Resting functional connectivity between amygdala and dlPFC predicts anxious temperament in the rhesus monkey

R. M. Birn[1], S. E. Shelton[1], J. A. Oler[1], A. S. Fox[2], R. J. Davidson[1,2], and N. H. Kalin[1]
[1]Department of Psychiatry, University of Wisconsin, Madison, WI, United States, [2]Department of Psychology, University of Wisconsin, Madison, WI, United States

Introduction:

Structural and functional connections between the amygdala and prefrontal cortex (PFC), which continue to develop late into adolescence, have been observed to be altered in adults with depression and adolescents with generalized anxiety disorder. Studies in children demonstrate that anxious temperament (AT), a trait-like phenotype that is evident early in life and is characterized by increased behavioral and physiological reactivity to mildly threatening stimuli, is an important risk factor for the later development of anxiety disorders, depression, and comorbid substance abuse. Little is known, however, about the brain alterations that mediate the development of these pathophysiologies. The goal of the current study is to investigate the resting-state functional connectivity of the amygdala and its relation to individual differences in anxious temperament.

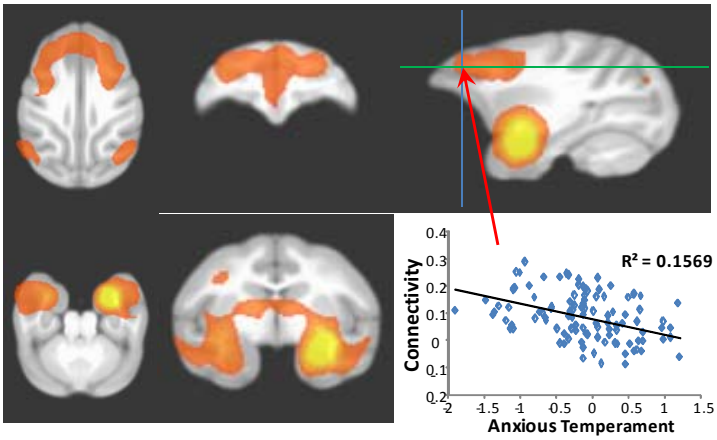
Methods:

In a prior study, Oler et al. examined individual differences in AT, and its relation to stress-induced brain activity with FDG-PET, in a large sample of young rhesus monkeys (n = 238, mean age = 2.4 yrs)[1]. AT in this case is a composite measure of temperament based on levels of freezing behavior, vocalizations, and plasma cortisol concentrations in response to a mildly threatening "no eye contact" condition of a "human intruder paradigm."[2] This study found a region encompassing the central nucleus of the amygdala (CeA) where brain metabolic activity was significantly correlated with the expression of AT. In our study, we examine the functional connectivity of this amygdala region using resting state fMRI [3] in a subset (n=107) of these animals.

A series of T2*-weighted MR images were acquired on a GE MRI 3T scanner while the subjects were anaesthetized with ketamine (15 mg/kg). Images were registered to correct for motion, slice-time corrected, converted to percent signal change, and spatially normalized to an average high-resolution anatomical derived from 238 monkey brains. Functional connectivity was estimated by computing the correlation of EPI time series between a seed region in the right CeA defined from the PET study and all other voxels in the brain. Average white matter and ventricular CSF signals were used as nuisance regressors.[4] These correlations were converted to Z-scores, and regressed against AT across subjects.

Results:

Significant functional connectivity ($p<10^{-12}$) was found between the right CeA and the left amygdala, bilateral dorsolateral prefrontal cortex, ventromedial prefrontal cortex, and bilateral bed nucleus of the stria terminalis (BNST) regions (see Fig 1). Across subjects, AT was significantly correlated with the functional connectivity between the right CeA and right dorsolateral PFC ($p<0.001$, uncorrected), with more anxious subjects exhibiting lower connectivity.



Resting-state functional connectivity with a region in the right amygdala ($p<10^{-12}$). The connectivity between right amygdala and right dorsolateral prefrontal cortex (dlPFC) is correlated with anxious temperament ($p<0.001$).

Conclusions:

Robust connectivity is observed between the CeA region of the amygdala and a number of regions, including the BNST, a region of the extended amygdala that has known projections from the CeA [5]. Furthermore, these preliminary data suggest that AT is associated with decreased prefrontal regulation of amygdala, and that amygdala-PFC connectivity is a potential biomarker of the risk for developing anxiety and affect-related psychopathology.

References:

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