Identifying the neural correlates of fear generalization during development

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Anxiety disorders, as a group, are the most common mental illnesses in the US, affecting about 25% of adolescents and 18% of adults. Symptoms typically begin in childhood or adolescence. Fear generalization, a defining feature of anxiety disorders, in which conditioned fear responses generalize to related stimuli, leads to maladaptive responses in a safe environment. A crucial gap in studies of anxiety is the lack of data on the neural correlates of fear generalization during development. This project will focus on studying the neural correlates of fear generalization during development using cutting edge techniques (whole-brain imaging and optogenetic techniques). In this project, I will investigate how fear generalization develops from early to late adolescence (**Aim 1**), assess the specific contribution of the dentate gyrus (DG), a subregion of the hippocampus (HPC), in mediating fear generalization behavior during mid-adolescence (P35) (**Aim 2**), and determine the whole-brain neural ensembles underlying fear generalization during sensitive developmental periods (**Aim 3**). In **Aim 1a,** I will use a contextual fear discrimination (CFD) task to assess fear generalization starting at early (P29), mid (P35), and late adolescence (P40) in order to understand when fear generalization behavior develops across adolescence. In **Aim 1b**, in order to distinguish between contextual and fear components, I will administer a radial arm maze (RAM) to asses contextual discrimination in mice at all ages as described in **Aim 1a**. In **Aim 2**, the individual DG neurons corresponding to an individual fear memory will be inhibited or stimulated by using two activity-dependent transgenic line, the ArcCreER^{T2} x Arch-enhanced green fluorescent protein (EGFP) and the ArcCreER^{T2} x ChR2-enhanced yellow fluorescent protein (EYFP) mice, respectively. These mouse line allows for the indelible labeling of cells expressing the immediate early gene (IEG) *Arc/Arg3.1* and allow for a comparison between the cells that are activated during the encoding of a memory and those that are activated during the retrieval of the corresponding memory. In **Aim 2a,** I will selectively express the inhibitory opsin Arch in *Arc*$^{+}$ cells activated during memory encoding to assess the necessity of individual DG neurons for CFD. In **Aim 2b,** I will selectively express the excitatory opsin ChR2 in *Arc*$^{+}$ cells activated during encoding to assess the sufficiency of these neurons for CFD. In **Aim 3**, I will use the ArcCreER^{T2} x EYFP mice to determine the whole-brain neural ensembles corresponding to fear generalization during development. Neural ensemble activity patterns will be correlated within the brain regions to create a brain network representing connectivity of brain regions. Successful completion of this study will help elucidate brain-behavior relationships underlying fear generalization during developmental sensitive periods.

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