Background: Changes in mood which are not correlated to apparent exogenous events are an integral part of normal behavior. In bipolar disorder, fluctuations of manic- and depressive behavior, which are often not associated with obvious external events, play a critical role. Despite the importance for normal and pathological behavior, the mechanisms underlying endogenous fluctuations in mood are virtually unknown. A major obstacle preventing progress of our understanding of this behavior has been the lack of appropriate animal models. Previously, we demonstrated that the transcription factor Otx2, which has been suggested as a susceptibility gene for bipolar disorder orchestrates the development of monoaminergic neurons.

Research Hypothesis: Overexpression of Otx2 leads to manic- and depressive-like behaviour

Aims: Here we use mouse mutants overexpressing Otx2, to study endogenous fluctuations in manic- and depressive-like behavior.

Methods: We used different behavioural and pharmacological paradigms to study manic-like behaviour in mice.

Results: We found that Otx2 mutants show in their home cage, extended periods of hyperactivity spontaneously alternating with periods of reduced activity. Repeated measurements in the open field demonstrated for Otx2 mutants increased intra-individual fluctuations in locomotor activity, habituation and different risk-taking behavioural parameters. Lithium, which is used for the treatment of bipolar disorder reversed behavioural alterations of Otx2 mutants.

Discussion: The medical implications of our findings are twofold. First, we provide insights into the molecular mechanisms underlying mood instability. Second, we provide an animal model that demonstrates endogenous fluctuation in manic- and depressive-like behaviour, which is a hallmark of bipolar disorder. Therefore, this paradigm will significantly facilitate the development of new drugs for this disorder.

Conclusions: We conclude that a dysfunction of Otx2 could play a critical role in the fluctuation of manic- and depressive behaviour by altering normal monoaminergic neurotransmission.

Key words: Bipolar Disorder, Animal Model, Otx2, Dopamine, Serotonin.