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Title: Distinct Opposing effects of predation stress on aggressive behaviour of *Tph2* Het and wild type mice

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Background: Tryptophan hydroxylase-2 (*Tph2*), the enzyme critical for synthesis of serotonin (5-HT) in the brain, plays a role in anxiety-, aggression- and depression-related pathologies. Complete genetic inactivation of *Tph2* function in null mutant mice (*Tph2*$^{-/-}$) leads to decreased levels of serotonin in the CNS, increased aggressive behaviour and conditioned fear responses. While initial studies have revealed a lack of significant behavioural changes and a limited reduction of 10-20%, in serotonin brain levels with partial genetic deficit of *Tph2* in heterozygous mice (*Tph2*$^{+/-}$), it was hypothesized that under stress conditions, these animals may display aberrant behaviours including elevated aggression that can be similar to behavioural phenotype of *Tph2*$^{-/-}$ mice, driven by an hypothesis based on numerous evidences that stress can decrease brain serotonin levels.

Aim: Compare aggressive and social behaviours of *Tph2*$^{+/-}$ and *Tph2*$^{+/+}$ (wild type), either naïve or stressed, as stress may induce excessive aggressive behaviour that is typical for intact *Tph2*$^{-/-}$, which may be associated to an eventual decreased in brain levels of serotonin.

Methods: Adult 3 m.o. male *Tph2*$^{+/-}$ and *Tph2*$^{+/+}$ were obtained from University of Würzburg and subjected to 5 days of predator stress (S) or assigned to a non-stress control group (NS), as described elsewhere, shown to alter 5-HT related gene expression in the CNS and

suppress hippocampal neurogenesis. Thereafter, animals were tested in a 5-day resident-intruder test (RIT) during 8 min, with adult male BALBc mice with non-aggressive behaviour as counter partners. Latency of the first attack, number of attacks, duration of fighting behaviour, following and roll over behaviours, as well as nose-nose and nose-anal interactions were scored over the last 4-min period off-line

Results: Predation stress has opposing effects on aggressive behaviour of mice, increasing displayed aggression in *Tph2*$^{+/-}$, reduced in WT mice. Furthermore, *Tph2*$^{+/+}$ shown growing scores of aggression across the 4-min testing period, whereas heterozygous mice demonstrated instant expression of aggression which progressively declined. Changes in non-aggressive social interactions tended to be reciprocal to the changes in aggressive behaviours with regard to the effects of genotype and stress. In line with original findings, no significant differences but an optical trend towards higher aggression were found in naïve *Tph2*$^{+/-}$ mice. On a course of 5 days of RIT testing, a progressively increased manifestation of aggressive behaviour was seen. Molecular studies are underway.