Commentary

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Locus Coeruleus Hyperactivity in Posttraumatic Stress Disorder: Answers and Questions

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The demonstration of locus coeruleus (LC) hyperactivity in individuals diagnosed with posttraumatic stress disorder (PTSD) is causing us to have flashbacks to an earlier era in PTSD research. By the 1980s, it seemed clear that inescapable stress produced effects in rodents that resembled aspects of PTSD and that these effects were somehow related to noradrenergic, particularly LC, hyperactivity (1). Furthermore, in nonhuman primates, fear-inducing stimuli activated the LC, while electrical or pharmacological activation of the LC increased the display of behaviors that resembled PTSD (2). Later, LC hyperactivity in PTSD patients was suggested by evidence of increased cerebrospinal fluid noradrenaline levels. As illustrated in Figure 1, LC neurons suppress each other via postsynaptic α_2 adrenergic receptors. Upon blockade of these receptors by yohimbine, PTSD patients experienced worsening of PTSD symptoms, including flashbacks, as well as metabolic suppression of prefrontal cortex that was suggestive of LC activation. Together this work pointed toward deficits in collateral inhibition of LC neurons mediated by deficits in α_2 adrenergic receptor function (3). More recently, reductions in norepinephrine transporters in the LC in PTSD patients (Figure 1) that might enhance the half-life of released norepinephrine provided a potentially synergistic mechanism for noradrenergic hyperactivity in PTSD (4). However, until now, we lacked direct evidence of LC hyperactivity in PTSD.

In an elegant study involving simultaneous functional magnetic resonance imaging (fMRI), pupilometry, and peripheral psychophysiological assessments, Naegeli *et al.* (5) provide the first direct evidence of LC hyperactivity in PTSD patients. Compared with people exposed to extremely stressful situations who did not develop PTSD symptoms, individuals with PTSD responded to blasts of loud noise with increased autonomic arousal, as reflected by tachycardia, increased skin conductance, and pupillary dilation; exaggerated startle response, as reflected by the number of eyeblinks; and hyperactivation of the LC and other structures. The LC is a challenging brain region to study with fMRI. It is a small structure that lies in the pons at the base of the fourth ventricle. It presents imagers with challenges related to establishing the appropriate anatomical boundaries, pulsatile artifact, and handling of tissue/ventricle contrast.

In this study, the role of the LC in mobilizing the heightened reactivity of neural systems to loud noise was less clear. LC hyperactivity did not correlate with PTSD symptoms or the intensity of elicited autonomic or startle responses. Instead, the magnitude of activation of the caudal dorsal premotor cortex and supplementary motor area was associated with autonomic reactivity and PTSD symptom severity. These regions receive dense input from the LC, but so do many other brain regions that did not differentially activate in the PTSD patients in this study. Thus, the role of the LC and other arousal- or fear-related regions, such as the amygdala, in the reported associations of regional brain activity with symptoms remains unclear.

Why were the LC and amygdala so weakly associated with PTSD symptoms? It is possible that these regions are permissive of but do not contribute directly to PTSD symptoms. This might be the case if LC activation mobilized attention or preparation for action. Other brain regions, including the lateral hypothalamus, may recruit autonomic arousal independent of the LC and downstream of the amygdala. However, the lack of involvement of LC in PTSD symptoms does not seem to be consistent with the effects of yohimbine in PTSD patients and the effects of LC stimulation on fear behaviors in primates. It is also possible that the nature of LC reactivity in the PTSD and non-PTSD populations reduced the statistical power to demonstrate this association. The authors note that although both PTSD and non-PTSD subjects found the noises similarly intense and unpleasant, LC activity increased only after loud noise in the PTSD subjects; thus, only half of the sample had enough variance in LC activity to generate the association with symptoms.

Why was LC activity increased by the loud noises only in PTSD patients? One possibility is that deficits in collateral inhibition in LC make it more prone to activation. Alternatively, as illustrated in Figure 1, "sensitization" of glutamatergic inputs to the LC, which come principally from the reticular activating system (nucleus paragigantocellularis), amygdala, and cortex, could also promote LC activation (6). Other differences between the PTSD and non-PTSD groups may have contributed to the findings. For example, the PTSD group had more subjects with childhood stressors than did the non-PTSD group, raising questions about the developmental impact of trauma with regard to LC hyperactivity. It is also possible that the PTSD patients were smoking more and consuming more alcohol and were more likely to be in a mild withdrawal state that might also have contributed to LC hyperactivity.

However, from a psychological perspective, one might speculate that everyone in the study found the loud noises unpleasant, but perhaps only the PTSD subjects found them threatening. LC activation may have reflected the perception of threat rather than the sensory aspects of the noise. In this regard, the testing context may have been an important contributor to the findings. While few people look forward to

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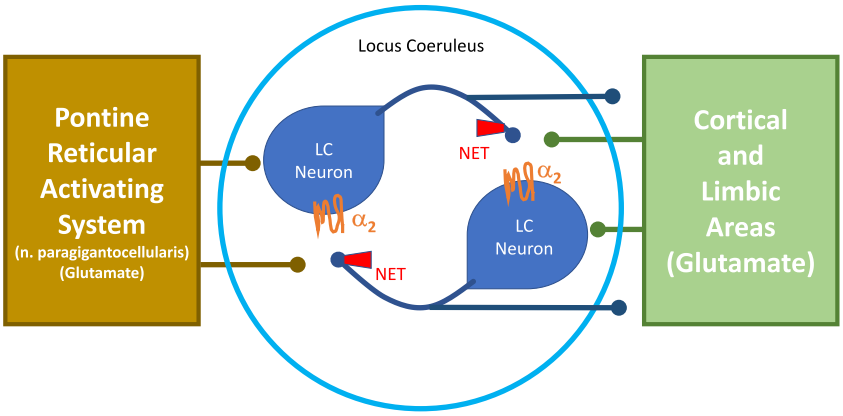

Figure 1. A depiction of mechanisms that might contribute to locus coeruleus (LC) hyperactivity in posttraumatic stress disorder. Within the LC, downregulation of α_2 adrenoceptors might reduce collateral inhibition within the LC, disinhibiting LC neurons and rendering them more reactive to excitatory input. Downregulation of norepinephrine transporters (NETs) also might prolong the half-life of synaptic norepinephrine, increasing the efficacy of noradrenergic neurotransmission. Sensitization of excitatory drive to the LC might arise through enhancement of glutamate synaptic efficacy from "bottom up" inputs to the LC, including the nucleus paragigantocellularis of the reticular activating system as well as "top down" inputs to the LC from the amygdala and cortex (references in the text).

the claustrophobic conditions of the fMRI test environment, these conditions may be particularly difficult for some traumatized people. This study did not describe adapting subjects to the test environment before testing, and therefore differential reactivity to the testing context may have influenced the findings of this study. For example, people with PTSD may not show increased baseline startle but they may exhibit increased startle when they believe the context is threatening (7). Furthermore, darkness, a common condition for fMRI testing, activates startle in people exposed to trauma regardless of whether they have PTSD symptoms (8). In the study by Naegeli *et al.* (5), all subjects had been exposed to trauma. The presence of a nonstressed group might have helped distinguish the consequences of stress from the impact of the presence of PTSD.

This study reactivates long-standing questions about the role and relative prominence of various nodes in fear and arousal circuits in PTSD symptoms. Do noradrenergic inputs into the amygdala help to recruit its involvement in PTSD symptoms? Alternatively, does activation of the amygdala recruit LC hyperactivity in PTSD? How important are regions implicated in establishing emotional context, such as the nucleus tractus solitarius and the anterior hippocampus (ventral hippocampus in animals) as moderators of the interplay of amygdala and LC? Furthermore, how important are cortical regions implicated in inhibiting fear responses or reappraising unpleasant but not dangerous stimuli? Some of these questions might be explored through future analyses of the fMRI data collected in this study. Answering other questions will require further investigation.

Is LC hyperactivity in the context of loud noise a useful biomarker for PTSD? The answer to this question is usually another question, "To what end"? From a diagnostic perspective, one would want to know whether LC activation was more useful than the increase in heart rate after exposure to reminders of the trauma, which was particularly good at identifying PTSD patients with re-experiencing, depression, and guilt (9). Also, one would want to compare it to startle as a diagnostic biomarker. As suggested by the studies cited above, many contextual factors influence startle amplitude in PTSD patients, making it an unstable assessment across subjects and settings. Furthermore, at high level of fear, the fear enhancement of the startle response is suppressed (10), and the nonlinearity of the startle response may reduce its utility as a diagnostic biomarker.

However, LC hyperactivity may have some utility as a biomarker for particular pharmacologic interventions from a precision medicine perspective. Specifically, the presence of LC hyperactivity in the context of loud noise might suggest that antiadrenergic medications would be useful treatments for arousal-related symptoms of PTSD (3). To the limited extent that they have been studied in randomized trials, antagonists of β-adrenergic receptors and agonists of α_2 adrenergic receptors do not appear to be effective preventive or therapeutic interventions for PTSD. In contrast, some data support the efficacy of α_1 receptor antagonists for nightmares and arousal symptoms of PTSD. In this case, LC hyperactivity might indicate the need for antiadrenergic treatment but it might not be an optimal measure of clinical change. This view would be consistent with the lack of correlation between LC activation and symptom severity in the current study. Furthermore, α_1 receptor antagonists appear to act at targets outside the LC, such as the spinal cord or cortex. Other biomarkers might be needed to provide an index of these effects.

In summary, after more than 30 years of discussion, we finally have direct evidence of LC hyperactivity in PTSD. This is an important new beginning for studies of the role of adrenergic hyperactivity in the neurobiology, prevention, and treatment of PTSD.

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