Commentary

Biological Psychiatry

The Complicated Relationship of Stress and Prefrontal Cortex

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The prefrontal cortex (PFC) is an integral component of stress-responsive circuitry and may coordinate high order adaptive responses to repeated exposure to stress (1). Accordingly, PFC dysfunction has been implicated in psychiatric disorders with symptoms that are manifested or exacerbated by stress (1,2).

A fundamental function of the PFC is to use representation to modify or "guide" behavior (3). Therefore, while the PFC may not be necessary for performing automatic or habitual behavioral responses to stress, it may be critical when the organism, by bringing online a representation, selects an optimal behavior in response to stressful events. Given this, how the PFC reacts and subsequently adapts to stressors is key to understanding its role in organizing behavior under stress. Recordings from rodent PFC neurons during stress exposure reveal that 1) an acute novel stressor may interfere with PFC function by activating the majority of its neurons (4) and thereby "over-engaging" the PFC so that it may not have the flexibility to provide sufficient influence for optimal or nonhabitual behaviors, and that 2) under normal circumstances, PFC neurons adapt quickly (or become less reactive) to repeated stress (Figure 1). This may potentially allow the organism to gain back behavioral flexibility despite exposure to stress. In vulnerable (or pathological) circumstances, this plastic function of the PFC may be disrupted, leading to a modified mode of stress reactivity in PFC neurons. Such dysfunctional reactions to stress may compromise the ability of the PFC to guide selection of an optimal behavioral response.

Although behavioral studies have long established that acute stress impairs cognitive functions that are dependent on the functional integrity of the PFC (1), mechanistic information about adaptive molecular and cellular responses of the PFC in response to stress are only recently beginning to emerge. Two articles in this issue of *Biological Psychiatry* (5,6) provide novel and mechanistically important information about distinct neuronal systems that may play a role in PFC adaptive responses to stress.

Uribe-Mariño *et al.* (5) describe a role for corticotropin-releasing factor, working through corticotropin-releasing factor receptor 1, in modulating PFC function hours after the first exposure to stress. They report that the cognitive impairment observed 6 to 8 hours after stress exposure can be reversed by intra-PFC corticotropin-releasing factor receptor 1 deletion or mimicked by intra-PFC corticotropin-releasing factor application. The time course of this effect (i.e., several hours after cessation of stress) is important because it can provide us with clues about poststress plasticity that may be critical for adaptive behavior. Along these lines, the authors report that the signaling pathway for this effect involves protein kinase A and cyclic adenosine monophosphate response element binding protein (CREB) phosphorylation. These findings complement other reports of corticotropin-releasing factor receptor 1– and monoamine-dependent (i.e., serotonin and dopamine) changes in protein kinase A and protein kinase C activity in the PFC in response to chronic stress (7), and therefore suggest that stress-induced plasticity may, in part, involve multiple neuromodulators in the PFC that converge onto the same signaling pathways.

McKlveen *et al.* (6) report that repeated stress produces a shift in the balance between excitatory and inhibitory neuronal responses, favoring inhibition of PFC projection neurons. Their data provide strong evidence that a glucocorticoid receptor–mediated mechanism increases gamma-aminobutyric acid release, which in turn reduces the activity of PFC glutamatergic afferents. The same stress paradigm produced cognitive deficits, suggesting a relationship between the increased inhibitory tone and PFC-mediated executive functions. This is an important observation, because an imbalance in excitatory-inhibitory cortical networks has been implicated in the etiology and expression of many psychiatric disorders (8). In addition, while these findings were mostly in vitro, they are consistent with recent electrophysiology studies in behaving animals performing a similar task under anxiety (9). In this recently published study, reduced activity of PFC pyramidal neurons also was observed, and reduced encoding of task events by these neurons was associated with impaired behavioral flexibility. Based on the findings of McKlveen *et al.*, an increase in synaptic inhibition in the PFC may have been critical for disrupted PFC neuron encoding of behavioral events reported by Park *et al.* (9).

A caveat with both studies—generalizable to most animal studies—is the experimental distinction made between acute and chronic stress paradigms. Uribe-Mariño *et al.* used a paradigm that involved measures made hours after the first exposure to stress. This may not test response to an "acute" stress per se but may primarily test the potential pattern of plasticity that is critical for the PFC to adapt to acute stress. McKlveen *et al.*, on the other hand, studied the impact of "chronic" stress (a commonly used 14-day variable stress), but at least some of the observed molecular or cellular changes they report after the 14-day exposure could have occurred within hours after exposure to the initial stressors. In fact, PFC neurons appear to exhibit remarkably rapid plasticity to stress because exposure to the same stressor, just a few hours later, leads to a significantly decreased response from the same neurons (Figure 1) (4). This pattern of plasticity also is evident when measuring glutamate efflux in the PFC, in that exposure to the same stressor a few hours later produced significantly smaller effects on glutamate release in the PFC but not in the hippocampus (10). Given this, the molecular machinery that is

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http://dx.doi.org/10.1016/j.biopsych.2016.09.008
Biological Psychiatry November 15, 2016; 80:728–729 www.sobp.org/journal
ISSN: 0006-3223

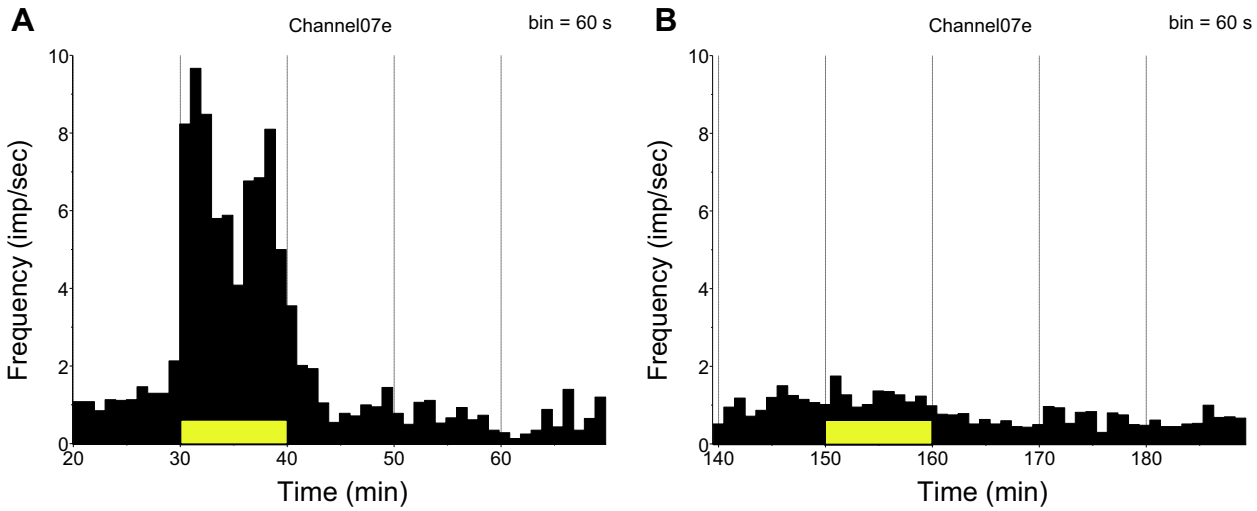

Figure 1. **(A)** Response of a single medial prefrontal cortex neuron during the first exposure to 10 minutes of novel restraint stress (yellow bar). About 40% of prefrontal cortex neurons show phasic responses to novel stress. **(B)** Response of the same neuron to the second exposure to restraint stress 2 hours later. imp, impulse. [Adapted from Jackson and Moghaddam (4).]

activated in the PFC after the first exposure to stress, such as that reported by Uribe-Mariño *et al.* (5), may be eventually critical for the cellular and neuronal network level changes observed by McKlveen *et al.* (6).

During novel stress exposure, PFC function may be transiently affected because the stressor overengages the PFC neurons. This is most likely a good thing, because it offers organisms the maximum capacity to support the behavioral choices needed to deal with a stressful or threatening stimulus. However, the PFC rapidly adapts so that it is no longer activated robustly in response to the same stressor. This may be because the organism has learned that the stimulus has no adverse outcome and will not require behavioral flexibility, or that the profound activation of the PFC during the first exposure to that stress has strengthened the synapses that support the optimal behavior. In a pathological state, a failure of the PFC to adapt normally to stress may compromise its ability to engage sufficiently to plan the optimal behavior. This would lead to response perseveration, coping failure, exaggerated or understated behavioral responses, and reduced flexibility of PFC neurons to respond to shifting contingencies. Building on the findings reported by Uribe-Mariño *et al.* (5) and McKlveen *et al.* (6), a key question for future research is which of the mechanisms they identify in the PFC play a critical role for optimal behavioral adaptation to stress, and which go awry in pathological conditions.

Acknowledgments and Disclosures

The author reports no biomedical financial interests or potential conflicts of interest.

Article Information

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Received Sep 13, 2016; accepted Sep 13, 2016.

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