Presentation Abstract

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Presentation Title:	Effects of stress on aversive learning require temporally precise serotonergic signaling
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Abstract:	Serotonin (5-HT) is implicated in affective control, and dysregulation of serotonergic systems is associated with stress-related affective disorders such as anxiety and depression. Multiple lines of evidence suggest that the serotonergic dorsal raphe nucleus (DRN) is critical for mediating the impact of stress on aversive processing. Although emotionally-relevant sensorimotor events occur over durations spanning milliseconds to minutes, previously used methods for silencing 5-HT activity operate over much longer timescales (hours to permanently). Thus, the causal relationship between sensorimotor events during aversive processing and the relevant timescales over which 5-HT activity mediates the impact of stress is unclear. To address these issues, we used temporally precise optogenetic silencing tools to examine the role of DRN 5-HT in stress-induced enhancement of auditory fear conditioning in which the tone-footshock contingency was reduced to 50%. This enabled silencing of DRN 5-HT activity on a timescale that was time-locked to the presentation of paired or unpaired tones and footshocks. Initial experiments indicated that immobilization stress led to enhanced conditional freezing during the tone test; this effect was observed only when stress preceded fear conditioning and not when it occurred after acquisition. Additional studies suggested that the stress-induced enhancement of fear learning depended on DRN activation as intra-DRN infusion of

a nonselective corticotropin-releasing factor receptor antagonist prior to, but not immediately after, acquisition blocked stress enhancement of freezing. We then selectively targeted Arch, a green-yellow light-driven silencing opsin, to 5-HT neurons by delivering a Cre-inducible adeno-associated virus carrying a reversed and double-floxed transgene encoding Arch-GFP into the DRN of SERT-Cre mice. Loose cell-attached in vivo recordings of 5-HT neurons revealed that these neurons were rapidly silenced during the delivery of green light (532 nm) to the DRN. Arch-mediated silencing of DRN 5-HT during unpaired tone presentations did not affect the ability of prior stress to enhance fear responding to the tone the next day. In contrast, when optical silencing of DRN 5-HT activity was restricted to tones paired with shocks, stress enhancement of the conditioned fear response was blocked. Silencing DRN 5-HT activity in either condition had no effect on freezing levels in Arch-GFP mice not exposed to stress. Our data suggest that DRN 5-HT mediates the effects of prior stressful experiences on aversive learning by augmenting the impact of specific, temporally delimited, sensory events.

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