BIOGRAPHICAL SKETCH

NAME: Hannah Twarkowski

eRA COMMONS USER NAME (credential, e.g., agency login): HTwarkowski

POSITION TITLE: POSTOCTORAL FELLOW

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Ruhr University Bochum, Germany	Bachelor of Science	09/2009	Biology
Newcastle University, UK	/	10/2010	Electrophysiology
Ruhr University Bochum, Germany	Master of Science	06/2012	Biology
Ruhr University Bochum, Germany	Ph.D.	11/2016	Neuroscience
Massachusetts General Hospital, Harvard Medical School, Boston, MA	Postdoctoral Fellowship	03/2017 - present	Neuroscience

A. Personal Statement

Currently, I am a Postdoctoral Fellow in Amar Sahay´s laboratory. Here, I have the opportunity to leverage my training in *in vivo* neurophysiology and gain more training in applying molecular tools to investigate neuronal ensemble dynamics in learning and memory in adulthood and aging. I studied general biology to get the broadest basic knowledge possible. At the end of my undergraduate training, it became more and more clear to me that my future lies in neuroscience especially in the field of hippocampal memory processes and how they contribute to age-related cognitive decline and psychiatric endophentypes. My Master's thesis focused on amyloid-beta associated changes in glutamatergic receptors. Inspired by that, and considering that Alzheimer´s disease is an age-related disease, I broadened my focus during my PhD thesis to include studies on aging and memory circuits. Here, I investigated the role of aminergic modulation in hippocampal synaptic plasticity in health, disease and aging. I demonstrated that aging in wistar rats is accompanied by deficits in dopaminergic and noradrenergic facilitation of synaptic plasticity in the dentate gyrus as early as 8-14 months of age. Following these results and evidence in the literature for a role for excitation-inhibition imbalance in the dentate gyrus-CA3 network, I was thrilled to learn that Amar Sahay and his team developed a molecular tool to specifically manipulate feedforward inhibition in this network. Here, I will investigate the specific role of feed-forward inhibition in dentate gyrus-CA3 network in young and aged mice in encoding long-term memory using *in vivo* imaging, molecular genetics and behavior. Overall, this project will allow me to strengthen my profile and potentially edify strategies to combat impairments in hippocampal memory processing.

B. Positions and Honors

Positions and Employment

2010-2011 Teaching assistant, Department of General Zoology and Neurobiology, Ruhr University Bochum, Germany

2012 – 2016 PhD fellow, International Graduate School of Neuroscience (IGSN), Ruhr University Bochum, Germany

2014 – 2016 Teaching assistant, Department of Neurophysiology, Ruhr University Bochum, Germany

2017 – pres. Postdoctoral Fellow, Center for Regenerative Medicine, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Other Experience and Professional Memberships

2012 – pres German Society for Neuroscience

2014 Co-Organizer, IGSN Symposium *'Cellular and subcellular mechanisms underlying Alzheimer's disease'*

2014 – pres Research School PLUS, Ruhr University Bochum, Germany, Reviewer

2018 – pres Society for Neuroscience, SfN

2018 – pres Frontiers in Integrative Neuroscience, Reviewing editor

Awards and Honors

2010 DAAD ERASMUS Internship grant

2012– 2014 Ph.D. fellowship International Graduate School of Neuroscience

2015 PR.INT travel grant, Research School Bochum

2018 HBI Young Scientist Travel Award

2018 – pres DFG Research Fellowship

C. Contribution to science

1. The 5-hydroxytryptamine4 receptor enables differentiation of informational content and encoding in the hippocampus.

In collaboration with a postdoctoral fellow, we investigated the role of the serotonergic 5-HT_4 -receptor in regulating synaptic plasticity in two different synapses in the hippocampus. I performed experiments on the perforant path-DG synapse and my colleague Hardy Hagena performed similar experiments on the mossy-fibre-CA3 synapse. Long-term synaptic plasticity, represented by long-term depression (LTD) and long-term potentiation (LTP) comprise cellular processes that enable memory. Neuromodulators such as serotonin regulate hippocampal function, and the 5-HT_4 -receptor contributes to processes underlying cognition. It was previously shown that in the CA1-region, 5-HT_4 -receptors regulate the frequency-response relationship of synaptic plasticity: patterned afferent stimulation that has no effect on synaptic strength (i.e., a θ_m-frequency), will result in LTP or LTD, when given in the presence of a 5-HT_4 -agonist, or antagonist, respectively. Here, we show that in the dentate gyrus (DG) and CA3 regions of freely behaving rats, pharmacological manipulations of 5-HT_4 -receptors do not influence responses generated at θ_m-frequencies, but activation of 5-HT_4 -receptors prevents persistent LTD in mossy fiber (mf)-CA3, or perforant path-DG synapses. Furthermore, the regulation by 5-HT_4 -receptors of LTP is subfield-specific: 5-HT_4-receptor-activation prevents mf-CA3-LTP, but does not strongly affect DG-potentiation. These data suggest that 5-HT_4-receptor activation prioritizes information encoding by means of LTP in the DG and CA1 regions, and suppresses persistent information storage in mf-CA3 synapses. Thus, 5-HT_4-receptors serve to shape information storage across the hippocampal circuitry and specify the nature of experience-dependent encoding.

***Twarkowski H**., *Hagena H., and Manahan-Vaughan D.The 5-Hydroxytryptamine4 (5-HT4) receptor enables differentiation of informational content and encoding in the hippocampus. Hippocampus 2016 Jul;26(7):875-91 (* joined first authorship)

2. Loss of Catecholaminergic Neuromodulation of Persistent Forms of Hippocampal Synaptic Plasticity with Increasing Age

In addition to the above described project, my PhD project focused on the modulation of long-term plasticity at the perforant path DG synapse by noradrenaline and dopamine. Here, I tested specifically healthy young and middle-aged rats. Neuromodulation by means of the catecholaminergic system is a key component of motivation-driven learning and behaviorally modulated hippocampal synaptic plasticity. In particular, dopamine acting on D1/D5 receptors and noradrenaline acting on beta-adrenergic receptors exert a very potent regulation of forms of hippocampal synaptic plasticity that last for very long-periods of time (>24 h), and occur in conjunction with novel spatial learning. Antagonism of these receptors not only prevents long-term potentiation (LTP) and long-term depression (LTD), but prevents the memory of the spatial event that, under normal circumstances, leads to the perpetuation of these plasticity forms. Spatial learning behavior that normally comes easily to rats, such as object-place learning and spatial reference learning, becomes increasingly impaired with aging. Middle-aged animals display aging-related deficits of specific, but not all, components of spatial learning, and one possibility is that this initial manifestation of decrements in learning ability that become apparent in middle-age relate to changes in motivation, attention and/or the regulation by neuromodulatory systems of these behavioral states. Here, we compared the regulation by dopaminergic D1/D5 and beta-adrenergic receptors of persistent LTP in young (2-4 month old) and middle-aged (8-14 month old) rats. We observed in young rats, that weak potentiation that typically lasts for *ca.* 2 h could be strengthened into persistent (>24 h) LTP by pharmacological activation of either D1/D5 or beta-adrenergic receptors. By contrast, no such facilitation occurred in middle-aged rats. This difference was not related to an ostensible learning deficit: a facilitation of weak potentiation into LTP by spatial learning was possible both in young and middle-aged rats. It was also not directly linked to deficits in LTP: strong afferent stimulation resulted in equivalent LTP in both age groups. We postulate that this change in catecholaminergic control of synaptic plasticity that emerges with aging, does not relate to a learning deficit *per se*, rather it derives from an increase in behavioral thresholds for novelty and motivation that emerge with increasing age that impact, in turn, on learning efficacy.

Twarkowski H., and Manahan-Vaughan D. Loss of Catecholaminergic Neuromodulation of Persistent Forms of Hippocampal Synaptic Plasticity with Increasing Age. Front Synaptic Neurosci. 2016 Sep 26;8:30

3. Dorsolateral septum somatostatin interneurons gate mobility to calibrate context-specific behavioral fear responses

Early in my postdoctoral fellowship, I joined this ongoing project lead by a senior postdoctoral fellow (Antoine Besnard). This project focused on the role of the dorsal lateral septum (DLS) in governing fear responses. Using a wide range of methods such as *in vivo* calcium imaging, retrograde virus tracing and optogenetic we identified a subset of somatostatin positive interneurons (SST interneurons) that receive direct input from CA3 and respond to foot shock in a contextual fear conditioning paradigm. Optogenetic inhibition or stimulation of these neurons bi-directionally modified freezing behavior in a conditioned context. We suggest that this subpopulation serves as regulator of mobility as part of a learned, context-specific fear response.

Besnard A, Gao Y, TaeWoo Kim M, **Twarkowski H**, Reed A K, Langberg T, Feng W, Xu X, Saur D, Zweifel L S, Davison I, Sahay A. Dorsolateral septum somatostatin interneurons gate mobility to calibrate context-specific behavioral fear responses. *Nat Neurosci*. 2019;22(3):436-446

Complete list of published work

https://www.ncbi.nlm.nih.gov/sites/myncbi/hannah.twarkowski.1/bibliography/58183288/public/?sort=date&direction=ascending.