CSC-RUB PhD Project Proposal

Title: Investigation of long-range GABAergic inhibitory control in transgenic rats using neuroanatomical tracing, gene expression analysis, and in vivo electrophysiology

Sector of research: Systems and cellular neuroscience, synaptic plasticity, neuromodulation

Degree awarded: PhD in Neuroscience

Keywords: memory mechanisms, synaptic plasticity, cortical plasticity, transgenics, optogenetics, neuroanatomical tracing, *in vivo* electrophysiology, fluorescence i*n situ* hybridization, rodent

Supervisor of PhD project: Prof. Dr. Denise Manahan-Vaughan, Medical Faculty, Dept. Neurophysiology, Ruhr University Bochum

Research focus of supervisor:

In my department we study the mechanisms underlying information storage and memory in the brain. In particular we want to understand how synaptic and cortical plasticity enables long-term information storage and memory retention. To do this we use a highly multidisciplinary neuroscientific approach including, for example, in vitro electrophysiology (patch clamp, multielectrode array, field potential recordings) and in vivo electrophysiology (single-unit, local field potential and brain oscillation recordings), optogenetics, chemogenetics, fluorescence in situ hybridization, immunohistochemistry, behavioral neurobiology, advanced signal analysis, wide-field calcium imaging and functional magnetic resonance imaging (fMRI) in rodents. PhD candidates typically start their project by focussing on developing strong expertise in one of these methods, but depending on the talent of the individual the methodological portfolio of the project is expanded. We investigate a wide range of processes involved in memory formation including the neurotransmitter basis, impact of neuromodulation, role of sensory input and affective state.

Publications:

Goh J, Manahan-Vaughan D (2013) Spatial Object Recognition Enables Endogenous LTD that Curtails LTP in the Mouse Hippocampus. Cerebral Cortex 23:1118-1125. doi: 10.1093/cercor/bhs089.

Kemp A, Manahan-Vaughan D (2012) Passive spatial perception facilitates the expression of persistent hippocampal long-term depression. Cerebral Cortex. 22: 1614-1621.

Hagena H, Manahan-Vaughan D (2011) Learning-facilitated synaptic plasticity at CA3 mossy fiber and commissural-associational synapses reveals different roles in information processing. Cerebral Cortex. 21:2442-2449.

Hoang TH, Böge J, Manahan-Vaughan D (2021) Hippocampal subfield-specific Homer1a expression is triggered by learning-facilitated long-term potentiation and long-term depression at medial perforant path synapses. Hippocampus. In Press. doi: 10.1002/hipo.23333

Manahan-Vaughan, D (2017) Learning-related hippocampal long-term potentiation and long-term depression, *pp* 585-609*. In: Learning and Memory: A Comprehensive Reference* (Second Edition) : Reference Module in Neuroscience and Biobehavioral Psychology. *Editor-in-Chief:* John H. Byrne. Elsevier. http://dx.doi.org/10.1016/B978-0-12-809324-5.21104-8. ISBN: 978-0128051597

Stacho M, Manahan-Vaughan D (2022) Mechanistic flexibility of the Retrosplenial Cortex enables its contribution to spatial cognition. Trends Neurosci. 45:284- 296. doi: 10.1016/j.tins.2022.01.007

H-index of the last 5 years: 34; **number of publications in the last 5 years**: >50

Summary of research plan

Background:

It is well established that GABAergic interneurons enable local inhibitory control of neuronal circuitry in the brain the serves to enhance signal-to-noise ratios and signal discrimination during information processing and storage. Many different kinds of GABAergic interneurons support this process. One member of the GABA interneuron family stands out, because it sends long-range projections through the brain. It is identified by its expression of glutamate decarboxylase 1 (GAD1) (Tomioka et al., 2005: doi: 10.1111/j.1460-9568.2005.03989.x). This projection contributes to neuronal oscillations in the hippocampus (Fuchs et al., 2001: doi: 10.1073/pnas.051631898). The hippocampus is our most important memory structure and enables the creation of long-term associative memories by means of synaptic plasticity (Manahan-Vaughan, 2017). Memory generalisation is prevented by the input-specificity of synaptic plasticity and this process is optimized by GABAergic receptors (Davies et al., 1991: doi: 10.1038/349609a0). To what extent *long-range* GABAergic projections are required for hippocampal synaptic plasticity and the creation of reliable memory engrams is unclear.

Study objective: The objective of the PhD project is to examine the role of long-range GABergic projections in hippocampal memory encoding in the rodent brain. The goals of the project are **1**. To study how long-range GABAergic projections reach the hippocampus using anatomical tracing in GADcre transgenic rats **2**. To explore using optogenetics how *specific* activation or inhibition of long-range GABAergic projections modulate hippocampal synaptic plasticity and memory encoding, **3**. To examine how disruption of long-range GABergic control alters neuronal gene encoding that is triggered by synaptic plasticity events in the hippocampus.

Expected Results: We are confident that the three main goals of the project will be achieved and will result in a number of high-ranking publications.

Methods: We will explore anatomical projections **of** long-range GABAergic projections from the neocortex to the hippocampus using tracing strategies in GADcre-expressing transgenic rats. We will trigger hippocampal synaptic plasticity in transgenic rats *in vivo* by means of electrophysiological stimulation. We shall use a combination of *in vivo* electrophysiology and optogenetics to study how modulation of long-range GABAergic projections contributes to the expression of synaptic plasticity and the acquisition of spatial memory engrams. Fluorescence *in situ* hybridisation will be used to identify immediate early gene expression in neurons that is triggered by hippocampal synaptic plasticity in the presence or absence of optogenetic manipulations of long-range GABAergic projections.

Candidate Requirements: Candidates should have studied neuroscience, neurobiology, or a related discipline**.** Experience with in vivo electrophysiology and/or FISH data, and strong statistical and programming skills would be highly advantageous. Experience in working with live rodents and an understanding of rodent neuroanatomy would be helpful. Good English language skills are required.

Motivation for CSC application: The successful applicant will receive stringent and in-depth training in the complex methodological skills that are required for conducting *in vivo* electrophysiological recordings and optogenetic manipulations in freely behaving (learning) rodents. He/She will be trained in the analysis of electrophysiological data, and experimentation and analysis skills for FISH). The Department of Neurophysiology is a vibrant environment that hosts scientists from all over the world and from a variety of scientific disciplines. PhD candidates will be supported by a highly skilled team of technicians and senior scientists, who ensure that an effective support system is always in place. The PhD project will be closely supervised by Prof. Manahan-Vaughan, who is internationally recognised in the field of synaptic plasticity and memory research. State of the art infrastructure and expertise is available for all elements of the project. PhD

candidates are integrated into the internationally renowned graduate programme of the International Graduate School of Neuroscience that provides state-of-the art training in neuroscientific and professional skills.