Enhanced limbic impaired cortical-loop connection onto hippocampus of NHE rats: application of resting state functional connectivity in a preclinical ADHD model

Zoratto F.*, Palombelli G. M.*, Ruocco L. A., Carboni E., Laviola G., Sadile A. G., Adriani W., Canese R.

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Due to a hyperfunctioning mesocorticolimbic system, the Naples-High-Excitability (NHE) rats have been proposed as a model for the meso-cortical variant of ADHD. Compared to Naples Random-Bred (NRB) controls, NHE rats show hyperactivity, impaired non-selective attention (large number of rearing episodes with very low scanning duration), and impaired selective spatial attention (low performance in an eight-arm radial maze). Alteration in limbic functions has been proposed; however, resulting unbalance among forebrain areas has not been assessed yet. In the present work, by resting-state functional Magnetic Resonance Imaging (fMRI) in vivo, we investigated the connectivity of neuronal networks belonging to limbic vs. cortical loops in NHE and NRB rats (n=10 each). Notably, resting-state fMRI was applied (3x10 min timeseries) using a multi-slice sagittal, gradient echo sequence. Voxel-wise connectivity maps at rest, based on temporal correlation among fMRI timeseries, were computed by seeding the hippocampus (Hip), nucleus accumbens (NAcc), dorsal striatum (dStr), amygdala (Amy) and prefrontal cortex (PFC) in both hemispheres. To summarize patterns of altered connections, clear directional connectivity was evident within the cortical loop, from PFC through the dStr and hence towards Hip: such communication was reduced in NHE rats, in association with less mesencephalic/pontine innervation. Conversely, enhanced network activity emerged within the limbic loop of NHE rats, from NAcc and PFC directly to the Hip, all of which received greater innervation from ventral tegmental dopamine. A tuneddown cortical loop, together with a potentiated limbic loop, may well serve a major role in controlling ADHD-like behavioral symptoms in NHE rats.

*equally contributed to this work as co-first authors

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