The default-mode network and amygdala dysfunction as a translational depressive endophenotype in a preclinical set

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Background: Treatment-resistant depression (TRD) remains a pressing clinical problem responsible for long-term disability and poses a considerable therapeutic challenge. Optimizing treatment requires better definition of the function and specificity of the involved brain circuits. The strain bred for negative cognitions (NC) represents a genetic animal model of TRD with high face, construct and predictive validity. We aimed to detect the brain imaging endophenotype which would discern depressive-like behavior from control behavior (positive cognitions, PC) and could be used in a preclinical set for validating new antidepressants. For this purpose we conducted a network analysis using graph theoretical approach and correlated the behavioral data with brain functional connectivity.

Methods: The 80th generation of rats bred on the basis of their susceptibility to develop stress-escape behavior in operant boxes was used in our experiments. 12 NC and 10 PC rats (262-394 g; 8-week old) participated in fMRI measurements at Bruker 9.4 Tesla animal scanner. The resting-state fMRI time series were acquired over 8.5 min in rats sedated with medetomidine. Behavioral testing was performed on the third day after an fMRI measurement. We used graph theory analytical approach (Brain Connectivity Toolbox) to calculate the brain network properties. We correlated the behavioral data with the changes in brain functional connectivity.

Results: The prelimbic cortex, one of the main default-mode network (DMN) hubs, and amygdala had increased nodal degree in NC rats (FDR-corrected). Also several other DMN regions (infralimbic and cingulate cortices, hippocampus) had increased nodal centralities. Depressive-like behavior positively correlated with the functional connectivity within the DMN circuit (prefrontal, cingulate and retrosplenial regions) and prefrontal-amygdala coupling.

Conclusions: Increased participation of DMN hubs and amygdala associated with depressive-like behavior might represent a vulnerability endophenotype. This parallels with the data in depressive patients and might reflect an increased inward tuning and self-focus, as well as fearful states observed in depression. This endophenotype could serve a translational target for testing new antidepressants in a preclinical set.