Ultra-high field imaging to delineate networks of fear and anxiety at rest

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Background: Amygdala subnuclei, the bed nucleus of the stria terminalis (BNST), and the habenula (Hb) are small key structures that participate in the processing of negative stimuli. While the neural circuits of fear and anxiety have been extensively studied in animals, human investigation has lagged due to the limited spatial resolution of standard neuroimaging tools. With ultra-high field neuroimaging we can now test, in humans, models developed in basic research. Using 7T-resting state fMRI (rs-fMRI), we contrast the intrinsic functional connectivity (iFC) of three critical nodes involved in responses to negative stimuli, the central nucleus of the amygdala (CeA), BNST and Hb. We expect to identify overlaps and uniqueness in these connectivity maps, to begin to delineate the specific functions of these nodes.

Methods: 32 healthy adults completed a 10min 7T rs-fMRI scan. The T1-weighted MPRAGE sequence was 0.7mm isotropic. The EPI sequence was 1.3mm isotropic with TR=2.5sec. Physiological signals were collected for noise-removal. We used AFNI processing stream (ANATICOR) (Jo et al. 2010) and non-linear normalization (Cox and Glen 2013). BNST and Hb were manually drawn by the authors (Torrisi et al., 2015; Lawson et al., 2013), and the CeA by an expert group (Nacewicz, et al. 2014). Functional data were smoothed with a 2.6mm kernel. The seed time-series were each correlated across the whole brain within an EPI mask representing coverage for >95% of the subjects. The resulting correlations were Fisher-transformed and entered into a group-level t-test, thresholded at p=1x10⁻⁶.

Results: Broadly, upon visual inspection of the three connectivity maps and within the boundaries of the selected threshold, the most salient findings were: (1) Medial PFC was minimally connected with BNST in contrast to substantial coupling with CeA and Hb; (2) Striatum was highly connected with BNST, and to a lesser extent to Hb and CeA; (3) Amygdala was not coupled with Hb; (4) Insula was highly connected with CeA, weakly with Hb and not with BNST; (5) CeA, BNST and Hb were all coupled with posterior cingulate, hippocampus, thalamus and periaqueductal gray matter (PAG).

Conclusions: From the perspective of the fear/anxiety network, the differential coupling with mPFC as well as striatum suggests separable roles for the CeA, BNST and Hb in the modulation of negative emotion (mPFC), and goal-directed behavior (striatum). All three structures were coupled with PAG, a region involved in coordinating responses to negative stimuli such as pain or defensive behavior. Of note, the Hb was not coupled with the amygdala, arguing for a potential secondary network for fear/anxiety, distinct from the amygdala network. Direct comparisons of these iFC maps, and correlations with behavioral measures, will clarify these conclusions.