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Biological Psychiatry

Neurobiological Insights Into Stress-Induced Attention Deficit

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At the start of the COVID-19 quarantine I found myself in the unenviable position of having to shut down my research. I told myself I would make the most of it by tackling my backlog of writing and data analysis. I imagined myself holed up in my home typing away as I powered through my to-do list. This ideal plan did not come to pass. Instead, I found myself distracted and uninspired, too preoccupied with the challenges our world was facing to do my best work.

Attention is a core executive function vital for navigating a complex world. In times of stress and turmoil, attentional control can become disrupted, hindering an individual's ability to function. This disruption, also referred to as an attention deficit, is a hallmark trait of several neurological conditions such as attention-deficit/hyperactivity disorder (ADHD). Despite the prominent importance of attentional ability, much is still unknown about how stress impacts the neural circuits of attention. Narrowing gaps in the current understanding of attentional control, Eck *et al.* (1) discovered that stress-induced attention deficits are linked with distinct neurobiological and molecular changes in major cortical regions.

In the current issue of *Biological Psychiatry*, Eck *et al.* (1) investigated the role of stress on the attention system in adult male and female rats. Variable stressors were administered via a daily episode of restraint, predator odor, or forced swim stressors for a total of 6 days. Control rats received comparable handling. Attention was evaluated via a sustained attention task that was designed for rats to learn to distinguish between signal trials, when a signal light indicated the availability of food reward versus nonsignal conditions (Figure 1). The sustained attention task was administered 30 minutes after the cessation of variable stress (or control handling) across all 6 days of experimentation.

Exposure to variable stressors impaired attention in both male and female rats. This fits within a larger body of literature demonstrating that stress impairs a wide array of executive functions. The authors performed several experiments to investigate how stress impacts neural functions of attention. They focused their investigation on the nucleus basalis of Meynert (NBM), which promotes attention through the activity of cholinergic neurons (1). The authors examined RNA expression of genes known to be associated with attention. Most excitingly they found that stressed males and females had a significant increase in *Dusp1* expression. DUSP1 is a phosphatase that induces dendritic hypertrophy. Increased cortical expression of *Dusp1* has been found in rodent models of ADHD (2). More broadly, differential expression of transcripts in the *Dusp* family have also been linked to depression and anxiety (3) and are an exciting new target for novel pharmaceuticals. While increased *Dusp1* expression is traditionally associated with hypertrophy of dopaminergic neurons, its role in the regulation of cholinergic neurons has yet to be investigated. The authors examined stress-induced changes in dendritic branching of cholinergic neurons in NBM and found increased length and complexity for both sexes. Taken together, these findings provide compelling evidence for an investigation into the relationship between DUSP1 and cholinergic hypertrophy. Further research into this relationship may also hold valuable information for researchers linking *Dusp* activity and anxiety behavior.

Although stressed male and female rats showed overall attention deficits, there were subtle sex differences on individual days. Notably, on the sixth day of testing stressed females no longer showed attention deficits while stressed males continued to have poor performance. This finding suggests that there may be sex differences in the effects of acute versus chronic stress on attention. This hypothesis is particularly compelling in light of findings at the neural circuit level and complements other research finding stronger negative impacts of stress on certain executive functions in males than in females (4,5).

The NBM has strong projections to the prefrontal cortex (PFC), which enhances attention through acetylcholine binding to nicotinic receptors (6). When examining performance of this pathway in stressed rats, the authors found decreased acetylcholine output in stressed males only, matching their impaired attention. This projection showed no change from baseline in females, running contrary to their overall attention deficits. However, this measure was taken after the sixth day of stress, when stressed females show improved attention. It is possible that neuroadaptation in females rescued NBM to PFC acetylcholine release by this time point. Another option is that because control females have lower baseline levels of acetylcholine activity, a floor effect occurred, preventing stress from lowering output any further. In nonstressed rats, Eck *et al.* (1) discovered that males have a higher baseline acetylcholine release than females. There are no sex differences in baseline attention, and therefore it is likely that further sex differences, such as increased nicotinic receptor density, may compensate for the decrease in cholinergic input in females. This is an interesting finding because it highlights sex differences in a neural mechanism of attention both at baseline and in reaction to stress. Attention encompasses many important aspects of behavior; understanding the neural mechanism for attention in both males and females can provide a wealth of valuable knowledge when trying to understand both neurotypical and neurodiverse behavior.

The findings outlined are interesting not only from a perspective of stress response and attention but also for a

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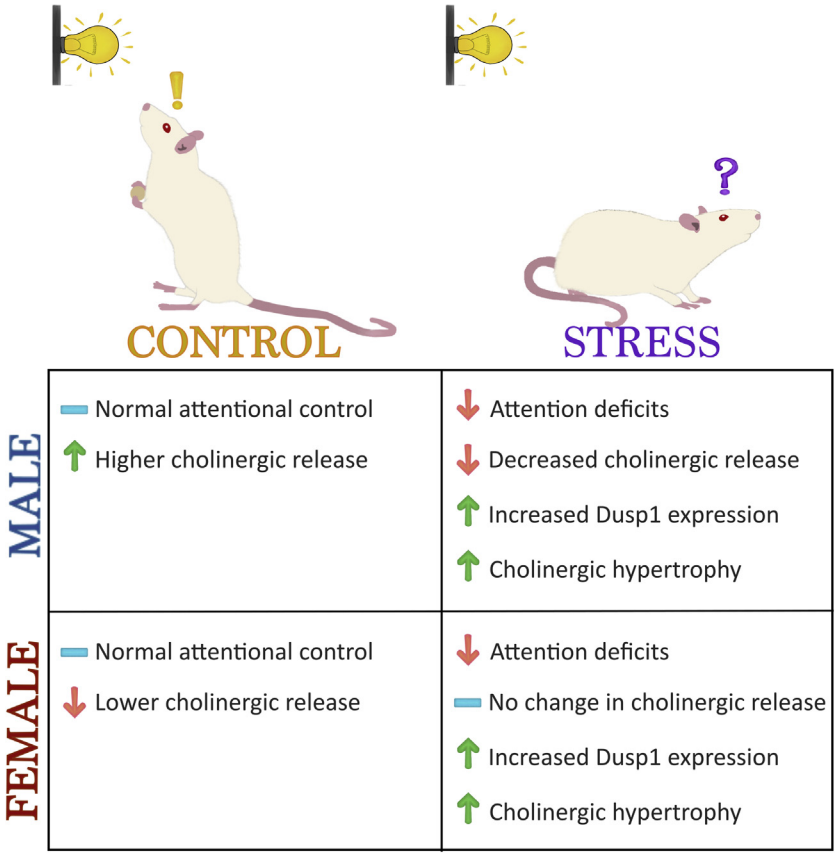

Figure 1. Stress impairs attentional control in both male and female rats while altering cortical functions in a sex-dependent manner. Eck *et al.* (1) showed that variable stress reduced performance in a sustained attention test for both male and female rats. *Dusp1* expression and hypertrophy of cholinergic dendrites were found in the nucleus basalis of Meynert for both sexes. Eck *et al.* (1) showed stress-dependent sex differences in cholinergic release from neurons projecting from the nucleus basalis of Meynert to the prefrontal cortex. Under baseline conditions, males showed higher acetylcholine release, while exposure to stress decreased release from this pathway for males only. These results show a clear negative impact of stress on attention both at the behavioral and neurological levels, and the authors also introduced interesting and important sex differences in a cholinergic pathway of attention.

better understanding of the role of the cholinergic system in ADHD. Genetic variability in *Dusp1* is associated with ADHD in humans (7), and cortical upregulation of *Dusp1* is found in rodent models of ADHD (2). Because of the prominent role the dopamine system plays in ADHD, previous work has focused on the relationship between *Dusp1* and hypertrophy of the dopamine system. Eck *et al.*'s findings (1) give cause for investigation into the relationship between Dusp1 and cholinergic neurons as well. The MBN is one of the most prominent sites of acetylcholine production and projection in the forebrain (8), a system linked to ADHD. Sparked by the relationship between nicotine consumption and the reduction of ADHD symptomatology, researchers have found nicotinic receptor agonists to have modest clinical benefits (9). While these results have not produced pharmaceutical interventions with the same efficacy as stimulant-based therapies, they do provide additional evidence clearly linking attention modulation and the cholinergic system.

ADHD is classified into 3 major subgroups: hyperactive/impulsive, inattentive, and combined. Females are more likely to be diagnosed with inattentive type ADHD than males (10), suggesting that there could be neurological sex differences contributing to how ADHD manifests behaviorally. The cholinergic system presents itself as an interesting point to consider in this context. Acetylcholine binds to both nicotinic and muscarinic receptors in the PFC. Activation of nicotinic receptors improves attention while activation of muscarinic receptors increases impulsive behaviors (6). Eck *et al.* (1) showed that male rats have higher acetylcholine release from the NBM to the PFC. While the sex difference in this projection was not associated with a difference in baseline attentional performance in a neurotypical rat brain, it may interact differently with other neurological phenotypes associated with ADHD. Findings also showed that stress decreased cholinergic activity in males but not females. As ADHD is often coupled with increased anxiety and is frequently comorbid with anxiety disorders (10), the study of circuit function under stress conditions can also lead to valuable insights into ADHD neurofunction. Understanding how sex differences in this system under control and stress conditions could provide key insights into mechanisms contributing to diversity in phenotypes observed with ADHD. Building off Eck *et al.*'s discovery, further investigation into nicotinic versus muscarinic receptor cell types in the PFC, coupled with mapping of NBM cholinergic projections onto the two receptor types, would be invaluable to our continued research into potential mechanisms of sex differences in ADHD.

Eck *et al.* (1) show a clear negative impact of stress on attention. They also observed the intriguing possibility of sex differences during acute versus chronic stress, with females showing attentional recovery by the end of testing. This fits into a larger body of emerging literature linking stronger negative

impacts of stress on executive functions in males. Stress-induced upregulation of *Dusp1* in the NBM coupled with growth in cholinergic dendrites highlights a need for research into the function of DUSP1 in cholinergic neurons. Empirical evidence of DUSP1-induced hypertrophy in cholinergic neurons would suggest new roles of the cholinergic system in the presentation of DUSP-related neural conditions. Investigation into NBM to PFC projecting cholinergic neurons revealed higher output at baseline in males, coupled with a stress-triggered decreased in male output. The sex-dependent activity of this circuit, in both control and stressed rats, warrants further investigation into the information of continuing circuits of attentional control, particularly via activity at nicotinic versus muscarinic receptors. Given that the cholinergic system is a modulator of both attention and impulsion, sex differences in this pathway may contribute to the differentiation of ADHD subtypes.

When faced with stressful conditions such as a pandemic, many of us will experience deficits in attentional control. The findings by Eck *et al.* (1) provide insights into the real physical changes that stress induces in the brain. A better understanding of these neurological responses adds insight that may help us all adapt more quickly to the next challenge that comes our way.

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