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Basomedial amygdala mediates top-down control of anxiety and fear.

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This paper represents an elegant, thorough and very careful examination of anatomical and physiological connectivity between the medial prefrontal cortex and the amygdala, connections known to be involved in the regulation of anxiety and fear behaviors. Using very discrete injections of viral vectors, the authors demonstrate convincingly that the ventromedial prefrontal cortex (comprising the infralimbic and dorsal peduncular cortical nuclei) projects directly and predominantly to the basomedial amygdalar nucleus (BMA), in addition to hypothalamic targets. In carefully controlled experiments, targeted optogenetic activation of the (glutamatergic -- they used a CAMKII promoter to restrict expression of the opsins to pyramidal cells) vmPFC projection to the BMA results in anxiolytic responses, seen in reduced avoidance of open spaces in the elevated plus maze (EPM) and open field tests, and reduced respiratory rates in anxiogenic settings such as in the open field. Similar behavioral changes were seen with activation of cell bodies in the vmPFC and of vmPFC terminals in the BMA. Conversely, optogenetic inhibition of vmPFC resulted in increased avoidance of open spaces, and increased respiration in anxiogenic settings. These effects were specific to vmPFC, and not generalizable to all mPFC.

They next demonstrated that activation of vmPFC and dmPFC respectively promoted and suppressed extinction learning in conditioned fear paradigms. Anatomical and physiological tracing experiments demonstrated that the vmPFC projected strongly to the BMA, avoiding the BLA, while dmPFC projections strongly projected to the BLA, avoiding the BMA. Physiological recordings in BMA indicated that glutamatergic vmPFC fibers innervate and excite both pyramidal cells and interneurons, and the interneurons appear to innervate the BMA pyramidal cells in an apparently feedforward manner. Conversely, dmPFC excites neurons in the BLA and the nearby intercalated (GABAergic) neurons.

They then targeted BMA-projecting vmPFC cells with a cre-expressing, retrogradely transported (canine adenovirus) virus, and injected an AAV expressing and cre-dependent excitatory opsin into the vmPFC to selectively induce channelrhodopsin in BMA-projecting vmPFC neurons. Under these conditions, photoactivation of the vmPFC resulted in a reduced freezing behavior and facilitated extinction. Next, in vivo recordings of BMA neurons in behaving animals demonstrated that they increased their firing rates during behaviors associated with overcoming fears (i.e., during exploration of the open arm of the EPM or when spending time in a lit compartment instead of in the connected darkened compartment.

Consistent with all this, opsin-mediated activation of BMA neurons resulted in anxiolytic behaviors such as decreased avoidance of open arms in the EPM, and reduced freezing in a cued fear paradigm, while inhibition of the BMA was anxiogenic in the open field test. Finally, the anxiogenic actions of chronic corticosterone on behavior could be reversed by acute stimulation of the vmPFC pathway.

The authors conclude that the BMA is a direct target of the vmPFC projections and that activation of this pathway is necessary and sufficient for anxiolysis, that BMA activity suppresses freezing and elevated-anxiety states; conversely, the ITC cells are mainly innervated by projections from the dmPFC. Because only specific vmPFC projections to the BMA are responsible for these actions, while massed stimulation of the entire vmPFC did not, they conclude that only a subpopulation of the vmPFC neurons are responsible for this action. Interestingly, the direct activation of the BMA results in increased fear extinction, this did not persist, whereas vmPFC stimulation of BMA results in stably increased extinction. This and other lines of evidence indicate that plasticity of the vmPFC projection is key to lasting extinction learning.

Overall, this is a breathtaking report, with many complementary, carefully executed methods applied to examine numerous alternative hypotheses related to their central hypothesis.

Disclosures
None declared

Abstract:

ABSTRACT

understanding of the cognitive regulation of affect, and provide pathways for intervention. Previous studies have suggested that dorsal and ventral mPFC subregions exert opposing effects on fear, as do... more »
subregions of other structures. However, precise causal targets for top-down connections among these diverse possibilities have not been established. Here we show that the basomedial amygdala (BMA) represents the major target of ventral mPFC in amygdala in mice. Moreover, BMA neurons differentiate safe and aversive environments, and BMA activation decreases fear-related freezing and high-anxiety states. Lastly, we show that the ventral mPFC-BMA projection implements top-down control of anxiety state and learned freezing, both at baseline and in stress-induced anxiety, defining a broadly relevant new top-down behavioural regulation pathway.
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