Aberrant resting-state functional connectivity in a genetic rat model of depression

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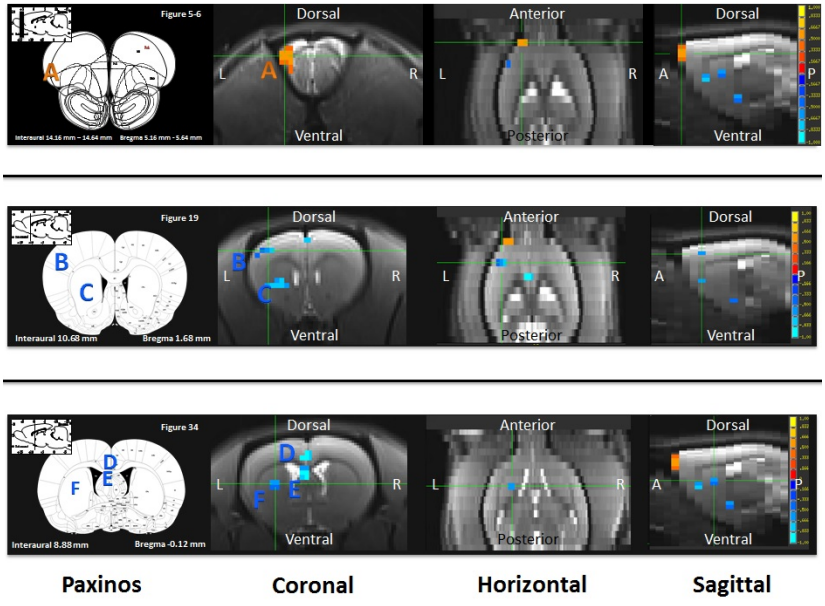
PURPOSE: Major depressive disorder (MDD) is a common disease with unknown etiology. Functional connectivity networks have been found to be dysregulated in a number of psychiatric diseases, including depression, but the cause or contribution of these anomalies has not yet been elucidated. Animal models of MDD are important for this purpose, because the topological properties of functional connectivity are conserved between humans and rodents [1]. This study aims at identifying aberrant connectivity patterns using fMRI using an established genetic rat model of MDD [2-4]. By comparing the MDD model Wistar More Immobile (WMI) with its control Wistar Less Immobile (WLI) we aim at pinpointing differences in connectivity which reflect the genetic and behavior findings previously reported in literature.

METHODS All MRI experiments were carried out on a Bruker 7 T (Clinscan, Ettlingen, Germany). Dexmedetomidine hydrochloride was used to sedate the animals during scanning (sub-cutaneous infusion). The agent has been shown to preserve awake connectivity patterns measured with fMRI [5]. A GRE anatomical whole brain reference image was acquired for each animal (ST = 1 mm in plane-resolution 0.273x0.273 mm^2). BOLD contrast-sensitive T2*-weighted gradient-echo echo-planar images (EPI) were acquired for resting-state data (200 volumes, 2 sec / Volume). Functional connectivity analysis was carried out using a seed-based cross-correlation analysis. A region of interest (ROI) was drawn encompassing the bilateral volume of the hippocampus of the template image, using a rat standard atlas as a reference (Paxinos). Time courses were extracted from all voxels, averaged, and then cross-correlated with that of every other voxel in the brain using eight regression parameters. The resulting seed-based cross-correlation map is a measure of each subject's hippocampal synchrony with the rest of the brain, thresholded at z=0.35. To detect differences in hippocampal networks between the WMI and WLI substrains, each resulting cross-correlation map was z-transformed and submitted to a T-test, adjusting for multiple comparisons and cluster size (p=0.05 in 3dClustSim in AFNI).

RESULTS: Shown in Figure 1 are the differences between WMI and the control WLI. Hyperconnectivity (i.e., WMI>WLI) was found with the left frontal association cortex/dorsolateral orbital cortex (top row, Cluster A). Hypoconnectivity was found with the left somatosensory cortex, the left ventral striatum partially inclusive of the nucleus accumbens core (middle row, Cluster B, C, respectively), the bilateral cingulate cortex, the bilateral lateral septum and the left caudate (bottom row, Clusters D, E, F, respectively).

DISCUSSION AND CONCLUSION Animal models are necessary to help us determine the connection between genes, gene expression, and functional connectivity. While fMRI findings in literature are diverse due to different networks examined and also due to different pathophysiologies of the disorder it appears that the common consensus is that hypoconnectivity between specific cortical and limbic areas (Savitz and Drevets, 2009) and hyperconnectivity between the prefrontal cortical sub-regions and other cortical regions (Hamilton et al., 2011; Sheline et al., 2010) is generally observed with neuroimaging studies. The substantial concordance of the present findings with the human literature together with the availability of brain transcriptomics data [2] for this model present a unique opportunity to integrate functional connectivity with brain region specific molecular networks and thus provide a set of tools to study MDD in a translational perspective.



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