Research of the Department of Behavioural Biology

The focus of professor Touma's research group is to generate and characterize clinically relevant animal models of inborn (trait) emotionality and stress reactivity in order to elucidate neurobiological, endocrine and molecular genetic mechanisms underlying affective disorders such as major depression. It is only with deep insight into these mechanisms that novel treatment strategies and promising targets for therapeutic interventions can be developed in the future.

The spectrum of our research includes projects at the genetic, proteomic and systemic level. We apply a variety of behavioural tests assessing emotionality, coping and cognitive functions along with neuroendocrine approaches to analyse neuropeptides and proteins involved in the activity and regulation of the hypothalamic-pituitary-adrenocortical (HPA) axis. Furthermore, we use paradigms addressing the interaction between genetic predispositions and environmental influences, shedding light on the epigenetic modification of behavioural traits and neurobiological endophenotypes.

Research interests:

- Genes, Hormones and the Brain
  - molecular genetic and neuroendocrine bases of behaviour
- Function and Regulation of the Stress Hormone Systems
  - focus: alterations in neurodegenerative and psychiatric disorders
- Gene-Environment Interactions, Epigenetics
  - modulation of genetic predispositions by social and non-social environmental factors
- Regulation of Energy Metabolism and Neuronal Functions
  - impact of metabolic changes on behavioural and neurobiological endophenotypes

Methods:

- Behavioural analysis and test paradigms
  emotionality and coping styles
  activity rhythms, learning and memory
  social behaviour, parental care
- Neuroendocrine investigations
  - testing reactivity and feedback regulation of the HPA axis
  - hormone measurements in plasma samples and microdialysates from specific brain areas (quantifying steroids, neuropeptides and neurotransmitters)
  - non-invasive monitoring of steroid hormone metabolites in faecal samples
- Functional neuroanatomy and pharmacology
  - gene expression profiling in different brain areas (microarray, in situhybridisation, real-time PCR)
  - neuronal plasticity measures and microdialysis
  - effects of neuromodulatory substances and drugs on emotionality and neuroendocrine responses

Study species:

- Laboratory mice
  - animal models of neurodegenerative and affective disorders (generated by selective breeding or targeted genetic manipulation)

In another research focus, Oliver Ambrée studies the interaction between the immune system, neuroplasticity and behavior. For a long time it has been assumed that the immune system and the central nervous system do not interact with each other due to the separation through the blood-brain barrier. However, new evidence suggests that a multi-faceted bidirectional communication between the immune system and the brain takes place, thereby influencing behavior as well. For example, if we suffer from an infection, the activation of the immune system and the release of immunological messengers (cytokines) ensures that we show typical sickness behavior.

In stress-associated diseases such as depression, activation of the immune system is frequently observed as well, however without a pathogen being detected. In such a case, the depressive symptomatology, which is very similar to the sickness behavior, can be understood as a maladaptive effect of a nonspecific activation of the immune system.

In our work on different mouse models applying behavioral, cellular and molecular techniques, we address the following questions:

1. How does the immune system mediate the effects of stress on behavior and how does it differ in stress-susceptible and resilient individuals?

Chronic stress can cause long-lasting changes in behavior. Our studies showed altered numbers of T cells, dendritic cells and inflammatory monocytes in chronically stressed mice. In addition, more monocytes were recruited to the brain in stressed animals (Ambrée et al., 2018, Ambrée et al., 2019). Stress-susceptible individuals showed an increased inflammatory activation (Ambrée et al., 2018). These findings suggest that the individual immune response affects stress at the behavioral level.

2. How do immunological factors influence neuroplasticity?

In the non-inflammatory state, immune cells release important growth factors that contribute to the health of many organs. Microglial cells, the immune cells of the brain, for example produce and release neurotrophic factors that regulate adult neurogenesis. We were able to show that an increased expression of the neurotrophic factor S100B, which is mainly produced by astrocytes, leads to increased neurogenesis and reduces anxiety in mice housed in an enriched environment (Buschert et al., 2013). Furthermore, experimental manipulation of adult neurogenesis also influences emotional behavioral responses to fearful stimuli (Sakalem et al., 2016).

Selected publications (by year of publication):

Ambree O, Ruland C, Zwanzger P, Klotz L, Baune BT, Arolt V, Scheu S, Alferink J (2019): Social Defeat Modulates T Helper Cell Percentages in Stress Susceptible and Resilient Mice. Int J Mol Sci 20: 3512.

Ambree O, Ruland C, Scheu S, Arolt V, Alferink J (2018): Alterations of the Innate Immune System in Susceptibility and Resilience After Social Defeat Stress. Front Behav Neurosci 12: 141.

Sakalem ME, Seidenbecher T, Zhang M, Saffari R, Kravchenko M, Wordemann S, Diederich K, Schwamborn JC, Zhang W, Ambree O (2017): Environmental enrichment and physical exercise revert behavioral and electrophysiological impairments caused by reduced adult neurogenesis. Hippocampus 27: 36-51.

McIlwrick S, Rechenberg A, Matthes M, Burgstaller J, Schwarzbauer T, Chen A, Touma C (2016): Genetic predisposition for high stress reactivity amplifies effects of early-life adversity. Psychoneuroendocrinology 70: 85-97.

Heinzmann JM, Kloiber S, Mattos GE, Bielohuby M, Schmidt MV, Palme R, Holsboer F, Uhr M, Ising M, Touma C (2014): Mice selected for extremes in stress reactivity reveal key endophenotypes of major depression: A translational approach. Psychoneuroendocrinology 49: 229-243.

Buschert J, Hohoff C, Touma C, Palme R, Rothermundt M, Arolt V, Zhang W, Ambree O (2013): S100B overexpression increases behavioral and neural plasticity in response to the social environment during adolescence. J Psychiatr Res 47: 1791-1799.

Knapman A, Kaltwasser SF, Martins-de-Souza D, Holsboer F, Landgraf R, Turck CW, Czisch M, Touma C (2012): Increased stress reactivity is associated with reduced hippocampal activity and neuronal integrity along with changes in energy metabolism. European Journal of Neuroscience 35: 412-422.

Refojo D, Schweizer M, Kuehne C, Ehrenberg S, Thoeringer C, Vogl AM, Dedic N, Schumacher M, von Wolff G, Avrabos C, Touma C, Engblom D, Sch¸tz G, Nave KA, Eder M, Wotjak CT, Sillaber I, Holsboer F, Wurst W, Deussing JM (2011): Glutamatergic and dopaminergic neurons mediate anxiogenic and anxiolytic effects of CRHR1. Science 333: 1903-1907.

Touma C, Gassen NC, Herrmann L, Cheung-Flynn J, B¸ll DR, Ionescu IA, Heinzmann JM, Knapman A, Siebertz A, Depping AM, Hartmann J, Hausch F, Schmidt MV, Holsboer F, Ising M, Cox MB, Schmidt U, Rein T (2011): FK506 binding protein 5 (FKBP5) shapes stress responsiveness: modulation of neuroendocrine reactivity and coping behavior. Biological Psychiatry 70: 928-936.

Knapman A, Heinzmann JM, Hellweg R, Holsboer F, Landgraf R, Touma C (2010): Increased stress reactivity is associated with cognitive deficits and decreased hippocampal brain-derived neurotrophic factor in a mouse model of affective disorders. Journal of Psychiatric Research 44: 566-575.

Touma C, Fenzl T, Ruschel J, Palme R, Holsboer F, Kimura M, Landgraf R (2009): Rhythmicity in mice selected for extremes in stress reactivity: behavioural, endocrine and sleep changes resembling endophenotypes of major depression. PLoS ONE 4 (1): e4325.

Touma C, Bunck M, Glasl L, Nussbaumer M, Palme R, Stein H, Wolferstätter M, Zeh R, Zimbelmann M, Holsboer F, Landgraf R (2008): Mice selected for high versus low stress reactivity: a new animal model for affective disorders. Psychoneuroendocrinology 33: 839-862.

Touma C, Ambrée O, Görtz N, Keyvani K, Lewejohann L, Palme R, Paulus W, Schwarze-Eicker K, Sachser N (2004): Age- and sex-dependent development of adrenocortical hyperactivity in a transgenic mouse model of Alzheimerís disease. Neurobiology of Aging 25: 893-904.

Touma C, Palme R, Sachser N (2004): Analyzing corticosterone metabolites in fecal samples of mice: a noninvasive technique to monitor stress hormones. Hormones and Behavior 45: 10-22.