Published in final edited form as:

Semin Pediatr Neurol. 2020 October ; 35: 100834. doi:10.1016/j.spen.2020.100834.

The role of the noradrenergic system in autism spectrum disorders, implications for treatment

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Abstract

Autism spectrum disorder (ASD) is frequently associated with anxiety and hyperarousal. While the pathological changes in the noradrenergic system in ASD are not entirely clear, a number of functional indices of the sympathetic/parasympathetic balance are altered in individuals with ASD, often with a high degree of inter-individual variability. The neuropsychopharmacological effects of α_2 agonists and β -adrenergic antagonists make agents targeting these receptors of particular interest. α_2 agonists have shown beneficial effects for attention deficit hyperactivity disorder (ADHD) and in other domains in individuals with ASD, but effects on core ASD symptoms are less clear. Case series and single dose psychopharmacological challenges suggest that treatment with β -adrenergic antagonists has beneficial effects on language and social domains. Additionally, psychophysiological markers and premorbid anxiety may predict response to these medications. As a result, β -adrenergic antagonists are currently being utilized in a clinical trial for improving core symptoms as well as anxiety in individuals with ASD.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social communication impairments and restricted, repetitive behaviors.¹ Pharmacological intervention can be an important component of treatment for ASD symptoms. However, most currently available agents target psychiatric symptoms associated with ASD. For example, antipsychotic medications target irritability and agitation,² and are the only agents approved by the Food and Drug Administration for ASD. New pharmacological approaches that can impact core symptoms of ASD would represent a significant advance. We will start by reviewing what is known about the impact of the noradrenergic system on cognition, focusing on the effects of targeting α_2 and β -adrenergic receptors and then turn to ASD, reviewing what is known about the noradrenergic system in ASD and then discussing how this might relate to pharmacotherapy in ASD.

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Effects in non-ASD Individuals

Effects of noradrenergic agents on cognition

Norepinephrine is a critical component of the arousal mechanism.^{3–5} The locus coeruleus contains a majority of the noradrenergic neurons in the central nervous system and sends extensive efferents throughout the brain.⁶ The prefrontal cortex, which is believed to be important for various types of cognitive flexibility,^{7–11} has afferent projections to the locus coeruleus in primates.¹² A range of other cognitive effects have also been described with noradrenergic agents, including effects on motor learning,¹³ response inhibition,¹⁴ working memory and emotional memory.¹⁵

α_2 adrenergic agonist effects in non-ASD individuals

In the periphery, α_2 adrenergic agonists inhibit the release of norepinephrine presynaptically, which suggests that they would have a similar effect as the postsynaptic β -adrenergic antagonists. However, α_2 agonists appear to have distinct cognitive effects. High-dose clonidine, an α_2 agonist, has been shown to improve immediate spatial memory in aged monkeys,^{16,17} an effect also found in younger monkeys,¹⁸ and believed to be mediated by action in the prefrontal cortex.¹⁹ Lower doses of clonidine, those that are typically utilized clinically in humans, demonstrate varying results at varying doses, resulting in impaired visual working memory, increased impulsive responses on planning tasks, and varying effects on spatial working memory.^{20,21} Pharmacological stimulation of the postsynaptic α_{2A} subtype of adrenoreceptors enhances the ‘signal’ in the signal-to-noise ratio, resulting in beneficial effects for attention deficit disorder patients.²² However, α_2 agonists do not appear to have the same effect on creative verbal problem-solving as β -adrenergic antagonists,²³ as will be described below.

β -adrenergic antagonist effects in non-ASD individuals

Research involving adolescents with stress-induced cognitive impairment without neurodevelopmental diagnoses demonstrated that treatment with the β -adrenergic antagonist propranolol significantly improved scores on the Scholastic Aptitude Test (SAT).²⁴ This finding suggests a role of the noradrenergic system in stress-related modulation of performance in some types of problem solving in certain individuals. Propranolol has also demonstrated efficacy in stress-induced impairment in performance on other tasks including public speaking in anxiety prone individuals.^{25,26}

Several early explorations into the mechanism of action of this effect utilized verbal problem solving tasks. One of these, the anagram task, had been widely used in studies of anxiety, demonstrating a decrement in performance in anxious subjects,^{27–29} and has furthermore been proposed as a marker of anxiety,³⁰ suggesting its utility in research on the influence of stress. An increase in activity of the noradrenergic system is known to occur in the setting of stress,^{31,32} and situational stressors have been shown to impair performance on other tests of cognitive flexibility.³³ Therefore the anagram task was utilized in studies investigating the effects of noradrenergic agents on network flexibility in verbal problem solving in individuals without a history of neurodevelopmental disorders. Anagram performance was

found to be significantly better after administration of β -adrenergic antagonists (propranolol) than after noradrenergic agonists (ephedrine).³⁴

Follow-up studies demonstrated that noradrenergic modulation of these aspects of cognitive flexibility appears to be mediated by a central mechanism rather than a peripheral mechanism, since performance is significantly better after propranolol (central and peripheral β -adrenergic antagonist) than after nadolol (peripheral-only β -adrenergic antagonist).³⁵ A central-only mechanism would be predicted by the modulatory effect of norepinephrine on the signal-to-noise ratio of neuronal activity within the cortex,³⁶ and the correlation between electronic coupling of noradrenergic neurons in the monkey with proportions of goal-directed versus exploratory behaviors.³⁷

However, in each of these studies involving anagrams, whereas performance on propranolol was significantly better than on ephedrine or nadolol, it did not significantly differ from placebo.^{34,35} Subsequent research demonstrated that propranolol is beneficial for network flexibility in problem solving particularly when the subject is struggling with the problem.³⁸ This might be expected since greater flexibility would be required for such situations where a greater network search is needed, and can actually impair performance when subjects are solving problems with ease.³⁸ However, in patients where noradrenergic activity is upregulated, such as in cocaine withdrawal, propranolol benefits performance on the simplest problems.^{39,40}

Further research that examined the interaction between propranolol and the cognitive effect of stress in individuals without any history of anxiety-related disorders revealed that propranolol reverses the impairment in anagram performance as well as other tasks involving semantic network flexibility under conditions of stress.⁴¹ Propranolol can also benefit performance on verbal problem-solving for the easiest problems in situations where there is a physiological or anatomical alteration of the language network that results in a loss of flexibility (e.g. Broca's aphasia due to stroke).⁴² Therefore, this pharmacology-stress interaction effect on cognition may represent a fundamental aspect of cognition in typical individuals and does not require the presence of an anxiety-related disorder or noradrenergic dysregulation.⁴³

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,⁴⁴ arousal from different sleep phases associated with differing noradrenergic tone,⁴⁵ and vagal nerve stimulation.⁴⁶ Rapid eye movement (REM) sleep, a state associated with decreased noradrenergic activity, enhances integration of weakly associated information for creative problem-solving,^{45,47} and is associated with high levels of spontaneous thought akin to those experienced in waking restful states.⁴⁸ These effects appear to be specific to the noradrenergic system and is not due to general anti-anxiety effects, since such cognitive effects do not appear to occur with non-adrenergic anxiolytics.⁴⁹

While tasks such as anagrams involve a search through a wide network in order to identify a solution ("unconstrained flexibility"), other cognitive flexibility tasks such as the Wisconsin

Cart Sort Test⁵⁰ involve set-shifting between a limited range of options (“constrained flexibility”). These two aspects of flexibility may not be modulated by the noradrenergic system in the same manner, with constrained flexibility possibly benefiting from increased noradrenergic activity.^{37,51} Specifically, as described above, decreased noradrenergic activity appears to benefit tasks such as anagrams when subjects are struggling or challenged by stressors,^{38,41} whereas increased set switching on a two alternative forced choice task is associated with increased noradrenergic tone in primate studies.^{37,51}

‘Constrained’ flexibility can be further divided into intradimensional and extradimensional set-shifting.¹¹ The dopaminergic system appears to affect intradimensional set-shifting,¹¹ while the noradrenergic system, specifically by action on the α_1 receptor, appears to modulate performance on extradimensional set-shifting.^{11,52} β adrenergic receptors in the noradrenergic system appear to modulate the ‘unconstrained’ flexibility.^{34,35,41} A systematic exploration of the effects of the noradrenergic system on intradimensional and extradimensional set-shifting as well as creative problem-solving is needed to better characterize these contrasting effects. Exploration of such comparisons has been initiated in an animal model, revealing no effects of β -adrenergic antagonists on reversal learning, intradimensional set-shifting, or extradimensional set-shifting. However, β -adrenergic show a significant benefit for the rodent required to shift to a highly novel solution in order to obtain reward.⁵³

Whereas the anatomical pathways by which the brain utilizes network flexibility in problem solving, such as in anagrams, are not yet understood, the frontal lobes appear to play a crucial role.^{7–10} In general, frontal brain regions, possibly localized to the dorsolateral prefrontal cortex, may guide the search by selective engagement of the posterior brain regions relevant to the type of problem being solved. Electroencephalographic data is supportive of a strong frontal-posterior network as evidenced by the strong coherence of tracings of such regions during “creative” tasks in various modalities.⁵⁴ Further support for this comes from evidence that right frontal lesions impair strategy shifting ability in patients whereas parietal lesions result in a general visuospatial information processing impairment in patients using a spatial task derived from an unconstrained visuospatial flexibility task, the Matchstick Test of Cognitive Flexibility.^{55,56} Furthermore, the recently reported effects of transcranial direct-current stimulation on frontal regions have demonstrated effects on creativity task performance,^{57–59} which relates to critical underlying regional neuropharmacological mechanisms. However, regional effects within the frontal lobes are important, since relative deactivation is observed in the dorsolateral prefrontal and lateral orbital regions with activation of frontal polar regions during jazz improvisation,⁶⁰ suggesting that it is actually disengagement by the dorsolateral prefrontal cortex that is important. Propranolol might be expected to have a modulatory effect the interactions between these anterior as well as posterior brain regions.

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.⁶¹ A subsequent study demonstrated that β_2 selective agonists enhance working memory in aging animals,⁶² suggesting opposing effects between β_1 and β_2 receptors on working memory, and explaining the lack of effect of the non-specific β -antagonist

propranolol on working memory in previous research.^{63,64} 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 system, cognition, and autism

The noradrenergic system in ASD

Agents that decrease activity of the noradrenergic system have been used for anxiolytic and behavioral purposes in ASD. Early reports indicated benefits in language and social behaviors in a consecutive case series of individuals with ASD treated with β -adrenergic antagonists.⁶⁵ Early reports also indicated benefits with other agents that act on the noradrenergic system. α_2 adrenergic agonists, drugs which act to presynaptically inhibit norepinephrine release, improve hyperactivity, impulsivity, hyperarousal and social relationships in double-blinded placebo-controlled crossover trials in individuals with ASD.^{66,67} In fact, marked improvement in behavior and verbal response has been reported in one case.⁶⁸ A number of researchers have demonstrated findings suggestive of increased noradrenergic activity in ASD, including increased plasma epinephrine and norepinephrine,^{69–70} and altered urinary excretion of various catecholaminergic metabolites.^{71,72} However, there may be a number of alternative explanations for these findings. Subsequent studies demonstrating no abnormalities in basal noradrenergic functioning have led to the suggestion that increased reactivity to clinical procedures such as blood drawing and urine collection in ASD may have led to the earlier atypical findings.⁷³ Furthermore, pathology is not found in the volume, cell counts, or cell density in postmortem tissue from the locus coeruleus in ASD.⁷⁴ Others, though, have proposed that the behavioral effects of fever in ASD⁷⁵ may be related to normalization of a developmentally dysregulated noradrenergic system.⁷⁶

While the nature of neuropathological changes of the noradrenergic system in ASD remain a question, there are a number of other lines of evidence that at least support autonomic dysregulation. For example, development of the autonomic nervous system function, as assessed by respiratory sinus arrhythmia, appears to follow a delayed trajectory in ASD.⁷⁷ Also, autonomic nervous system responses have been proposed as markers for joint attention in ASD,⁷⁸ and individuals with ASD have blunted responses to social evaluative stressors.⁷⁹ Regardless of the ambient activity of the noradrenergic system in ASD, though, other evidence suggests a potential for benefit from noradrenergic blockade in ASD, as will be discussed below.

α_2 adrenergic agonist treatment in ASD

As stated above, early reports suggested improvements in hyperactivity, impulsivity, hyperarousal, and social relationships in small double-blinded placebo-controlled crossover trials of clonidine,^{66–67} and with marked improvement in behavior and verbal response in one reported case.⁶⁸ However, beneficial effects have been primarily observed for ADHD in ASD since these early reports. Subsequent small open label studies of clonidine, widely used for ADHD,^{80–81} demonstrated beneficial effects on sleep as well as attention deficits, hyperactivity, and aggression.⁸² Similar effects on ADHD were also observed for another α_2

agonist, guanfacine, in another small double-blinded placebo-controlled crossover trial.⁸³ The noradrenergic reuptake inhibitor atomoxetine, also widely used for ADHD, has also demonstrated benefit for ADHD in ASD.⁸⁴ However, individuals with ASD and ADHD tend to be less responsive to ADHD treatment than individuals with ADHD without ASD.⁸⁵

β-adrenergic agonist treatment in ASD

Hope for possible targeting of the core aspects of ASD may come from β-adrenergic antagonists. A range of theories have been proposed to account for the core features of autism, including inability to comprehend the perspectives of others (“theory of mind”),⁸⁶ inability to utilize context in understanding the environment (“central coherence”),^{87,88} inability to process emotional information,^{89–92} impaired executive function,^{93–95} and global/local processing biases towards the local,⁹⁶ among others. As a manifestation of decreased utilization of context, research has supported the hypothesis that individuals with ASD have a restriction of flexibility of access to the semantic network, including decreased semantic clustering in verbal memory,⁹⁷ and a failure to utilize syntactic and semantic context when recalling words.^{98–100} False memories can be induced in typically developing individuals by providing semantic and associative relationship in word lists and visuospatial task. Individuals with ASD perform superior on such ‘false memory’ task because they don’t use context.^{101,92,102} Individuals with ASD do utilize semantic information to some extent in memory performance, as is demonstrated by previous research including other ‘false memory’ studies,¹⁰⁶ but not to the same degree as typical subjects. Research using functional connectivity fMRI (fcMRI) has demonstrated a potential neural substrate for such decreased semantic network flexibility by showing a decrease in the interrelation between active brain regions in ASD. This was initially described in fMRI studies performed during sentence comprehension tasks,¹⁰³ in addition to executive function tasks,¹⁰⁴ believed to be related to the under-connectivity between distant cortical regions in ASD.¹⁰⁵

Thus, an agent that could affect the semantic network and other information networks might be of benefit in ASD. Therefore, we examined the effects of pharmacological agents that might impact network flexibility among individuals with ASD. In our early work, we examined the effect of propranolol on network flexibility in high-functioning adults with ASD using simple verbal problem solving tasks. We did not expect individuals without neurodevelopmental diagnoses to benefit.³⁸ Due to their decreased flexibility of access to networks, we expected that individuals with ASD would have a selective performance benefit from propranolol.

As expected, based on our previous examination of the interaction between task difficulty and the effects of propranolol on network access in verbal problem solving,³⁸ our pilot study demonstrated an impairment in performance on these simple anagrams with propranolol in individuals without neurodevelopmental diagnoses. However, as indicated by a significant drug by group interaction, the effect of drug on performance in individuals with ASD was significantly different from controls, with ASD subjects performing better with propranolol on the same task.¹⁰⁷ This finding was present despite no significant difference between groups in age, IQ or overall performance on the anagrams in the placebo condition. Early evidence suggested that propranolol increases functional connectivity in ASD. As

performance in individuals with ASD is believed to be related to the restricted flexibility in the language network in ASD,¹⁰⁹ these fMRI data lend some support to the proposed mechanism of action of propranolol on network access,¹⁰⁸ However, in subsequent studies, propranolol was found to have diverging effects on resting state connectivity within various subregions of the default mode network.¹¹⁰

Subsequent small single dose, double-blind, placebo-controlled crossover psychopharmacological challenge studies revealed improved performance on semantic fluency tasks,¹¹¹ and working memory tasks.¹¹² More recently, these benefits in ASD with propranolol have also been observed in the social domain, including decreased time spending looking at mouths (despite typical time spent looking at eyes in this high functioning population),¹¹³ and improved performance on a structured conversational task.¹¹⁴ Additionally, a subsequent study has revealed that baseline anxiety and psychophysiological markers predict response to propranolol on verbal problem solving in ASD.¹¹⁵ A recent review of the literature has suggested propranolol as a promising agent for emotional, behavioral, and autonomic dysregulation in ASD,¹¹⁶ but randomized controlled trials are still lacking.

As described above, previous work has demonstrated that whereas effects of propranolol on the networks in verbal problem solving can be difficult to detect in individuals without neurodevelopmental diagnoses,^{34,35,38} a beneficial effect of the drug occurs in the setting of a psychosocial stressor,⁴¹ and cocaine withdrawal,⁴⁰ believed to be due to noradrenergic upregulation, also observed in individuals without such stressors when encountering more difficult problems.³⁸ Whereas it is not certain whether norepinephrine is upregulated in ASD,^{69–74} or whether the restriction is more connectomic in nature,¹⁰⁵ our preliminary findings begin to suggest that propranolol also has some benefit for performance of the hyper-restrictive networks proposed by network models of ASD, as is characterized in Figure 1.^{109,117,118} As a result, we are currently performing a double-blind, placebo controlled clinical trial to examine the effect of serial doses of propranolol in ASD, targeting the social domain, and secondarily language and anxiety, while determining whether baseline psychophysiological measures, fcMRI, or baseline anxiety symptomatology predict best responders ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT02871349) Identifier: [NCT02871349](https://clinicaltrials.gov/ct2/show/study?term=NCT02871349)).

Future directions

While the current clinical trial will begin to answer whether propranolol has a possible role in the treatment of core symptoms of ASD, a number of questions will remain. Further research also will need to investigate related noradrenergic or anxiolytic agents for their role in ASD in this setting. Additionally, as the participants in the present trial were sufficiently high functioning to participate in the social and language assessments, it will remain to be determined the potential for benefit from such agents in lower functioning patients. Furthermore, as this agent is already widely used in infants to treat infantile hemangioma,¹¹⁹ this also facilitates the possibility of exploring its effect in a younger patient population during early brain development when neuroplasticity is high. The possibility of combining propranolol with early behavioral interventions may also be a very promising approach.

The potential effects of propranolol on comorbid conditions associated with ASD may also be of interest, given, for example, the alterations observed in sympathetic/parasympathetic balance and stress reactivity associated with gastrointestinal symptomatology in ASD.^{120,121} Finally, the role of this class of agents in managing aggressive behaviors warrants further exploration, for patients with whom this is an issue, as benefits have been suggested in other patient populations,^{122–125} and previous findings have suggested that this may extend to ASD patients.^{65,126} The potential for helping to manage behaviors while minimizing the adverse effects that are associated with other medications currently utilized in this setting is promising. A trial to investigate this aspect has recently been funded and is currently being planned by other investigators.

Acknowledgements:

This research was funded by NINDS (K23 NS43222-Beversdorf) and a pilot grant from NAAR (National Alliance for Autism Research), HRSA (1R40MC19926), DOD (AR150091)

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BASELINE **PROPRANOLOL** **Figure 1.**

Theoretical proposed representation of the signal-to-noise in the cortical networks as affected by propranolol, based upon the findings of Hasselmo et al⁵¹ on the effects of norpinephrine in the cortex. Black arrows indicate a greater response to the most dominant signal input, such as representation of an attended stimulus. White arrows indicate the response to non-dominant signal input, such as intrinsic or associative fiber inputs, the 'noise' in the model. In many circumstances, it is optimal to respond rapidly to the dominant signal (top). However, in some cases, such as in solving a challenging problem, access to the

‘noise’ may be essential. Therefore, a relative suppression of the dominant signal and relatively enhanced access to the ‘noise’ that is believed to occur with propranolol (bottom),^{109, 117, 118} can benefit individuals solving such problems. This is proposed to be how problems without an immediately accessible answer may be solved more readily in this condition. Additionally, this may represent how patient populations with impaired flexibility of network access, such as individuals with ASD for social communication functioning, may have a greater beneficial response.

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