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Neuropsychopharmacological regulation of performance on creativity-related tasks

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Abstract

A number of factors affect performance on tasks associated with creativity. Two pharmacological systems in particular have 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.

Keywords

Creativity; convergent; divergent; stress; norepinephrine; dopamine; working memory; set shifting

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.

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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 coeruleus 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 Card 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••]. 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, and 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]. 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 and the HPA axis in the effect of stress on cognitive processes associated with creativity.

Effects of the noradrenergic system outside the setting of stress, however, are more dependent on the situation. Studies of the effects of propranolol outside of the setting of stress revealed how task difficulty might impact the effect of the drug on performance on convergent tasks [11••]. A drug proposed to benefit a broad search of a network might be expected to yield a greater benefit when problems are more challenging, requiring greater access to the ‘noise’ in the signal-to-noise ratio in order to solve the problem, as is discussed further below. In this exploration, propranolol was found to be beneficial for a range of verbal problem solving tasks requiring network flexibility when the subject was struggling, but did not confer benefit (and in some cases even impaired performance) when the subject was solving problems with ease [11••]. The benefit was seen both for the subjects who had the greatest difficulty solving the problems, and for the most difficult problems across all subjects [11••] (Table 2). Also, consistent with this, performance on creativity tasks has been found to be better in the setting of ‘leaky sensory gating’ as indicated by the P50 ERP [24••], which is of particular interest given recent evidence from neuroimaging studies that demonstrate increased gain in the precision of cortical representations associated with both markers of baseline catecholamine levels and administration of the norepinephrine transporter blocker atomoxetine [25]. Propranolol can also benefit performance on verbal problem solving for the easiest problems in situations where there is upregulated activity of the noradrenergic system due to cocaine withdrawal [26] and psychosocial stress [8••], or where there is a physiological or anatomical alteration of the language network resulting in loss of flexibility due to conditions such as autism spectrum disorder (ASD) (for both convergent task effects [27] and divergent task effects [28]) and benefits are also seen for naming in Broca’s aphasia due to stroke [29]. More recently, these benefits in ASD with propranolol have also been observed in the social domain [30] (Table 2).

The variation in the effect of noradrenergic drugs between patient groups, as observed in cocaine withdrawal, ASD, and aphasia, may be of critical importance in the use of adrenergic drugs in attention deficit disorder. Early theories proposed that arousal and optimal performance might be best described by an inverted U-shaped curve, suggesting such a relationship for the noradrenergic system. While markedly increased arousal or noradrenergic tone might result in hyper-arousal and inability to perform a task in most individuals, a person with attention deficit disorder might be, at baseline, at a suboptimal, underaroused, point on the inverted U-shaped curve associated with low noradrenergic tone and require stimulants to perform optimally. Animal data suggest that there is an optimal point of tonic activity of the locus coeruleus which tends to support the emergence of phasic activity, associated with focused or selective attention [10•]. Noradrenergic transmission is known to be genetically weaker in some patients with attention deficit disorder [31]. The effects of drugs on creativity in this population warrant further study. Preliminary evidence suggests that the effect of stimulants on creativity is limited [32].

The relationship between noradrenergic tone and performance on creative verbal problem solving tasks can also be observed in the performance impacts of alterations in noradrenergic tone induced by changes in posture [33], sleep phase [34], and vagal nerve stimulation [35]. Rapid eye movement (REM) sleep, a state associated with decreased noradrenergic activity, enhances integration of weakly associated information for creative problem solving [34,36] and is associated with high levels of spontaneous thought akin to those experience in waking restful states [37]. These effects appear to be specific to the noradrenergic system and not due to general anti-anxiety or arousal effects, since such cognitive effects do not appear to occur with non-adrenergic anxiolytics/sedatives [38].

Evidence from models derived from activity in brain slice preparations support an effect of norepinephrine on the signal-to-noise ratio of neuronal activity within the cerebral cortex [39]. Performance on the anagram task is also better after administration of propranolol than after the peripheral-only β -adrenergic antagonist nadolol [40], also suggesting that this effect of propranolol is mediated centrally rather than as a result of peripheral feedback. Presumably, propranolol increases access to 'noise', which in this case would be represented by increased associational input that might be adaptive for solving more difficult problems where the most immediate response is not optimal [8•]. Recent evidence suggests that propranolol increases functional connectivity during language tasks in autism spectrum disorders, lending some support to the proposed mechanism of action of propranolol on network access [41], but the effects on resting state connectivity are dependent on the subnetwork assessed [42]. The effect of propranolol on task performance has not yet been incorporated in imaging studies, as the previous imaging study assessed functional connectivity with fMRI (fcMRI) during a task where all subjects performed at ceiling [41].

Less is known about the specific cognitive effects of β_{-1} and β_{-2} adrenergic receptors. However, in one animal study, endogenous β_{-1} selective activation impaired working memory [43]. A subsequent study demonstrated that β_{-2} selective agonists enhance working memory in aging animals [44], suggesting opposing effects between β_{-1} and β_{-2} receptors on working memory. Further research will be necessary to better understand the specific cognitive effects due to action at selective subtypes of β -adrenergic (β_{-1} and β_{-2}) receptors.

Noradrenergic agents are also known to have a range of other cognitive effects. However, the noradrenergic effect on emotional memory deserves particular comment. An enhancement of memory due to emotional arousal may contribute to the development of intrusive memories in clinical conditions such as posttraumatic stress disorder [45,46], and centrally acting β -adrenergic receptor antagonists are known to reduce this memory enhancement effect [47,48]. More recently, propranolol has been used to block the return of fear when combined with exposure therapy in phobias [49]. The relationship between creativity and the emotional effects of the noradrenergic system are in need of further exploration.

The Dopaminergic system

Beyond the well known role played by the dopaminergic system in motor regulation, as evidenced by the motor impairments in Parkinson disease, the dopaminergic system has a range of cognitive effects, including aspects of executive function closely related to

creativity. Research in animal models has demonstrated varying effects of dopaminergic agents on set shifting tasks, differing according to which receptor subtype each agent impacts [50]. Among set-shifting tasks, this effect appears to be specific to intradimensional set-shifting [5•] (Table 1). Whereas agonists for both D1 and D2 receptors did not affect set shifting, D2 antagonists impaired set shifting [51]. In further support of a role of the dopaminergic system in executive function, the ability to maintain and flexibly alter cognitive representations in response to environmental demands is known to be impaired in Parkinson's disease [52•]. Computational models propose that phasic stimulation of D2 receptors in the striatum drives flexible adaptation of cognitive representations which are maintained by the prefrontal cortex [53], which contrasts with the effect on priming which appears to be mediated by D1 receptors [54,55]. Receptor specificity of effects on creativity is not known. However, dopaminergic agonists targeting D2/D3 receptors were found to have no effect on convergent task performance as assessed by verbal problem solving [56]. It should be noted that, regarding study in pathological populations, the interaction between dopaminergic agonists and Parkinson's disease and their effect on cognition is complex for set-shifting as well as working memory. Early in Parkinson's disease, greater dopaminergic depletion in the dorsal striatum leads to impaired adaptation in responses and updating in working memory, which is improved by L-dopa (a dopamine precursor, administration of which results in activation of all dopaminergic receptors), while working memory itself benefits less from the administration of L-dopa. However, L-dopa also can excessively enhance reward biases due to effects on the relatively intact ventral striatum [52•]. These other cognitive effects of the dopaminergic system are discussed further below.

Regarding effects on other related executive functions, in healthy subjects those with lower working memory capacity tend to benefit from increased prefrontal function with dopaminergic stimulation [57]. This is likely related to the fact that dopamine synthesis capacity in the striatum is related to working memory capacity, such that those with the least working memory capacity also have less dopamine, and therefore benefit from dopaminergic stimulation [58•], suggesting an inverted U-shaped relationship between performance and dopaminergic function. In animal models this effect on working memory appears to be mediated by action at the D1 receptor [59]. Dopamine also appears to be critical for a range of other aspects of cognition involving frontal-subcortical circuits, including the temporal coupling of deliberation and execution during decision making, as dopamine replacement reverses the delay specific to decision-related hesitations, independent of motor slowing, in situations requiring decision-making in uncertainty in patients with Parkinson's disease [60].

Another critical role of dopamine has recently become apparent with the development of pathological gambling in the setting of treatment with dopaminergic agonists [61]. This has contributed to a greater understanding of the roles of dopamine in decision making, revealing that dopamine neurons encode the difference between expected and received rewards, and interact with other neurotransmitter systems to regulate such decision making [62•]. The relationship between this effect of dopamine and creativity is also in need of further exploration.

In order to begin to examine how dopaminergic agents might play a regulatory role in the function of distributed networks such as semantic networks, the effect of L-dopa on

functional connectivity during fMRI was examined using a non-priming language task: a word categorization task. An isolated increase in connectivity was observed with L-dopa between the left fusiform gyrus and the receptive language areas, with no other region pairs affected [63]. Since the left fusiform gyrus is considered the visual word form receptive area, this would appear to fit with the effects on priming, as the interaction between this fusiform area (critical for visual word form recognition) and Wernicke's area (critical for processing word meaning) would be essential for priming effects. However, since the predominant target among cortical areas for dopaminergic projecting fibers is the frontal lobe, such an effect of L-dopa on these posterior regions seems unexpected. Subsequent evidence using independent component analysis of fMRI data during language tasks suggests that the posterior effects of L-dopa may be mediated indirectly by the fronto-thalamic connections from the areas containing the frontal projections of the dopaminergic fibers [64]. Subsequent fMRI studies examining the effect of L-dopa during priming revealed changes in region-of-interest (ROI) activation with drug in the dorsal prefrontal cortex, medially and laterally, anterior cingulate, left frontal operculum, and left middle temporal gyrus [65], which also may suggest an indirect frontal-posterior interaction.

Other recent research has suggested a more direct relationship between the dopaminergic system and creativity. Studies examining rate of eyeblink, proposed to be a marker of dopaminergic activity [66], demonstrated an inverted U-shaped relationship between eyeblink rate and creativity as assessed by an alternate uses task (AUT) and the remote associates task (RAT) [67]. Genetic studies demonstrate a relationship between D2 receptor polymorphisms and a composite creativity score as well as performance on verbal creativity, as assessed by object use fluency and sentence fluency from three words [68••]. Catechol-O-methyltransferase (COMT) gene polymorphisms, critical for the metabolism of both norepinephrine and dopamine, have been shown to affect performance on insight-based problem solving [69•]. Additionally, gray matter volume in dopaminergic subcortical regions as well as the right dorsolateral prefrontal cortex were found to be positively associated with divergent thinking performance (fluency for unusual uses and unimaginable things) with voxel-based morphometry using MRI [70], and a negative association in the relationship between thalamic D2 receptor densities and performance on verbal, figural, and numerical fluency tasks with receptor binding studies using positron emission tomography [71]. report of a single case describing changes in artistic behavior with dopaminergic agonists in Parkinson's disease has also been cited as evidence for a relationship between the dopaminergic system and creativity [72]. However, the potential for this pathology having effects on interest in (as well as obsession with) artistic output, as well as potential effects on style in such cases are hard to disentangle from other aspects of creativity [73]. Enhanced performance on several creativity-associated tasks, though, has recently been reported under dopaminergic therapy in Parkinson's disease [74••]. While this array of supportive data for a role for the dopaminergic system in creativity is of interest, the distinction between the roles of the noradrenergic and dopaminergic systems in creativity is in need of further study.

Other systems

The cholinergic system is another neurotransmitter system involved in modulating the signal-to-noise ratio within the cortex by suppressing background intrinsic cortical activity

[75], thus modulating efficiency of cortical processing of sensory or associational information [76]. Studies in rodents demonstrate that acetylcholine is critical for both top-down and bottom-up processing of stimuli, mediated by action on the prefrontal cortex [77]. However, despite clear effects on signal-to-noise ratio in the cortex as well as memory effects [78], effects on the type of unconstrained cognitive flexibility modulated by the noradrenergic system have not yet been demonstrated.

Our understanding of the role of individual neurotransmitter systems in cognition has significantly progressed in recent years. However, these systems do not act in isolation. Complex interactions occur between them, which are only beginning to be understood. For example, action at D2 dopaminergic receptors and at NMDA glutamate receptors appear to interact in their effects on set-shifting [50,79]. Also, as described above, the dopaminergic system appears to preferentially affect intradimensional set-shifting [5•], while the noradrenergic system, specifically by action on the α_1 adrenergic receptor, appears to preferentially modulate performance on extradimensional set-shifting [5•,12]. However, noradrenergic innervation of dopaminergic neurons, by action on α_1 adrenergic receptors, is also known to directly inhibit the activity of the dopaminergic neurons [80]. In addition, the effects of drugs on cognition also depend on location of action when isolated brain regions are studied [81•]. Finally, the mechanism by which the regulatory neurotransmitters act is beginning to be more fully understood, with potential pharmacological approaches targeting these second messenger systems, which are the downstream intracellular pathways that are triggered by the binding of the neurotransmitter at the extracellular receptor [31,82]. These factors will all need to be accounted for in future studies of creativity.

The serotonergic system, with neurons in the dorsal raphe nucleus projecting throughout the forebrain and neocortex, has long been known for its effects on mood and various psychiatric conditions, and is also responsive to stress [83]. However, recent research is revealing that the serotonergic system and its interaction with other neurotransmitter systems serve important cognitive roles as well. Recent evidence suggests that the balance between the serotonergic and dopaminergic systems appears to be critical for processing of reward and punishment [84]. While tryptophan depletion enhances punishment prediction but does not affect reward prediction [85], serotonergic neurons appear to signal reward value [62•]. Furthermore, prefrontal serotonin depletion affects reversal learning, but not set-shifting [86] (Table 1). potential role in creativity is also suggested for the serotonergic system. Performance on figural and numeric creativity tasks has been associated with polymorphisms of the tryptophan hydroxylase gene TPH1 [68••], and both the number solved and the prevalence of use of insight on the compound remote associates task was positively associated with high positive mood [87•], also suggesting a role of the serotonergic system. Furthermore, recent work has suggested that polymorphisms of the serotonin transporter SLC6A4 genotype may impact the effect of psychosocial stressors on performance on 'unconstrained' convergent tasks [88], supporting a role for at least an interaction between the serotonergic system, stress, and creativity-related task performance.

Future Directions

As our understanding of neurotransmitter interactions, localized effects, and other types of neurotransmitters and neuropeptides grows, it will also need to be integrated with our advances in understanding of epigenetic regulatory factors, in order to fully understand how complex phenomena such as creativity are carried out in the brain. Furthermore, the recently reported effects of transcranial direct-current stimulation on creativity task performance [89,90,91] may relate to critical underlying regional neuropharmacological mechanisms. And regional neuropharmacological effects are becoming increasingly important, as evidenced by recent work revealing regulation of maintenance or deviation from previously learned behavioral strategies based on tonic and phasic stimulation of dopaminergic projections specifically to the prefrontal cortex [92], and effects specific to selective large-scale brain networks as monitored moment-by-moment with exposure to aversive video content [93•].

In addition to the patient populations described above where certain aspects of creative performance may be affected, recent evidence has demonstrated relationships between genetic markers for schizophrenia, bipolar disorder, and professional affiliations associated with creativity in large population studies [94•,95•]. Better understanding of modulatory effects on performance on creativity tasks may result in clinical benefits for patients with a wide variety of clinical syndromes. This understanding also may allow for the possibility of optimization of performance, for example, how to overcome effects on cognition induced by stressful situations where creativity may be impaired. Finally, non-pharmacological approaches that are likely related to pharmacological systems will have increasing importance, as several studies have shown positive effects of meditation on performance on creativity tasks [96•]. Additionally, it should also be noted that critical reviews of the older literature on psychedelics and their potential effects on creativity has received recent attention [97], which may become important in future discussion of this topic as we begin to understand their mechanisms.

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HIGHLIGHTS

- While stress is known to affect creativity, the mechanism is still emerging
- Noradrenergic effects on creativity differ from other types of cognitive flexibility
- Dopaminergic effects on creativity appear distinct from noradrenergic effects.

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]

Table 2.

Summary of effects of pharmacological systems associated with creativity

Pharmacological system	Effects
NORADRENERGIC	Beta-adrenergic effects on convergent tasks under stress [8] and in pathological states [26,27], and with challenging tasks[11]
	Beta-adrenergic effects on divergent tasks in pathological states [28]
	COMT gene polymorphisms effect on insight-based problem solving [69]
DOPAMINERGIC	Inverted shaped relationship between eyeblink and the Alternate Uses Task and the Remote Associates Task [67]
	No effect of D2/3 agonists on convergent tasks [56] Beneficial effects on creativity-associated tasks with dopaminergic therapy in pathological states [74]
	D2R polymorphism effect on composite creativity scores and verbal creativity performance [68] COMT gene polymorphisms effect on insight-based problem solving [69]
	Dopaminergic region volume base morphometry correlates with divergent thinking performance [70] PET D2 receptor density related to performance on fluency task [71]