information through each stage of memory (Sara, 2010; Shohamy and Adcock, 2010; Murty and Adcock, 2017). At the neural level, dopamine and norepinephrine neurons are ideally positioned to coordinate cognitive selectivity processes across the brain due to their widespread anatomical projections to regions that support attention and memory processes (Likhtik and Johansen, 2019) and their ability to modulate neural excitability (Devilbiss and Waterhouse, 2004; Kroener et al., 2009).

Yet while much work implicates these systems in enhancing memory for information that is encoded intentionally, it is less clear whether they have distinct effects on incidental memory. This is primarily due to significant overlap between the conditions that trigger the release of dopamine and norepinephrine, such as rewarding, threatening, or novel situations (Sara, 2009; Shohamy and Adcock, 2010; Clewett and Murty, 2019). At the same time, there are numerous neural connections between the dopaminergic and noradrenergic systems (Hansen, 2017), and recent evidence suggests that dopamine and norepinephrine can be coreleased by the same brainstem nuclei (Kempadoo et al., 2016; Takeuchi et al., 2016). As a result, the effects of these neuromodulators on neural processing often occur in tandem, which limits our ability to measure their distinct influences on brain activation and behavior.

To address these important issues, Hauser et al. (2019) used pharmacological manipulations to disentangle the influence of dopamine and norepinephrine on two aspects of incidental memory: (1) stronger incidental encoding of task-relevant versus task-irrelevant stimulus features; and (2) memory modulation driven by reward-induced arousal. In a between-subjects, placebo-controlled study, participants were administered amisulpride, a dopamine antagonist selective to D2/D3 receptors; propranolol, a norepinephrine antagonist selective to β-adre-noceptors; or placebo. To examine biases in memory selectivity, participants were shown common words in uncommon, difficult-to-read fonts and rated the readability of each word. In addition, a random reward was delivered at the end of 25% of the trials to examine the effects of arousal on overall memory encoding. After a 20 min delay, participants performed a word recognition memory task in which half of the previously studied words were shown in the same font as during encoding, whereas the other half were shown in a different font.

The first question Hauser et al. (2019) addressed was whether manipulating D2/D3 receptors or β-adrenoreceptors affected biased memory selectivity for the studied words. One strong possibility for how these receptor subtypes might accomplish this is by increasing neural gain (Aston-Jones and Cohen, 2005; Eldar et al., 2013), a process by which patterns of high neural activation are further excited, whereas patterns of low neural activation are further inhibited. Neural gain has also been found to be strongly affected by endogenous arousal levels and catecholamine release, lending additional support to the idea that drugs that modulate norepinephrine and dopamine signaling should impact the selectivity of neural and memory processing (C. M. Warren et al., 2016).

To query gain-like effects in memory, the authors cued word recognition using

either the task-relevant (font) or task-irrelevant (semantic) features of the words. The authors reasoned that this font manipulation would shed light on which stimulus features were successfully encoded, with the predicted high gain state selectively amplifying processing of the most "activated" stimulus feature. Because this encoding task prioritized the word's readability over its semantics, it was hypothesized that a state of high neural gain (validated by a pupil response index) would lead to better subsequent memory for words displayed in the same font compared with words displayed in a different font from encoding. The results revealed that, although both the placebo and propranolol (blocked norepinephrine) groups showed better memory for same-font than for different-font words, the amisulpride group (blocked dopamine) did not. These findings suggest that, under conditions of high neural gain, biased memory selectivity driven by attention to salient, task-relevant stimulus features (e.g., font) was dependent on D2/D3 function and independent of β-adrenoceptor function.

The second question the authors addressed was whether reward-related arousal (indexed by pupil dilation when rewards were delivered) modulated word recognition regardless of font type. They found that, whereas the placebo and amisulpride groups showed significantly better memory for words that were followed by reward, the propranolol group did not. This suggests that the arousal-induced memory benefit was only dependent on β-adrenoceptor function. Together, these findings reveal divergent effects of norepinephrine and dopamine on incidental memory, with dopamine facilitating memory based on task-relevant stimulus features under states of putatively high neural gain and norepinephrine affecting memory more broadly under reward-induced arousal.

**Dopamine rather than norepinephrine supports biased memory selectivity, which may pervade multiple stages of memory processing**
A growing body of work suggests that dopamine may enhance memory selectivity for salient information across multiple stages of memory (Shohamy and Adcock, 2010; Murty and Adcock, 2017). However, because the experiment in Hauser et al. (2019) was conducted within a single session, it is unclear which stage was affected by amisulpride to reduce memory selectivity. First, amisulpride may have

reduced the preferential encoding or postencoding consolidation of salient stimulus features (i.e., font). Past work shows that this drug abolishes enhanced memory for highly emotional stimuli, which tend to be prioritized due to their salience and relevance to survival (Gibbs et al., 2007). Moreover, this amisulpride effect was observed 1 week after encoding, suggesting that the drug affected early stages of memory processing as opposed to retrieval. Dopamine may also serve to broaden the scope of attention and encoding processes (Clewett and Murty, 2019), such that individuals would encode both task-relevant perceptual features and task-irrelevant semantic information. This broadening of encoding may have left more information available to cue subsequent word retrieval, leading to better memory for different-font words.

Another, nonmutually exclusive possibility is that D2/D3 receptor blockade reduced biased memory selectivity by upregulating hippocampal pattern completion at retrieval (Clos et al., 2019), a process by which partial sensory cues lead to a spread of activation through entire hippocampal memory representations (Duncan and Schlichting, 2018). Here, the semantic information in the word displayed in a different font could be acting as a weaker, partial memory cue for the original word, creating an opportunity for dopamine to modulate pattern completion. While the authors' neural gain hypothesis predicts that the drugs should affect memory for both same-font and different-font words, a pattern completion hypothesis predicts that the drugs should primarily influence memory for different-font words. A qualitative assessment of the data seems to support the latter possibility, with amisulpride predominantly improving memory for different-font words and having little effect on memory for same-font words.

This potential enhancement in pattern completion under amisulpride could be possible due to the interdependence of dopamine receptor families, as antagonizing D2/D3 is not necessarily thought to block all dopamine signaling, but rather to allow excitatory D1 states to predominate. Thus, the current results could also have been driven by enhanced D1-type receptor states of excitation (Kahnt and Tobler, 2016, 2017). The predominant D1 state induced by amisulpride could, then, potentially facilitate a pattern completion process that allows the partial cue to activate the remainder of the

representation, thereby leading to successful word recognition.

Interestingly, the authors linked potential gain-related effects on memory selectivity specifically to D2/D3 receptors, despite norepinephrine being predominantly implicated in enhancing neural gain (Aston-Jones and Cohen, 2005; Mather et al., 2016). Considering the task performed, the null effect of β-adrenoreceptor blockade on memory selectivity may have been due to endogenous arousal levels not being high enough to engage the effects of β-adrenoreceptors on memory. This interpretation is rooted in the idea that β-adrenoreceptors may enhance neural gain (i.e., selectivity) by upregulating strong glutamatergic input that transmits high priority, task-relevant representations (Mather et al., 2016). However, because β-adrenoreceptors have a low binding affinity for norepinephrine, they are only likely to be engaged under very high levels of arousal, such as during emotional or motivationally significant events. Supporting this idea, Hauser et al. (2019) specifically linked the arousal-enhancing effects of reward on overall word recognition to β-adrenoreceptors, suggesting that phasic increases in arousal are necessary for norepinephrine to boost memory (Mather et al., 2016).

**Norepinephrine rather than dopamine may mediate the beneficial effects of surprise-related arousal on immediate memory**
When specifically targeting the effects of arousal on incidental memory, Hauser et al. (2019) found that, whereas the control and amisulpride (blocked dopamine) groups showed enhanced memory for words associated with surprising rewards, the propranolol group (blocked norepinephrine) showed no such enhancement. At first blush, it may be surprising that amisulpride did not reduce the effects of arousal on memory, given that the mnemonic benefits of reward delivery are often associated with dopamine signaling (Shohamy and Adcock, 2010). However, this lack of a D2/D3 receptor effect may be due to the delay between study and test: increasing evidence suggests that dopamine's effects on reward-related memory may only emerge after a period of consolidation (Murayama and Kitagami, 2014; Stanek et al., 2019). Thus, because Hauser et al. (2019) only tested memory after a 20 min delay, it is possible that there was not a long enough delay for dopamine elicited by reward to selectively consolidate reward-related information.

In future studies, manipulating the delay between encoding and retrieval would be beneficial for two reasons. It would enable researchers both to measure whether reward-related effects of norepinephrine and dopamine on incidental memory differ as a function of consolidation and to disentangle the effects of these two neuromodulators on encoding and retrieval processes (as discussed above).

Another possible reason why amisulpride did not affect the arousal-related memory boost was that the rewards were delivered randomly. This unpredictability may have reduced the utility of generating predictions about potential reward outcomes, which would prevent the dopaminergic system from generating prediction errors (Schultz, 1997). While previous work suggests that prior rewards may be able to enhance memory in an immediate memory test, these effects are driven by the prediction errors elicited by rewards rather than by the reward's absolute value (Jang et al., 2019). Integrating a learning component into the experiment of Hauser et al. (2019) (i.e., manipulating the predictability of reward via a characteristic of the word itself) might therefore uncover effects of D2/D3 receptor blockade on memory, as the dopaminergic system would more likely be engaged when an expectation of reward is violated. In this type of design, reinforcement learning models could also be fitted to the data to explicitly measure the degree of reward prediction error, which may predict the likelihood that the mnemonic benefits of reward are blocked under amisulpride (Rouhani and Niv, 2019).

In conclusion, Hauser et al. (2019) used pharmacological manipulations to disentangle both dopamine's role in memory selectivity and norepinephrine's role in arousal-mediated memory. In future studies, an examination of the interactions between attention, arousal, and reward structure could help to further dissociate the role these neuromodulatory systems play in memory processing. Importantly, combining fMRI with targeted pharmacological manipulations would also enable more direct measurements of how catecholamines influence the dynamic reorganization of the large-scale functional brain networks that coordinate attentional and memory selectivity (M. Warren, 2016; Murty and Adcock, 2017). While the role of dopaminergic and noradrenergic systems in modulating cognitive states has been well established, further characterization of their interdependence would reveal fundamental principles of how the brain captures and stores specific information in memory.

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