Diffusion Tensor Imaging (DTI) Demonstrates that Prefrontal-Amygdala White-Matter Tracts Relate to Anxious Temperament and Amygdala Metabolism.

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Monkey Model of Behavioral Inhibition

Human Children:
- Increases in freezing behaviors
- Increased levels of basal cortisol
- Increases in right frontal brain asymmetry
- Decreased spontaneous vocalizations
- Increased amygdala responsivity to novelty in early adulthood

Rhesus Monkeys:
- Increases in freezing behaviors
- Increased levels of basal cortisol
- Increases in right frontal brain asymmetry
- Decreased spontaneous coo vocalizations
- Increased amygdala metabolism

The Neural Circuit of Behavioral Inhibition: Previous Findings (see references)

Amygdala / Extended Amygdala

- Amygdala lesions decrease freezing and coo vocalizations
- Amygdala and BNST region metabolism positively correlate with freezing and anxious temperament

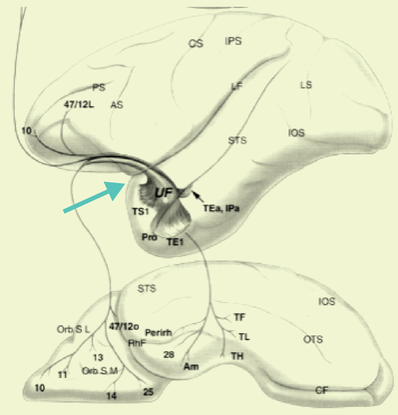
Orbital Frontal Cortex (OFC)

- OFC lesions decrease freezing
- OFC region metabolism **does not** significantly correlate with freezing

Anxious Temperament (Behavioral Inhibition)

If OFC metabolism isn't predicting behavior, could it be the connections between the OFC and the amygdala that predict anxious temperament?

The uncinate fasciculus (shown to the right; image from Schmahmann & Pandya, 2006) is thought to connect the amygdala and other anterior temporal structurs to the prefrontal cortex. We predicted structural differences in this region would predict anxious temperament.



We predicted FA in tracts that connect the OFC to the Amygdala should predict:

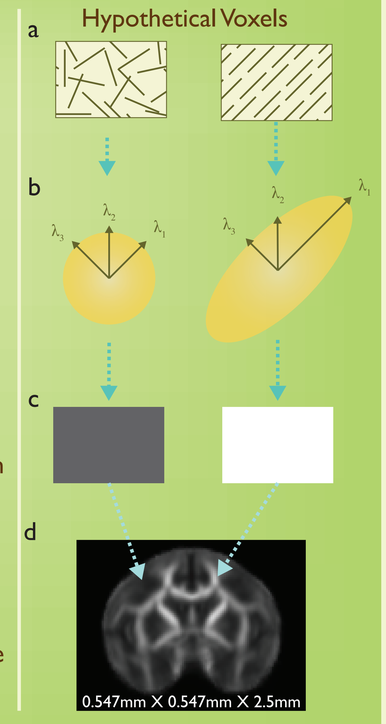
1) Individual differences anxious temperament

2) Amygdala metabolism

Defining Fractional Anisotropy (FA)

$FA = sqrt(1/2) * \{ sqrt[(\lambda_1-\lambda_2)^2 + (\lambda_2-\lambda_3)^2 + (\lambda_3-\lambda_1)^2] / sqrt[\lambda_1^2 + \lambda_2^2 + \lambda_3^2] \}$

Diffusion Tensor Imaging (DTI) measures how water diffuses in the brain, and was used to compute an indirect measure of white-matter integrity (FA; a). We first estimated the direction and rate at which water flows in each voxel of the brain (b). FA is then computed according to the equation above. The resulting FA measurements have higher values (c: shown in white) when water diffuses more in one direction than the other two (i.e. non-sphere-like) and lower values (c: shown in gray) when water diffuses equally in all directions (i.e. sphere-like). FA values are higher in white-matter and in tracts that move in a consistent direction as can be seen in the voxelwise FA map (d). We performed voxelwise analyses on the FA maps across subjects according to the equations below. Resulting t-maps were computed to determine if β_{13} and β_{23} were significantly different from zero.



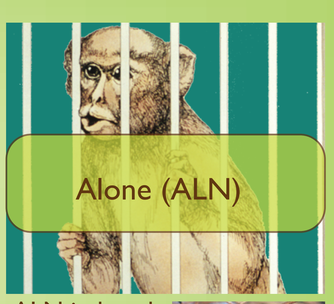
$FA = \beta_{10} + \beta_{11}*Age + \beta_{12}*WMP + \beta_{13}*AnxiousTemperament$

$FA = \beta_{20} + \beta_{21}*Age + \beta_{22}*WMP + \beta_{23}*AmygdalaMetabolism$

Defining Anxious Temperament

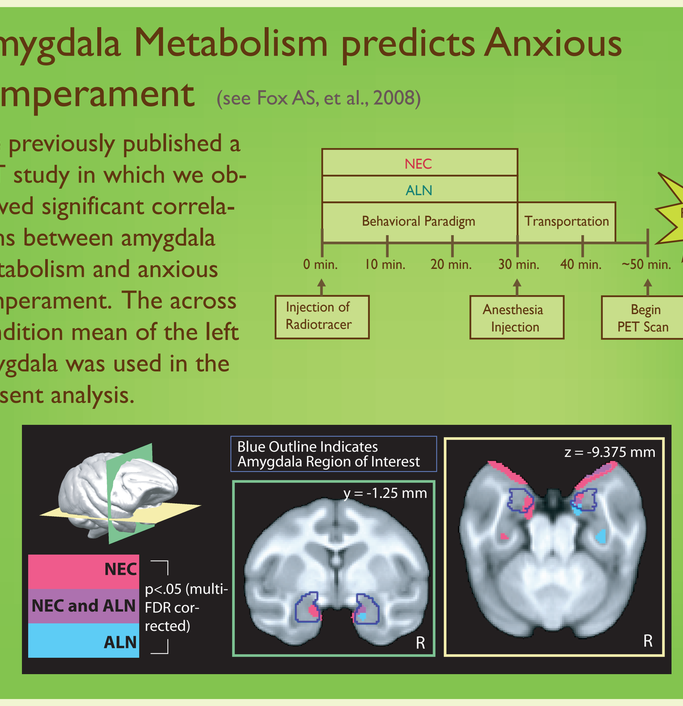
Anxious Temperament = (NEC-Freezing + NEC-Cort - ALN-Cooing + ALN-Cort)

NEC induced freezing.

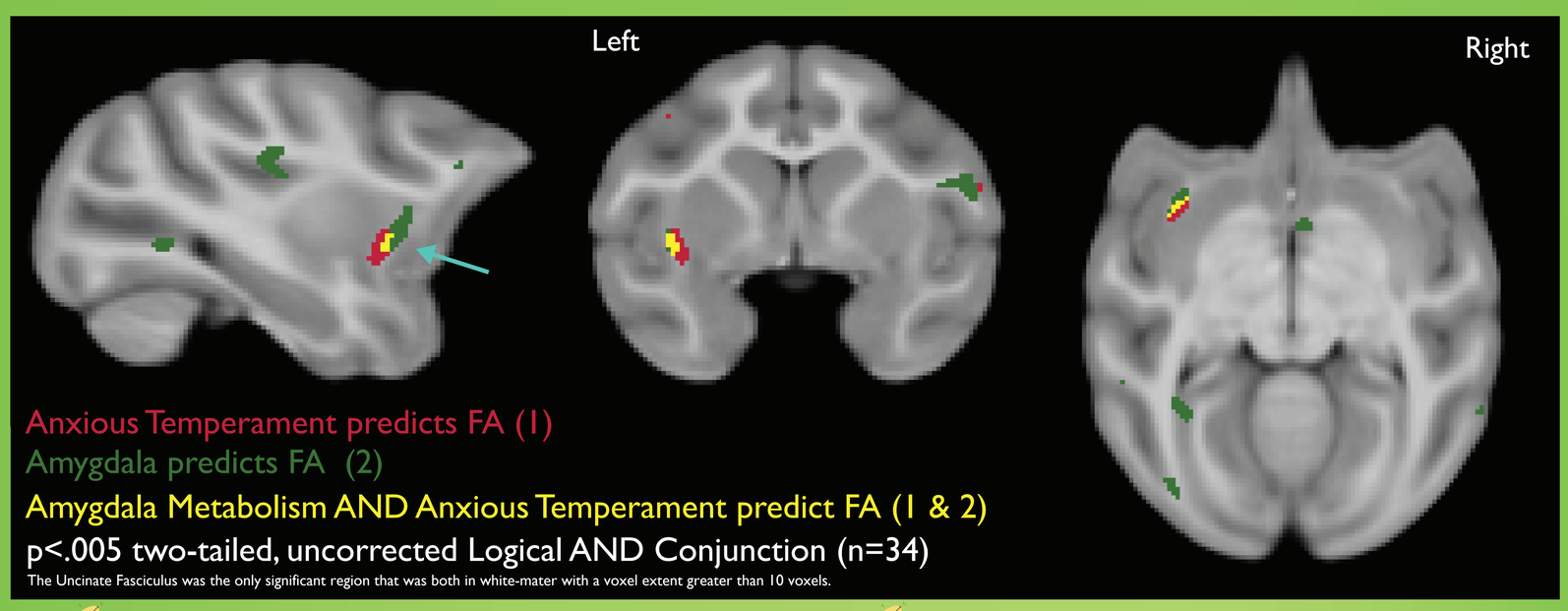


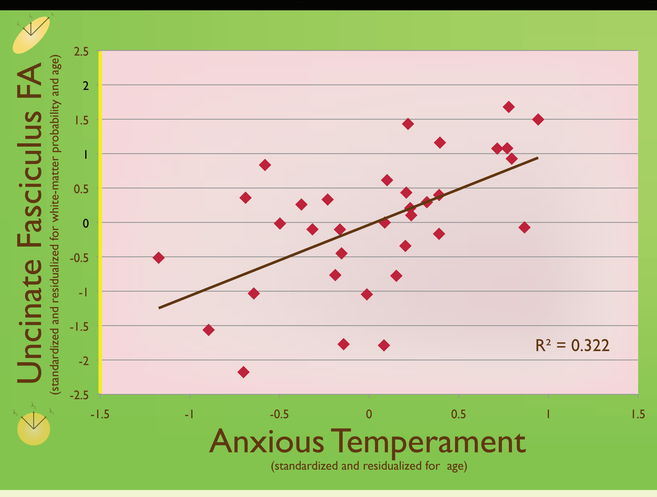
ALN induced cooing.

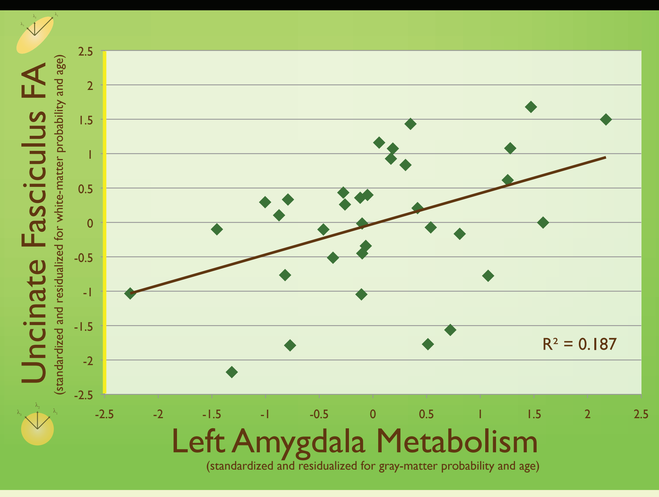
Our model of anxious temperament is a measure conceptually related to the construct of behavioral inhibition, in which we measure naturalistic behaviors (freezing and cooing) and endocrine responses (cortisol) in rhesus monkeys exposed to different stressful contexts (NEC and ALN conditions). (Fox AS et al., 2008)



Anxious Temperament and Amygdala Metabolism Predict FA in the Uncinate Fasciculus.







Amygdala Metabolism predicts Anxious Temperament (see Fox AS, et al., 2008)

We previously published a PET study in which we observed significant correlations between amygdala metabolism and anxious temperament. The across condition mean of the left amygdala was used in the present analysis.

A Note on Localization

Ungerleider, Gaffan & Pelak (1989) argued that transection of the uncinate fasciculus leaves inputs to the pfc from the amygdala intact. Petrides and Pandya (2007) suggest that this was because the transection performed by Ungerleider and colleagues was in the extreme capsule (seen left) and dorsal to what they are defining as the uncinate fasciculus. The region reported here is in a region consistent with the Petrides & Pandya definitions. (image from Schmahmann & Pandya, 2006)

Conclusions

Individual differences in structural connections between the OFC and amygdala predict anxious temperament and amygdala metabolism.

Further work is needed to determine the exact nature of the observed FA differences.

Combining Measurements of Behavior with Brain Function and Brain Structure are essential to for understanding the development of anxiety.

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