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Neuropsychopharmacological regulation of performance on creativity-related tasks

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A number of factors affect performance on tasks associated with creativity. Two pharmacological systems in particularly been identified as important for their impact on creativity, the noradrenergic system and the dopaminergic systems. Furthermore, stress is also established as an important factor impacting performance, most likely mediated by its effects on these neurotransmitter systems. Herein, we review the current literature on the relationships between stress, the noradrenergic system, the dopaminergic system, and other pharmacological factors and their effects on performance on tasks associated with creativity.

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Many recent advances have occurred in the understanding of the neural mechanisms involved in creativity. However, less is known about the conditions that affect optimal performance on creativity tasks. This is of particular importance for optimizing the conditions that can affect creativity-related task performance. One critical component of regulation of task performance is the neuropsychopharmacology of creativity. Better understanding of the neuropsychopharmacology of creativity may allow a greater opportunity for intervention in particular settings, and may also reveal insight into nonpharmacological approaches that can target these same mechanisms. Most work in this area thus far has revealed effects of the catecholaminergic systems—the dopaminergic system and the noradrenergic system, which appear to play a critical role in regulating performance on tasks related to creativity. Some evidence is also beginning to be explored for other systems as well. However, the literature on pharmacological effects on other executive functions highly interrelated with creativity, such as set-shifting and working memory, dominates in contrast to the literature on effects on creativity-related tasks. Evidence suggests that the distinctions between creativity and these other executive functions may be quite critical, as will be discussed.

Noradrenergic system

The noradrenergic system is most widely recognized for its role in arousal [1,2]. The locus coerulees contains the majority of noradrenergic neurons, that project throughout the central nervous system [3]. The prefrontal cortex, important in a range of types of cognitive flexibility [4,5•], projects fibres to the locus coeruleus in primates [6]. However, cognitive flexibility can be utilized as a term to describe a range of rather distinct tasks. Cognitive flexibility, when utilized to describe verbal problem solving tasks, such as anagrams and the compound remote associates task [7], involves a search through a wide conceptual space in order to identify a solution ('unconstrained flexibility'), and is often utilized in creativity-related research. Generally, performance on such tasks improves with decreased noradrenergic activity [8••]. Furthermore, this can be subdivided into tasks where the unconstrained search converges onto on correct answer (convergent tasks), or tasks where the search involves generation of multiple potential 'creative' responses (divergent tasks) [9•]. Other cognitive flexibility tasks, such as the Wisconsin Cart Sorting Test, involve set-shifting between a limited range of options ('constrained flexibility'). This type of cognitive flexibility may not be modulated by the noradrenergic system in the same manner. Evidence suggests that constrained flexibility may potentially benefit from increased noradrenergic activity [10•]. 'Constrained' flexibility can be further subdivided into intradimensional and extradimensional set-shifting [5•]. Intradimensional shifts require shifting to responses to novel sets of stimuli from within the same sensory domain (such as shifting from choosing between two odors to responding to two novel odors), whereas extradimensional shifts require shifting to stimuli from a different sensory domain (such as shifting from choosing between two odors to responding to two textures). Decreased noradrenergic activity appears to benefit tasks such as solving anagrams when subjects are struggling or challenged by stressors [8••,11••], whereas increased set switching on a two-alternative forced choice task is associated with increased

noradrenergic tone in non-human primates [10•]. The dopaminergic system appears to affect intradimensional set-shifting [5•], while the noradrenergic system, specifically by action on the α -$_1$ receptor, appears to impact performance on extradimensional set-shifting [5•,12]. The β -adrenergic receptors in the noradrenergic system, though, appear to regulate performance on 'unconstrained' flexibility tasks [8••,11••]. A systematic exploration contrasting the effects of the noradrenergic system on set-shifting as well as creative problem solving is needed to better characterize these effects. One such exploration has been initiated in an animal model, revealing no effects of β -adrenergic antagonists on reversal learning, intradimensional set-shifting, or extradimensional set-shifting, but a significant benefit from administration of β -adrenergic antagonists on performance of a task requiring the rodent to shift to a novel solution in order to obtain reward [13•] (Table 1).

Studies in humans have explored the effects of the β -adrenergic receptor blocker propranolol. This drug blocks β -adrenergic receptors throughout the brain as well as in the periphery, while not affecting other noradrenergic receptors. Most of these studies have focused on convergent tasks among 'unconstrained cognitive flexibility' tasks involving problem solving, where the end-product of the task involving cognitive flexibility is the production of on single correct solution to a problem, such as finding the single correct response on the compound remote associates task, or the correct word that solves an anagram [8••,11••]. Effects are not known on divergent tasks among the 'unconstrained cognitive flexibility' tasks, where subjects are required to produce multiple alternative responses.

In the periphery, α_{-2} adrenergic agonists inhibit release of norepinephrine presynaptically, which would lead one to consider that they have a similar effect as the postsynaptic β-adrenergic antagonists, as both are utilized clinically to lower blood pressure utilizing this mechanism. However, α_{-2} agonists have distinct cognitive effects. High-dose clonidine, an α_{-2} agonist, has been shown to improve immediate spatial memory in monkeys [14], believed to be mediated by action at the prefrontal cortex [15].

Table 1

Summary of executive functions and the pharmacological systems targeting these functions based on animal studies

Cognitive flexibility task	Pharmacological system
Reversal learning	serotonin (as illustrated by 5-HT depletion) [86]
Intradimensional set-shifting	Dopamine (D2) [5•,51]
Extradimensional set-shifting	Noradrenergic (alpha-1) [5•,12]
Problem solving in an 'unconstrained' cognitive flexibility task	Noradrenergic (beta) [13•]

Pharmacological stimulation of the postsynaptic α_{-2A} subtype of adrenoreceptors decreases noise and results in beneficial effects for attention deficit disorder patients [16]. However, α_{-2} agonists do not appear to have the same effect on creative verbal problem solving as occurs with β-adrenergic antagonists, at least for convergent tasks [17].

The cognitive effects of stress are mediated by pharmacological systems, and as such, discussion of stress effects and pharmacological systems are intertwined. Stress is long known to impair performance on tasks requiring creativity in healthy individuals [18]. Stress is also known to increase activity of the noradrenergic system [19], as well as the hypothalamic pituitary adrenal (HPA) axis. Drugs that block the noradrenergic system in the brain, specifically via action on β-adrenergic receptors, have long been used to mitigate stress-induced impairment in performance on tasks including public speaking or test taking in anxiety-prone individuals. Research involving healthy adolescents with a history of stress-induced cognitive impairment during exams has demonstrated that treatment with the β-adrenergic antagonist propranolol significantly improved scores on the Scholastic Aptitude Test (SAT) [20]. Exploration of these mechanisms will also allow a greater understanding of the processing of information involved in creativity. Furthermore, the effects of stress and the noradrenergic system on cognition are not limited to patients with known stress-induced cognitive impairment. The role of action on the β-adrenergic receptors during 'unconstrained' cognitive flexibility has received recent attention in creativity research in healthy individuals, along with the effects of stress in such individuals. Administration of a well characterized social evaluative stressor involving public speaking and mental arithmetic resulted in impaired performance on creative verbal problem solving requiring flexibility of access to lexical, semantic and associative networks in individuals without any history of anxiety-related disorders [8••]. This impairment was abolished by the administration of propranolol [8••] (Table 1). This effect on individuals without any history of an anxiety-related disorder suggests that the effects of stress and the noradrenergic system represent a fundamental aspect regulating cognitive performance, not a phenomenon limited to specific patient populations, such as those with an anxiety-related disorder. However, the effect of propranolol in this study does not exclusively implicate the noradrenergic system, since propranolol has also been shown to block the corticosterone-induced impairment of working memory [21]. Furthermore, administration of cortisol is associated with a number of effects, including effects on a variety of executive functions [22], with action on the prefrontal cortex corticotropin-releasing factor receptor 1 recently identified as the target involved for specific stress-induced executive dysfunctions, including reversal learning and temporal order memory [23]. Therefore, future work must disentangle the roles of the adrenergic system