NEUROSCIENCE
NEWSLETTER
Georg-August-Universität Göttingen · International Max Planck Research School

JUNE 2017

The Neuroscience Program...

on the Move

Welcome to the 5th Neuro-Newsletter published by the Göttingen International Master/PhD/MD-PhD Program and International Max Planck Research School (IMPRS) for Neurosciences.

As many of our members already know, the International Max Planck Research School for Neurosciences (IMPRS) has been formally transferred from the Max Planck Institute for Biophysical Chemistry (MPIbpc) to the Max Planck Institute for Experimental Medicine (MPIem) in July 2016. This transit to the MPIem, where the first lectures of the program took place, is due to the fact that many members of the MPIbpc scientists in the Neuroscience program retired or are about to retire, so that the majority of IMPRS faculty members is now located in the MPIem.

In April 2017, the new members of the Neuroscience Program Committee were elected during the plenary faculty meeting, and the newly formed committee unanimously voted for Nils Brose as the new Dean of the IMPRS and for Martin Göpfert as the new Spokesperson of the MSc/PhD/MD-PhD Program for Neurosciences. They take over the leadership from Detlev Schild (founding member and Spokesperson until 2016) and Gregor Eichele (IMPRS Dean from 2011 until 2016). The new speakers and committee members cordially thank their predecessors for creating, guiding, and shaping the Neuroscience program over the past 17 years. Their commitment, enthusiasm, and hard work has provided the basis for the success of the program and its future development. (please refer to the program's websites for the list of the

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newly elected members of the Program Committee).

The new board will be responsible for filing the application to continue the IMPRS funding for the next 6 years beyond the current funding period, which ends in December 2018. The 'IMPRS 18plus' call launched in March 2017 allows successful schools to apply for further funding, and the proposal is due end of June 2017. While established and successful structures, like the comprehensive one-year predoctoral Master training phase will definitely be preserved, the dynamic development of the field of neuroscience will be reflected in the teaching canon, which is continuously adapted to include new research foci and the development of the local Neuroscience faculty. Whereas classical cellular and molecular approaches and high resolution imaging techniques will remain core elements in the curriculum, systemic and functional imaging approaches making use of the fMRI facilities at the German Primate Center and University Medical Center will be integrated in the teaching program. In addition, investigations of mechanisms of neurodegenerative diseases using high resolution imaging approaches with possible clinical applications will be in the focus of the Biostructural Imaging of Neurodegeneration (BIN) institute operated by the UMG and the Göttingen section of the German Center for Neurodegeneration (DZNE) supported by the Helmholtz Society. The directors of both institutes (BIN, Silvio Rizzoli; DZNE, André Fischer) are both long-standing members of the Neuroscience program and will integrate the research topics of their institutes into the teaching agenda of our program.
Beyond the research and teaching efforts on the Göttingen Campus, the increasing number of our alumni, who are steadily moving into leadership positions in academia and industry worldwide, bears great potential with respect to career development for our doctoral students. Accordingly, the alumni of the Neuroscience program together with those from our partner IMPRS for Molecular Biology are about to form a worldwide professional 'Göttingen-Alumni' network, which will help our graduates to get first-hand information on various professional career pathways in science and industry. And in addition to strengthening the ties to our alumni, the integration of young investigators into the program, which has been a key element of the program since it started, will be promoted by further developing career-related services to the benefit not only of Neuroscience students, graduates, and post-graduates but also the doctoral students of the GGNB Graduate School.

In parallel to our alumni program, the doctoral students of the Neuroscience program also take their career opportunities into their own hands, for instance by organizing the Neurizons symposium. This student-organized meeting allows for direct personal interactions between participants. By bringing young PhD students at the beginning of their scientific career into contact with renowned neuroscientists, the Neurizons symposium helps our students to get integrated into the scientific community. In addition to the scientific program, the Neurizons format includes career-related workshops with our alumni, meetings with representatives from companies, and technical workshops. Neurizons 2016 was a great success and attracted more than 300 participants to the Göttingen Campus. The organization team for the next Neurizons meeting has already been formed and plans the next symposium for end of May 2018.

Apart from the IMPRS renewal, the continuous third party research funding is of key relevance to the Göttingen Neuro-community. In fact, the Neuroscience program faculty members are contributing to six existing DFG-funded consortial research programs (SFBs) in the natural sciences on the Göttingen Campus. Congratulations to Silvio Rizzoli, who is the Speaker of the newly approved SFB 'Quantitative Synaptology', which is directly related to the core areas of teaching of the Neuroscience program. In addition, faculty members also contribute to two proposals that will be submitted for the Excellence Initiative, extending the long tradition of the Nanoscale Microscopy and Molecular Physiology of the Brain Cluster of Excellence CNMPB.

Nils Brose
Speaker International Max Planck Research School

Martin Göpfert
Speaker MSc/PhD/MD-PhD Program

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Molecular synergy:

How does an intronic microRNA support its motherly gene in developing neurons?

by Mateusz C. Ambrozkiewicz

Developmental mechanisms that guarantee uncompromised neocortical patterning encompass neuronal fate acquisition, migration of nerve cells and activity-dependent refinement. Counterintuitive as it may seem, neurons undergo an impressive morphological transformation during development. Excitatory neurons of the cerebral cortex emanate from a pool of progenitors located at the ventricular and subventricular zone of the dorsal telencephalon. Neural precursor and progenitors cells, including radial glial cells (RGCs) undergo series of self-renewing, proliferative divisions and generate immature neurons in consumptive mitoses. Those cells initiate migration to acquire their laminar identity in the cerebral cortex.

The vast majority of migrating newborn neurons reaching the subventricular zone has a multipolar shape. Neuronal migration into the developing cortical plate requires transition out of the multipolar stage. Differentiating neurons of the neocortex generated by radial glia adopt a characteristic bipolar morphology, with a long process extending to the pia (also called a leading process, LP) and another one, emanating from the antipode of the soma, that extends to the surface of the embryonic ventricle – a trailing process (TP) (Ambrozkiewicz and Kawabe, 2015). Notably, those initial morphological rearrangements bear fundamental consequences for neuronal polarity, as the LP gives rise to the apical dendrite of a pyramidal neuron and the TP extends tangentially into the intermediate zone. Molecules that promote the transition to polarized morphology in developing neurons – like filamin A, doublecortin or lissencephaly 1 – supervise cytoskeletal stability by affecting microtubules or actin filaments (Barnes and Polleux, 2009; Cardoso et al., 2002).

Disruptions to multipolar-bipolar transitions often result in arrested radial migration or affect laminar patterning. Such cellular pathologies may lead to anatomical disturbances, altered neuronal connectivity or behavioral disruptions as observed in severe neurodevelopmental disorders, like periventricular nodular heterotopia, lissencephaly or autism spectrum disorder. Acquisition of axon-dendrite fates by neurites and proper laminar positioning of a developing nerve cell ascertain uninterrupted establishment of neuronal networks in the mature brain. It is very tempting to speculate that both processes are causally interconnected and that molecular repertoire crucial for establishment of neuronal polarity is required for uncompromised migration of cortical nerve cells. Identifying morpho-regulatory underpinnings of both developmental processes are of essential importance for our understanding of molecular pathways that go awry in neurodevelopmental diseases.

We were particularly interested in WW Domain Containing E3 Ubiquitin Protein Ligase 1 and 2 (Wwp1 and Wwp2) and their role in acquisition of polarity in developing neurons. In *C. elegans*, an orthologue of murine *Wwp1* has been functionally correlated to Synapses of Amphids Defective A and B (SAD-A and SAD-B) kinases. Despite a well-established role in regulating presynaptic homeostasis in neurons (Inoue et al., 2006), SAD kinases govern axon-dendrite polarity establishment in worm and mouse (Barnes et al., 2007; Kishi et al., 2005). Because of the high degree of homology and functional redundancy of Wwp1 and Wwp2 and their possible involvement in axon acquisition, we transfected shRNAs to simultaneously knock-down Wwp1 and Wwp2 to primary neurons. We then cultivated neurons until 7 days *in vitro* (DIV) and performed immunocytochemistry for molecular markers for dendrites and axons. We were astonished to discover that after double knock-down of Wwp1 and Wwp2 (Wwp1/2 dKD) nerve cells projected more than one axon.

To test if *Wwp1* and *Wwp2* are required for establishment of polarity *in vivo*, we took advantage of *in utero* electroporation. This method allows to transfect a pool of cortical progenitors residing on the surface of the embryonic ventricle with DNA of interest. Due to the fact that laminar identity of cortical neurons is interwoven with timing of neurogenesis (neurons of deeper layers are born first; upper layer neurons are born later), *in utero* electroporation allows to target neuronal progenitors of well-defined fates (Saito, 2006). Notably, developing cortical neurons of upper layers transfected with Wwp1/2 dKD constructs displayed aberrant multipolar morphology as compared to bipolar controls. Strikingly, Wwp1/2 dkD lead to altered laminar positioning of cortical nerve cells *in vivo* (Figure 1 A, D). In brains of newborn mice, nerve cells with reduced levels of Wwp1 and Wwp2 presented with not one, but multiple LPs (Figure 1 B). In line with that observation, at postnatal day 10 (P10), Wwp1/2 dKD lead to loss of

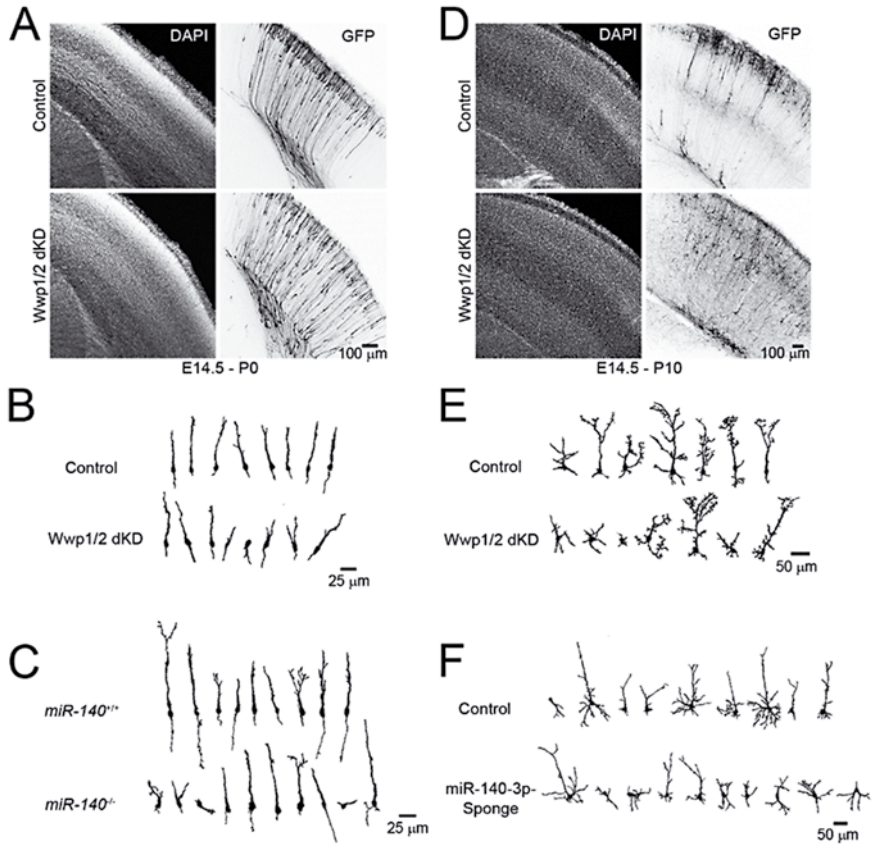

Fig. 1: Wwp1, Wwp2 and miR-140 are indispensable for neuronal development. (A-E) Cortical progenitors were *in utero* electroporated (IUE) at E14.5. (A, D) Images of DAPI staining and GFP fluorescence in coronal section of a P0 (A) and P10 (D) mouse brain after IUE with control sh-RNA (top panel), or two sh-RNAs to knock-down Wwp1 and Wwp2 (Wwp1/2 dKD). (B, E) Tracings of P0 (B) and P10 (E) neurons in control (top panel) and in Wwp1/2 dKD (bottom panel) brain. Depicted neurons reflect quantified frequencies of certain morphological class for each condition. (C) Tracings of P0 neurons in miR-140+/+ (control, top panel) and in miR-140-/- (miR-140 knock-out, bottom panel) brain. (F) Tracings of P10 control neurons (top panel) and in nerve cells expressing miR-140 knock-down construct (miR-140-3p-Sponge, bottom panel).

pyramidal morphology of upper layer neurons and formation of nerve cells with multiple apical dendrites (Figure 1 E). We subsequently analyzed formation of polarity and neuronal migration in Wwp1 and Wwp2 double knock-out mice and corroborated previous findings to conclude that both ubiquitin ligases are indispensable for uncompromised neuronal development.

Interestingly, *Wwp2* gene harbors a locus of *miR-140* and concomitant expression of both, Wwp2 and intron-retained miR-140 has been reported in non-neuronal tissue. microRNAs (miRNAs) comprise an evolutionarily conserved molecular mechanism to post-transcriptionally control gene expression (Lee et al., 1993; Wightman et al., 1993). Approximately half of the known human miRNAs is located in the introns of protein coding genes (Radfar et al., 2011). Intronic miRNAs and their host genes are thought to act synergistically in one molecular pathway or function as mutual antagonists (Hinske et al., 2014).

We were intrigued by the possible implications a relationship between a *Wwp2* host gene and its intragenic *miR-140* have in developing neurons. Remarkably, we could prove that both acquisition of axon-dendrite polarity, neuronal migration and morphology of upper layer cortical neurons were disrupted in neurons devoid of *miR-140* (Figure 1 C, E). Genetic ablation of *miR-140* phenocopied loss of *Wwp2* and its homolog *Wwp1* in developing neurons (Figure 1). Importantly, as quantified by Western blotting experiments and Real Time PCR, detrimental effects of *miR-140* and *Wwp1* and *Wwp2* loss in neurons did not depend on reciprocal miR-host gene interaction. That in turn implied that miR-140 and Wwp1/2 orchestrate neuronal development through two independent signaling cascades.

We then sought downstream molecular pathways controlled by *miR-140* in developing neurons. We hypothesized that genetic deletion of *miR-140* relinquishes translational repression it exerts on its interactome. Therefore in *miR-140* knock-out brain, targets of miR-140 are up-regulated as compared to wild-type controls. To identify putative miR-140 targets, we subjected *miR-140* wild-type and knock-out brain samples to label-free quantitative mass spectrometry. In the list of gene products up-regulated in *miR-140* knock-out samples, we looked for those that possess putative miR-140 binding sites,

making posttranslational repression possible. Within candidate genes, of particular interest was Fyn kinase. *Fyn* has been described to play an important role in orienting apical dendritic shaft in developing pyramidal neurons (Sasaki et al., 2002). Modulating *Fyn* levels by gene dosage studies has been reported to result in migration defects of cortical neurons (Kuo et al., 2005; Simó and Cooper, 2013).

In the developing cortex, *miR-140* knock-out results in up-regulation of Fyn. We then mimicked the molecular context of *miR-140* deletion by overexpressing Fyn in upper layer neuron progenitors *in vivo*. Notably, up-regulation of Fyn phenocopied morphological aberrances and migration delay of cortical nerve cells, we observed upon *miR-140* loss. Next, we generated a construct encoding EGFP fused to a fragment of Fyn mRNA spanning miR-140 binding sites. This enabled us to design a relatively easy assay based on co-transfection of miR-140 and EGFP fusion construct (Rybak et al., 2008). By quantifying EGFP fluorescence, we provided evidence that miR-140-mediated Fyn regulation was due to direct binding of miR-140 to Fyn mRNA.

Notably, Fyn level was unchanged upon brain-specific double *Wwp1* and *Wwp2* knock-out, supporting our hypothesis that miR-140 and Wwp1/2 act synergistically in neuronal development, but employing independent downstream molecular mechanisms. To further investigate possible epistatic interactions between host *Wwp2*, homologous *Wwp1* and intronic *miR-140*, we performed triple knockdown experiment (TKD) in cortical progenitors of upper layer neurons by *in utero* electroporation. We hypothesized, that if the trio of molecules indeed acts in distinct signaling cascades, TKD would exacerbate polarity defects observed for Wwp1/2 dKD or *miR-140* knock-out neurons. Intriguingly, not only were the morphological defects in developing cortical neurons drastically augmented, but also TKD nerve cells seemed to have lost their laminar identity – a phenomenon that we failed to observe in our study before. This unambiguously excluded the possibility of epistasis between *Wwp1/2* and *miR-140*. Taken together, we provided experimental evidence that ubiquitin ligases of Wwp subfamily and miR-140 act in synergy to regulate neuronal development by employing distinct molecular signaling cascades.

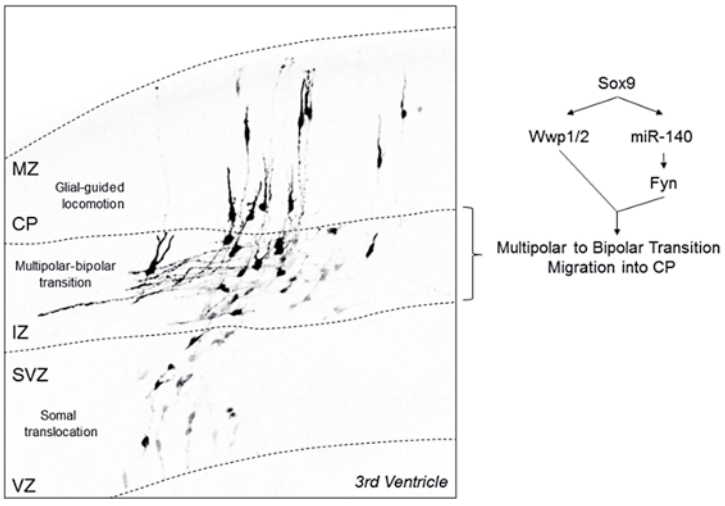

Fig. 2: Sox9-Wwp1/2-miR-140-Fyn constitute a molecular axis to regulate morphology of cortical neurons. A scheme depicts EGFP fluorescence signals in E15.5 coronal section of a mouse brain after *in utero* electroporation at E13.5. After consumptive mitosis of progenitors at the ventricular zone (VZ), immature nerve cells initiate somal translocation. Neurons in the subventricular zone (SVZ) and lower intermediate zone (IZ) undergo multipolar – bipolar transition prior to migration into the cortical plate (CP) to reach the marginal zone (MZ).

Both, *miR-140* and *Wwp2* seem to be major targets of Sox9 transcription factor in cartilage (Li et al., 2014). Developmental profiling revealed striking resemblance of *Sox9* and *Wwp2* expression patterns in the developing cortex. It was therefore tempting to speculate that Sox9 serves as a major regulator of *Wwp2/miR-140* duo in neurons, too. Indeed, both knockdown and genetic deletion of *Sox9* resulted in pronounced loss of pyramidal morphology in developing neurons and altered laminar distribution of cortical nerve cells. Further, down-regulation of Sox9 in cultured cortical neurons resulted in decreased levels of Wwp2 and miR-140; moreover, surprisingly also levels of Wwp1 were reduced. Using luciferase assay, we then showed Sox9-dependent transcriptional induction of promoters of both genes: *Wwp1* and *Wwp2/miR-140*.

Altogether, we described a molecular axis composed of transcription factor Sox9, ubiquitin ligases Wwp1, Wwp2, intron-retained miR-140 and downstream Fyn kinase in orchestrating axon-dendrite polarity acquisition and migration of cortical neurons in developing murine cortex (Figure 2).

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We believe our study provides novel molecular insights into the concepts of cortical assembly and offers an elaborate mechanistic description of a signaling cascade regulating acquisition of axon, laminar distribution and pyramidal morphology of developing neurons (Ambrozkiewicz et al., 2017).

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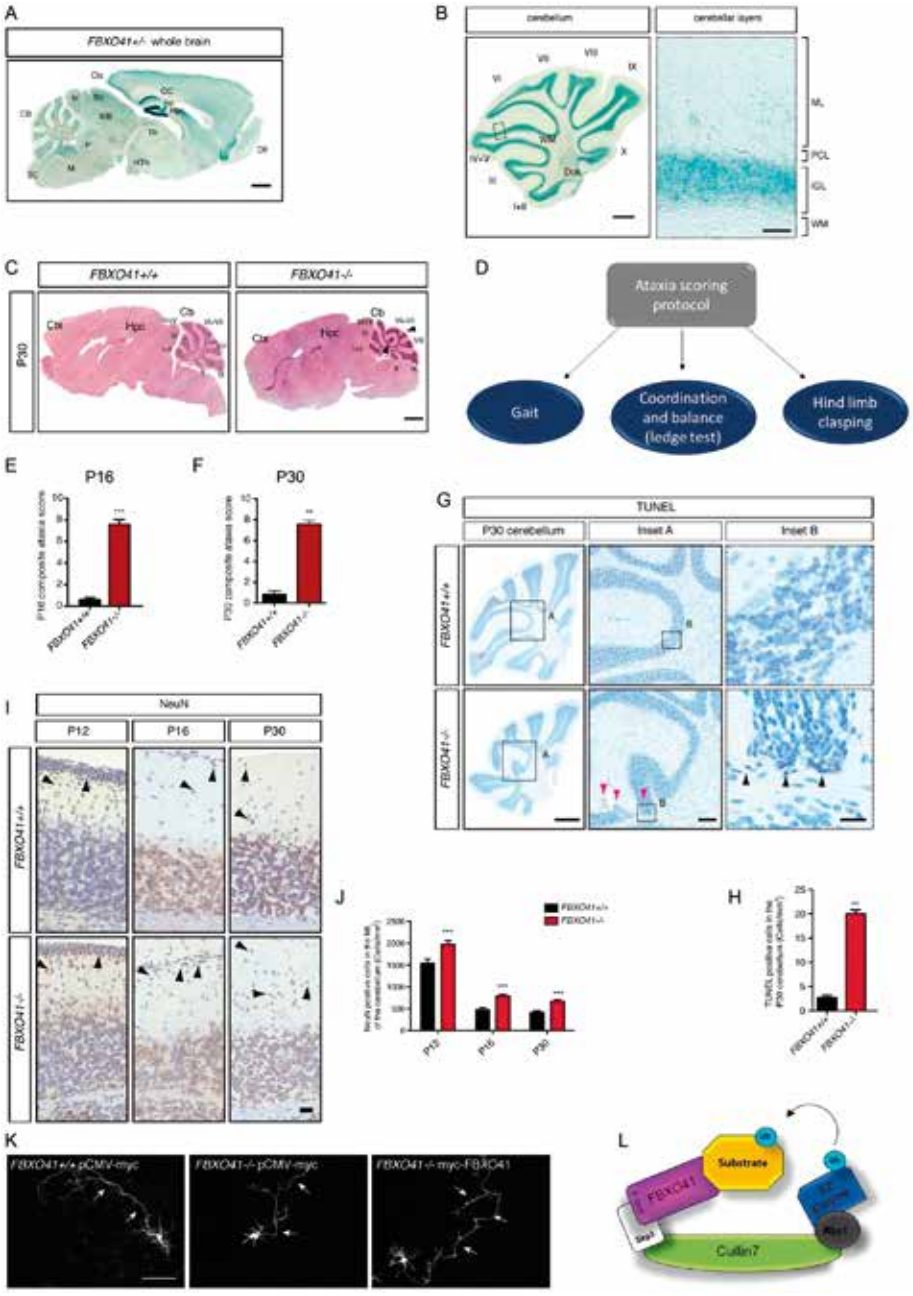
Tip of the ice berg

First attempts at understanding the function of FBXO41 in the CNS *by Chaitali Mukherjee*

Neurodevelopment is a fundamental process that is tightly orchestrated by events such as neurogenesis, neuronal migration, morphogenesis and synaptogenesis, which ultimately shape the brain. These events are governed by the interplay of cell-extrinsic and intrinsic mechanisms. In the recent decades, the ubiquitin proteasome system has emerged as a crucial cell-intrinsic regulator of neurodevelopment and disease. In this study, we report that loss of FBXO41 results in severe ataxic motor symptoms in mice, together with defects in granule neuron migration, impaired axon growth and neurodegeneration in the cerebellum. Additionally we discovered FBXO41 as the second F-box protein to form an atypical SCF-like E3 ligase complex together with Skp1 and cullin7. Collectively we identify the yet unstudied CNS-specific F-box protein FBXO41 as a key regulator of cerebellar development.

The cerebellum often called the little brain is crucial for proper gait and motor coordination. This becomes increasingly clear when one observes that atrophy or cerebellar malformations are often associated with a host of motor symptoms (Chizhikov and Millen 2003, Assadi, Leone et al. 2008, Millen and Gleeson 2008). Several developmental disorders for example Dandy walker malformations, Jouberts syndrome and the Cayman type ataxia are a direct consequence of improper cerebellar development (Millen and Gleeson 2008, Reeber, Otis et al. 2013).The cerebellum has a defined morphology and cytological architecture with a foliated appearance. Cytologically the cerebellum can be divided into 3 major layers- the molecular cell layer (ML), Purkinje cell layer (PCL) and the internal granule layer (IGL). The ML houses the Purkinje cell dendritic branches, the granule cell axons and certain variety of GABAergic inter neurons. Then lies the PCL that is a single cell layer of Purkinje neuron cell bodies arranged in a row. Below that is the IGL densely packed with cerebellar granule neurons (CGNs) (Altman and Bayer 1978, White and Sillitoe 2013). To ensure proper cerebellar development, events such as neuronal differentiation, migration and morphogenesis must occur in a well-coordinated manner. CGN migration is one of the most critical and final events to take place during cerebellar development that ensure proper lamination and circuitry of the cerebellum. In the course of mouse embryonic development, CGN progenitors migrate rostrally from the rhombic lip to reach the cerebellar anlage. Once there, these cells proliferate to give rise to the external granule layer (EGL), the outer most cell layer of the developing cerebellum. Following proliferation, postnatally in mice, these progenitors differentiate and start migrating inwards across the ML to reach the IGL where they take up residence. Towards the end of cerebellar development the CGNs have occupied the IGL and formed the parallel fibers that form synapses with the Purkinje cell dendrites. The EGL completely disappears by the 2nd post-natal week (Altman and Bayer 1978, White and Sillitoe 2013). The entire process of CGN migration is a very tightly regulated event, orchestrated either by various cell extrinsic factors and cell-intrinsic mechanisms (Sillitoe and Joyner 2007, White and Sillitoe 2013). While cell intrinsic mechanisms like transcription factors, kinases and cytoskeletal modulators have been extensively studied in the context of neurodevelopment, the Ubiquitin proteasome system (UPS) and its players have only gained prominence in the last two decades(Kawabe and Brose 2011). Studies for example have identified the multi-subunit E3 ligase Cdh1APC as a major regulator of neurodevelopment and neuronal morphogenesis (Konishi, Stegmuller et al. 2004, Kannan, Lee et al. 2012).

Our lab had previously done a screen for brain enriched UPS related proteins, where FBXO41 was identified as one of the promising candidates. Through biochemical analysis we found that FBXO41 was in fact exclusively expressed in the central nervous system (CNS) and was completely absent from other tissues. Its expression also seemed to increase during the course of embryonic neurodevelopment and retained a steady state expression throughout the life of the animal. The CNS-specific expression of FBXO41 made it an even more exciting candidate to study further. During my PhD thesis I worked on characterizing the FBXO41 knockout (KO) mouse that was previously generated in the lab. This was a conventional knockout mouse where the entire FBXO41 gene was replaced by a LacZ neomycin reporter cassette. When looking at the expression of FBXO41 within the adult mouse CNS, by LacZ staining (expression of LacZ corresponds to FBXO41 expression, as the LacZ is expressed under FBXO41 promoter), it became clear that, not only is FBXO41 a CNS-specific protein but it also had an exclusively neuronal expression. It was expressed in the grey matter (GM) of the brain and being completely absent from the white matter (WM) (**Figure**



1A). This was further verified using biochemical techniques like western blot and RT PCR (Mukherjee, Holubowska et al. 2015). Generating the FBXO41 KO mice enabled us to get further insights into the function of this neuronal CNS-specific protein. We noticed that the FBXO41 KO mice had a reduced body weight and lifespan with 80% of the KO mice dying within the first 2 post-natal (P) weeks and very rarely some surviving up until the age of 2 months. Histological analysis of the P30 adult FBXO41 KO mice brain revealed no overall gross morphological differences when compared to the P30 wildtype brains, except for the cerebellum. The FBXO41 KO mice cerebellum had a rather deformed appearance, with a distorted folia IV+V and a collapsing folia VI+VII (**Figure 1C**) (Mukherjee, Holubowska et al. 2015). This was very interesting, as our KO mice apart from being smaller also had a severely ataxic gait and other motor deficits. The FBXO41 KO and wildtype mice were subjected to a battery of behavioral paradigms designed to study ataxia like motor symptoms (ataxia scoring protocol) at ages P30 and P16 (Guyenet, Furrer et al. 2010) (**Figure 1D**). To access the severity of the phenotype the mice were scored from 0 to 3, 0 being no phenotype and 3 being the most severe manifestation of the phenotype. The FBXO41 KO

Fig. 1: (A) Sagittal section showing Lacz staining of P30 FBXO41+/- mice brain. The blue LacZ staining corresponds to the expression of FBXO41. **(B)** Sagittal section of the P30 FBXO41+/- mouse cerebellum, stained for LacZ. **(C)** Sagittal sections of FBXO41+/+ (wildtype) and FBXO41-/- (KO) mice brains stained for H&E. Arrow represents distorted cerebellar morphology. **(D)** Schematic depicts the behavioral tests and parameters measured as a part of ataxia scoring protocol. **(E, F)** Combined ataxia score of FBXO41 +/+ and -/- mice at P16 and P30 respectively. **(G)** Representative image of P30 FBXO41 +/+ and -/- mice cerebella stained for TUNEL. **(H)** Quantification of G. **(I)** Representative images of P12, P16 and P30 FBXO41+/+ and -/- mice cerebella stained for neuronal marker NeuN, depicting the CGN migration deficit. **(J)** Quantification of NeuN positive neuronal density in the ML of FBXO41+/+ and -/- mice at the represented ages. **(K)** Image showing the axon growth deficits in cultured CGNs from FBXO41+/+ and -/- mice. **(L)** Schematic representation of the formation of FBXXO41 Cul7 SCF E3 ligase complex. Figures adapted from (Mukherjee, Holubowska et al. 2015)

mice always performed significantly worse in all the testes, thus they got a significantly higher combined ataxia score at both ages P30 and P16, when compared to their wild type littermates (**Figure 1E,F**). On taking a closer look at the expression of FBXO41 in the cerebellum (LacZ), it became clear that FBXO41 as previously established had a neuronal expression, but it also appeared to be highly expressed in CGNs (in the IGL) and was completely absent from the ML and the PCL (**Figure 1B**). Owing to its CGN specific expression in the cerebellum and abundant neuronal expression in other parts of the brain, we reasoned that FBXO41 could be important for neuronal cell health and survival. If true, then the abnormal cerebellar architecture of the P30 FBXO41 KO mice could be due to increased cell death. To test our hypothesis we carried out histological analysis of the FBXO41 KO mice cerebella at P30 as well as P16, using TUNEL assay. TUNEL assay specifically stains the nuclei of dead cells. We saw significantly higher number of dead cells (TUNEL+) in the cerebella of FBXO41 KO mice at P30 (no significant increase in TUNEL+ cells was observed in other regions of the brain) (**Figure 1G,H**). We also carried out an *in vitro* neuronal survival assay in cultured mouse CGNs which confirmed our findings that FBXO41 was crucial for survival of CGNs. Interestingly while we observed increased cell death of in the P30 FBXO41 KO cerebellum, we did not notice any signs of cell death, astrogliosis or increased activation of microglia at in the FBXO41 KO mice cerebellum at P16. We also did not observe a distorted cerebellar morphology at this age when compared to the wildtype mice. This was very puzzling because, at P16 although there were no signs of neurodegeneration, the FBXO41 KO mice still showed ataxic gait and motor symptoms of the same severity at that of the P30 FBXO41 KO mouse. This suggested other underlying functions of FBXO41 apart from neuronal survival that might be contributing to the motor symptoms of the KO mice. Further histological investigation revealed neuronal migration disturbances in the cerebellum of FBXO41 KO mouse, already observable from P12. On analyzing the cerebellum of the FBXO41 KO mice and their age matched wildtype littermates at three different ages – P12, P16 and P30, it became apparent that the FBXO41 KO mice had delayed or slower migration of CGNs from the EGL to the IGL. While in the wild type mice CGN migration was already complete by the second post-natal week, in comparison we observed that the P12 FBXO41 KO mouse cerebella had a thicker EGL and at P16 while the wildtype no longer had an EGL, the FBXO41 KO mouse cerebella still had thin EGL left. At all ages we observed more number of neurons migrating across the ML in the FBXO41 KO mice when compared the wild type (**Figure 1 I, J**) (Mukherjee, Holubowska et al. 2015). This observation together with *in vivo* electroporation experiments done in neonatal rat pups confirmed that loss of FBXO41 leads to delayed migration of CGNs (Holubowska, Mukherjee et al. 2014, Mukherjee, Holubowska et al. 2015).

Neurite extension and axon outgrowth are events that are vital for proper connectivity of the brain and are closely associated with neuronal migration. Very similar to neuronal migration, axon growth is also an event that is is governed by various cell extrinsic and cell intrinsic mechanisms (Kawabe and Brose 2011). Since several of the molecular players of neuronal migration also influence axon growth, we wondered if FBXO41 apart from playing a role in neuronal migration, also contributed to axon growth. We cultured CGNs from FBXO41 wild type and KO mice and observed indeed loss of FBXO41 lead to shorter axons (**Figure 1K**). Axon length in the KO mouse neurons was restored when FBXO41 was over expressed in them. Interestingly, other neuronal culture experiments also revealed excess of FBXO41 lead to longer axonal length. Thus, identifying FBXO41 as a positive regulator of axon growth. Having identified a role for the yet unstudied protein FBXO41, we went on to characterize it at a molecular level. FBXO41 belongs to a family of Fbox proteins, which function as substrate recruiting adaptor proteins of several multi-subunit E3 ligases. The ubiquitin proteasome system typically has three major players- 1. The E1 ubiquitin activating enzyme that activates ubiquitin by the cleavage of ATP. 2. The E2 ubiquitin conjugating enzyme, that is responsible for conjugating ubiquitin or ubiquitin chains onto selected protein substrates. And last but not the least, 3. The E3 ubiquitin ligases, the most versatile player of the three with more than 600 members of this family identified so far.E3 ligases are responsible for recruiting specific protein substrates for ubiquitination by the E2 enzyme (Maupin-Furlow 2011). Fbox proteins together with the scaffold proteins from the Cullin family and adaptor proteins such as Skp1 form one of the most widely studied multi-subunit E3 RING type ligase families. In this type of multi-subunit

E3 ligases, the Scaffold protein binds the E2 enzyme that brings the ubiquitin, the small adapter proteins help bind the scaffold to the Fbox proteins. The Fbox proteins in turn function as the variable or interchangeable part of the complex, as they bind to specific protein substrates and recruit them to the complex for ubiquitination (Zheng, Schulman et al. 2002). Since, FBXO41 belongs to the Fbox protein family; we went on to test if it also formed a multisubunit E3 ligase complex. One of the most abundant members of RING type cullin E3 ligases are those that form the Skp1-Cullin1-Fbox protein (SCF) complex, thus we wondered if FBXO41 would also form a classical SCF complex. Interestingly, while FBXO41 did interact with the adaptor protein skp1 (via its Fbox domain), it failed to interact with Cullin1.

On testing other members of the cullin family by co-immunoprecipiation assays (Cullin1,2,3,4,5 and 7 (Skaar, Pagan et al. 2013)) we found that FBXO41 instead binds to Cullin7 (Cul7).Cell based ubiquitination assay experiments also confirmed FBXO41 SCF Cul7 to be an active and functional E3 ligase capable of ubiquitination (**Figure 1L**). Interestingly the only other Fbox protein identified so far to form an atypical SCF complex with Cullin7 instead of Cullin1 is Fbxw8. Fbxw8Cul7 SCF was also found to influence cerebellar development and be crucial for CGN dendrite growth (Sarikas, Xu et al. 2008, Litterman, Ikeuchi et al. 2011). Armed with this information, we wondered if the atypical SCF formed by FBXO41Cul7 SCF could be its analogue that influences not dendrite but axon growth. We tested our hypothesis in cultured CGNs, wherein we observed while over expression of full length FBXO41 resulted in longer axons, deletion mutants of FBXO41 that no longer bind with either Skp1 or to Cul7 lost their axon growth promoting effect.These results suggest that the axon growth promoting function of FBXO41 is a direct consequence of its ability form the active FBXO41Cul7 SCF E3 ligase.

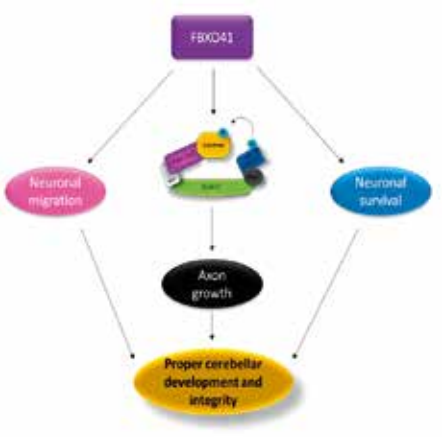


Fig. 2: Schematic summarizes the key findings of my PhD, which defines a role for FBXO41 in Neuronal migration and neuronal survival. Additionally we identify FBXO41 Cul 7 SCF, as a novel E3 ligase that is a positive regulator of axon growth. Taken together FBXO41 was identified as a key regulator of proper cerebellar development.

With all of the above results and observations taken together, we report FBXO41, a neuronal CNS-specific protein, as the second known Fbox protein to form an atypical SCF type E3 ligase with Skp1 and Cul7. We additionally showed that it is crucial for proper neuronal migration, axon growth and cell survival in the developing cerebellum, thus identifying FBXO41 as a key regulator of proper cerebellar development (**Figure 2**). However, there are several unanswered questions that would be very interesting to pursue further. For starters, identifying new protein targets and substrates of the E3 ligase FBXO41 Cul7 SCF would not only help shed light on to its mechanism of action in axon growth, but may also point to other unidentified functions it may have. Additionally it will be interesting to determine if neuronal migration and neuronal survival are also a result of the ligase activity of FBXO41 Cul7 SCF. Finally, since FBXO41 is abundantly expressed throughout the brain, with very high expression in the cortex, cerebellum and the hippocampus, it is imperative to study the role of FBXO41 in other regions of the brain. Use of brain region specific FBXO41 conditional KO mice models might enable us to study the contribution of loss of FBXO41 in terms of behavior and physiology in different brain regions in an age dependent manner (embryonic neurodevelopment vs old age), without compromising on the lifespan of the animal.

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A novel approach ...

to study the neurotransmitter uptake machinery in glutamatergic and GABAergic synaptic vesicles

by Zohreh Farsi

In order to maintain high-fidelity synaptic transmission, synaptic vesicles (SV) must quickly load thousands of neurotransmitter molecules [1] within the few seconds of SV recycling [2]. The current model for neurotransmitter loading begins with the generation of an electrochemical proton gradient across the vesicular membrane. This gradient is formed by the vacuolar H^+-ATPase (V-ATPase), which pumps protons into the lumen [3]. Vesicular transporters then use the energy provided by this gradient to sequester molecules into the lumen of SVs. Although a number of ion co-transport and exchange mechanisms have been identified [4, 5], challenges associated with assaying the electrochemical gradient in distinct vesicle subpopulations have hindered the development of a unifying model. Here we used single-vesicle imaging to resolve how the electrochemical gradient is regulated in glutamatergic and GABAergic SVs [6]. With full characterization of the electrochemical gradient we were able to unravel the transport mechanism of vesicular GABA transporter (VGAT), demonstrating that it functions as a GABA/H^+ exchanger with no other ion required in its transport cycle.

Accumulation of protons in the lumen of SVs by V-ATPases results in formation of an electrochemical proton gradient ($\Delta\mu_{H+}$) across the membrane. The contribution of the electrical ($\Delta\psi$) and chemical (ΔpH) components of this gradient to the uptake of a given neurotransmitter is dependent upon its net charge [7]. At neutral pH, anionic glutamate transport is thought to be driven mainly by $\Delta\Psi$ [8] while transport of predominantly uncharged GABA utilizes both components [5]. Considering the distinct bioenergetic reuirements for loading glutamate and GABA, we tested whether the two components of the $\Delta\mu_{H+}$ are regulated differently in these vesicles [6]. SVs purified from transgenic mice expressing super-ecliptic pHluorin (pH-sensitive GFP) in the vesicular lumen (spH-SVs) [9] were imaged using total internal reflection fluorescence (TIRF) microscopy to accurately measure luminal pH changes above pH 6 (Fig 1A and B). In addition, we used the voltage sensitive dye VF2.1.Cl [10] to quantitatively measure changes in membrane potential across the lipid bilayer of single SVs (Fig 1C and D). After measuring ΔpH or $\Delta\psi$, antibody labeling against VGAT or vesicular glutamate transporter 1 (VGLUT1) allowed for unequivocally distinction of GABAergic from glutamatergic SVs.

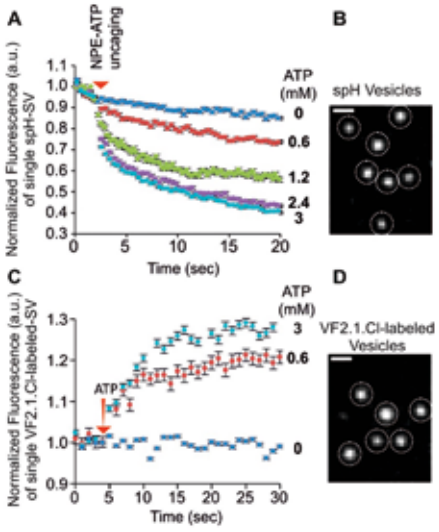
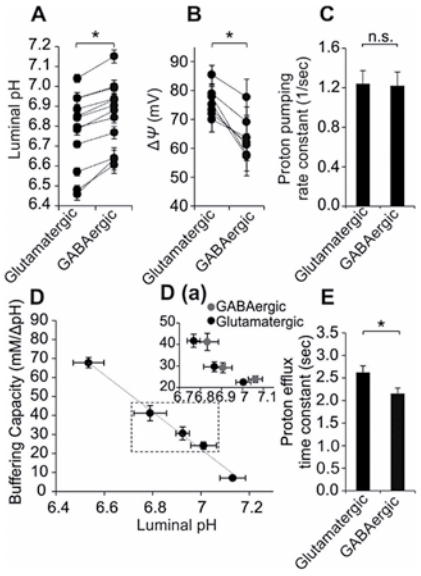


Fig. 1: Imaging of $\Delta\mu_{H+}$ in gluatamatergic and GABAergic SVs. (A) Averaged spH time-trace in response to NEP-ATP uncaging by a UV flash. (B) Representative image of spH-SVs. (C) Averaged VF.2.1.Cl time-trace in response to ATP addition. (D) Representative image of VF2.1.Cl-labeled SVs. Dashed circles in (B) and (D) indicate detected SVs. Scale bars, 1 µm. In (A) and (C), the traces in the absence of ATP show the photobleaching of the probes and error bars represent SEM from more than 500 single SVs.

Interestingly, comparison of glutamatergic and GABAergic vesicles revealed significant differences in the electrochemical gradient generated within these two vesicle subclasses. We observed that upon acidification, a 17.79 ± 6.9 mV greater electrochemical gradient (11.99 ± 5.2 mV larger $\Delta\psi$ and 0.1 ± 0.03 larger ΔpH) was formed across the membrane of glutamatergic vesicles compared to that of GABAergic vesicles within the same population (Fig 2A and B). There are three main determining factors of $\Delta\mu_{H+}$ magnitude that may account for the observed difference between these vesicles: the rate of proton influx, the amount of free protons in the lumen, and the rate of proton efflux [11]. We therefore first tested whether the proton pumping speed differed between these SV types. Higher acidification rates resulting from higher copy-number of active pumps in glutamatergic vesicles could explain the greater $\Delta\mu_{H+}$, however no significant difference was observed between glutamatergic and GABAergic SVs (Fig 2C). This is not unexpected, as past quantitative proteomic comparison revealed no significant difference in the copy number of V-ATPases subunits between vesicle subpopulations [12]. Next, since the amount of

Fig. 2: The magnitude of $\Delta\mu_{H+}$ is smaller in GABAergic SVs. Luminal pH and (A) and $\Delta\psi$ (B) of acidified glutamatergic and GABAergic SVs ($P = 2.7 \times 10^{-5}$ and 0.03, respectively). Note that the variations in luminal pH are partially due to different ATP concentrations in some of the experiments (0.6-3 mM). Two circles connected via a dashed line represent one experiment. (C) The proton pumping rate constants of glutamatergic and GABAergic SVs were measured in glycine buffer at 2.4 mM ATP. No significant difference was observed between these SV populations. n.s = not significant ($p > 0.05$). (D) Buffering capacity as the function of luminal pH. A stronger buffering effect was measured at lower luminal pH, a phenomenon which has been observed in other organelles as well [18]. This implies that dominant luminal buffers of SVs have pK_a–values lower than 6.5. No difference was observed in magnitude of buffering capacity between glutamatergic and GABAergic SVs (inset (D(a)). Red dashed line presents linear fit to data. (E) Proton efflux time constant of glutamatergic versus GABAergic SVs ($P = 0.03$). Data in (A) and (B) represent mean ± SEM from on average 450 glutamatergic and 160 GABAergic SVs per experiment, in (C) and (E) represent mean ± SEM from on average 50-100 single SVs compiled from independent experimental replicates with an R-squared value > 0.7, and in (D) represent SD of 3-5 experimental replicates.

free protons in the lumen and thus magnitude of ΔpH across the membrane is determined by the luminal buffering capacity of the vesicles, we tested whether this differed between these SVs. We observed that in both vesicle populations, buffering capacity increased as the lumen of vesicle acidified but there was no significant difference in magnitude of buffering capacity (Fig 2D and D(a)). With still no explanation for the observed difference, we measured the proton efflux rate in these vesicles. To do this, SVs were first equilibrated in an acidic bath solution, and then proton efflux rate was measured upon formation of a pH gradient across the membrane by fast exchange of the bath solution with an alkalinizing buffer. Interestingly, significantly faster proton efflux was measured in GABAergic compared to glutamatergic SVs (Fig 2E). This indicates higher proton permeability (P_{H+}) in these SVs (P_{H+} = 15.2 x 10^{-3} and 13.5 x 10^{-3} cm.sec^{-1} in GABAergic and glutamatergic SVs, respectively). The greater efflux rate in GABAergic vesicles shifts the dynamic equilibrium of luminal protons and lowers $\Delta\mu_{H+}$, accounting for the measured difference between these vesicles.



In order to better understand the mechanism behind the greater proton efflux in GABAergic SVs, we sought to determine whether it is protein mediated or the result of leakage through the membrane. Since the total flux of protons through the membrane is directly proportional to the surface area of the vesicle [11], we first measured the diameter of SVs (d_{SV}) by electron microscopy, using immunogold labeling to distinguish between vesicle types (Fig 3A). In order for the higher proton efflux of GABAergic SVs to be attributed to a larger surface area, these vesicles would need to have diameter ~ 9 nm larger than glutamatergic vesicles. No significant difference in diameter was measured (dSV = 45.5 ± 8.1 and 45.8 ± 10.3 for glutamatergic and GABAergic SVs, respectively), suggesting a protein-mediated mechanism. Since the protein content of glutamatergic and GABAergic SVs is highly similar and only the vesicular transporters are exclusively present in each vesicle population [12], we hypothesized that VGAT contributes to proton efflux in GABAergic SVs. In line with this view, we observed that within each acidification measurement there was a clear positive correlation between the luminal pH of acidified GABAergic SVs with the intensity of labeling with antibody against VGAT, indicating that SVs with greater VGAT copy numbers have greater proton permeability (Fig 3B).

Although there is a lack of direct evidence, it is assumed that VGAT functions as a GABA/H^+ antiporter [5]. If this antiport mechanism were to exist, we would expect the apparent proton efflux of GABAergic SVs to be enhanced by the presence of GABA. Indeed, by including 10 mM GABA in the alkalizing buffer we observed significantly increased proton efflux from GABAergic vesicles (Fig 3C) whereas that of glutamatergic vesicles remained unchanged (Fig 3D), providing the first

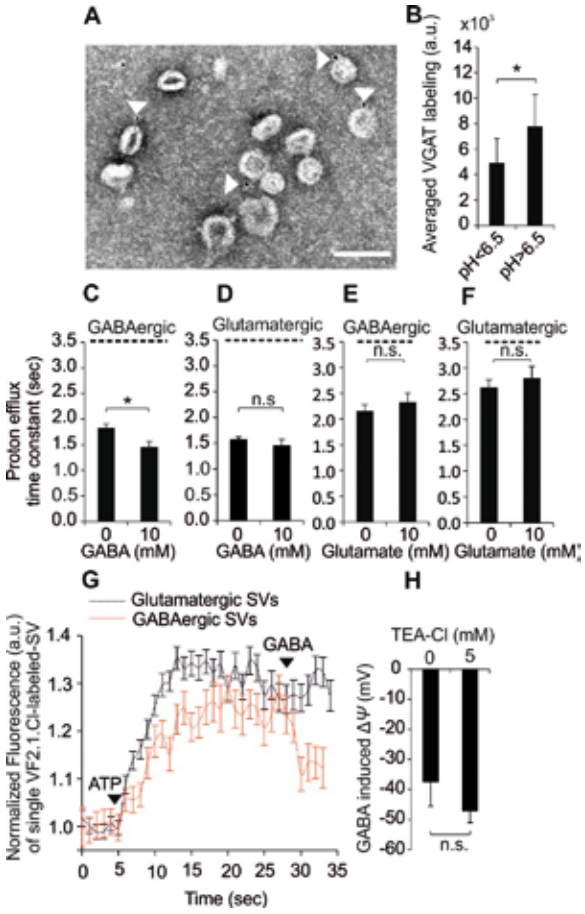


Fig. 3: VGAT functions as a GABA/H⁺ exchanger. (A) Representative EM picture of immunogold labeled SVs (negative staining). Purified SVs from mouse brain were labeled with antibodies against VGAT (Synaptic Systems). White arrowheads show labeled SVs, non-labeled SVs were considered glutamatergic [19]. Scale bar is 100 nm. (B) Correlation between luminal pH of acidified GABAergic SVs with intensity of antibody against VGAT (P = 0.011). Error bars represent mean ± SD of 7 independent experiments. Proton efflux time constant of (C) GABAergic and (D) glutamatergic SVs in the presence and absence of GABA [P = 7.7 × 10^{-3} in (C)]. Proton efflux time constant of both GABAergic (E) and glutamatergic (F) SVs slightly, but not significantly, increased in the presence of 10 mM glutamate in the alkalinizing buffer. In line with previous reports [8, 20], these data indicate that in contrast to GABA and glycine, uptake of glutamate is not coupled to stoichiometric proton efflux. Data in (C-F) represent mean ± SEM from on average 50-60 single SVs compiled from 5 experimental replicates. (G) Averaged VF.2.1.Cl time-trace in response to addition of 3 mM ATP and 10 mM GABA, indicating changes in Δ associated with GABA uptake in GABAergic (red trace) but not in glutamatergic (black trace) SVs. Error bars represent SEM of 50 and 392 SVs in red and black traces, respectively. (H) Changes in Δ induced by addition of GABA to acidified SVs in the absence and presence of 5 mM TEA-Cl in the bath solution. Error bars represent mean ± SD of 3-5 independent experiments.

incontrovertible evidence that VGAT does in fact functions as a GABA/H⁺ exchanger. The same result was obtained with 20 mM glycine, which is another substrate of VGAT [6]. Glutamate had no significant effect on proton efflux rate in any of the vesicle populations (Fig 3E and F).

The GABA/H⁺ antiport mechanism, although supported by some studies [13-16], has been challenged recently by a proposed GABA/Cl^- co-transport mechanism [17]. Although the measurements above were performed in complete absence of chloride and thus are clearly not the result of a GABA/Cl^- co-transport mechanism, we characterized the effect of GABA on membrane potential in the presence and absence of Cl^- to clarify any regulatory effect of this ion. We observed that the addition of GABA to acidified SVs in the absence of Cl^- partially dissipated the electric potential across the membrane (Fig 3G). Since GABA has no charge at neutral pH, this provides additional evidence that GABA transport is coupled to proton efflux from the vesicular lumen. If a coupled GABA/Cl^- co-transport mechanism was present in addition to GABA/H⁺ antiport, GABA induced charge dissipation should be significantly greater in the presence of Cl^-. However, we observed only a slight increase in this value (Fig 3H), ruling out any prominent transport of Cl^- by VGAT [17].

Altogether, our work presents a novel approach to quantitatively characterize both components of the electrochemical gradient in distinct vesicle populations. We showed that the regulation of the $\Delta\mu_{H+}$ is indeed different in glutamatergic and GABAergic SVs. Moreover, with assaying the $\Delta\mu_{H+}$ in the presence of the neurotransmitters we were able to unravel the transport mechanism of VGAT, providing direct evidence that it functions as a GABA/H⁺ exchanger.

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A new mouse model ...

for Parkinsonian-Pyramidal Syndrome *by Siv Vingill*

Parkinson's Disease (PD) is a severe diagnosis that impacts life quality of both affected people and their friends and family. Understanding the mechanisms of disease is crucial when it comes to developing new treatments and preventive measures. Genetic variants of PD can provide insight into these pathways. In this project we have investigated the role of *FBXO7*, a newly described PD-related gene, in neuronal function. We have characterized *FBXO7* knock-out mouse models and found the FBXO7 protein to be crucial for neuronal function and involved in proteasomal activities in the cell.

During the last decades we have made tremendous leaps in terms of increased living standards. We have vaccines, better nutrition and many diseases are easily treated or have been eradicated. As a result we live longer, healthier and (hopefully) happier lives. However, there is a downside; with an aging population comes aging-related diseases and we now see rising numbers of people suffering from amongst others Alzheimer's and Parkinson's disease.

The key to better treatments and delayed progression of the disease is a thorough understanding of why neurons die in these diseases. For this we need good model systems, either through human or animal cells. Genetic research of PD has led to several new genes being connected to familiar and sporadic variants of the disease. Although some of these genetic cases present as subsets of PD, the symptoms are similar and we can use them to model the degeneration of dopaminergic neurons in the substantia nigra as seen in PD [2]. In this way we gain understanding into a rare genetic disorder, but hopefully touch general principles behind the neurodegeneration seen in PD so we can help both people suffering from genetic variants as well as sporadic PD patients.

Many of the genes involved in PD have poorly characterized functions and one of these is *FBXO7*, whose mutations cause a subset of PD known as Parkinsonian-Pyramidal Syndrome [3, 4]. The Stegmüller lab has a profound interest in a specific subset of proteins that have been shown to be essential for many processes both in the development and the degeneration of cells, namely the E3 ligases. FBXO7 is one of these [5, 6]. They are a part of the ubiquitin proteasome system and responsible for the recognition of specific proteins for degradation or functional modification. This process is essential for all cells, but especially for neurons where a precise timing of protein expression makes them able to respond and transfer signals in their quick and elegant manner. Although some targets of its ubiquitination activity have been identified [7], little was known about FBXO7's role in neurons and how its disruption leads to symptoms corresponding to Parkinson's disease.

With a recessive inheritance pattern and patients showing lower protein levels, we hypothesized that we were looking at a loss-of function mechanism and chose knock-out mice as our way to model the disease [1].

After an initial characterization we found that the *FBXO7-/-* mice die prematurely around 21 days after birth. These mice are about half the size of their litter mates and much weaker, but agile and able to run around when not challenged. Most PD mouse models of recessively inherited genes have shown few or no symptoms, so this early deterioration was unexpected. However, since FBXO7 is expressed throughout the entire body, this could be due to other cell types than neurons. We therefore decided to use a conditional knock-out system where Cre was expressed under different promoters, so that FBXO7 would be knocked out only in the relevant neuronal subtypes. Mutations in *FBXO7* cause Parkinsonian-Pyramidal Syndrome; where the Parkinsonian symptoms are due to a dysfunction of the dopaminergic system in the basal ganglia, while the pyramidal symptoms arise from dysfunction of the excitatory pyramidal neurons of the cortex. We used Tyrosine Hydroxylase (TH) to knock FBXO7 out in catecholaminergic neurons (TH-Cre;fl/fl), amongst those the dopaminergic neurons of the substantia nigra [8], and neuronal helix-loop-helix protein-1 (NEX) to target the pyramidal neurons of the cortex and hippocampus (NEX-Cre;fl/fl) [9]. This enabled us to dissect the Parkinsonian and the pyramidal symptoms and investigate loss of FBXO7 in specific neuronal subtypes as well as the entire body.

When we knocked out FBXO7 using TH-Cre to target the dopaminergic neurons, we initially observed no difference in the behaviour of these mice compared to age-matched controls. We therefore initiated collaboration with Camille Lancelin in Till

Marquardt's lab, where they had the DigiGait system, which allows you to visualize the walking pattern of mice. She found that the TH-Cre;fl/fl mice had shorter stride length and increased stride frequency which is similar to the more conventional MPTP mouse model of PD. And as the animals aged further, we could see that they started to move around less in the open field (**Figure 1A**) and had problems keeping up with their age-matched controls on the more challenging rota-rod test (**Figure 1B**). Overall we could see a decline in the motor behaviour of these mice from two to twelve months, with symptoms comparable to the slowness of movement and gait disturbances seen in PD.

To model pyramidal symptoms we knocked out FBXO7 in the excitatory pyramidal neurons of the cortex and hippocampus. These neurons are essential for primary communication between muscles and brain and disturbances in these neurons can lead to spasticity, dystonia and disturbed reflexes in humans. The NEX-Cre;fl/fl mice showed hind limb clasping at an early age (**Figure 2A**) and were tense and had jerky movements when handled for the first time. However, to our surprise the NEX-Cre;fl/fl mice showed a

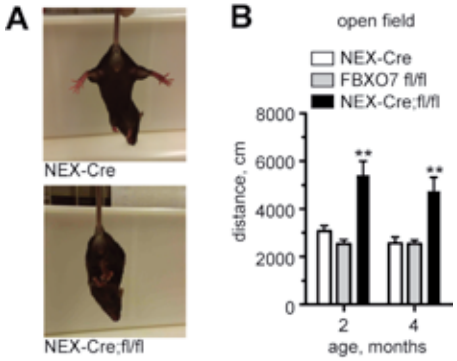

Fig. 2: NEX-Cre;fl/fl mice show hind-limb clasping (A) and hyperactivity in the open field (B) already at two months of age.[1] Copyright © 2016 by John Wiley Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.

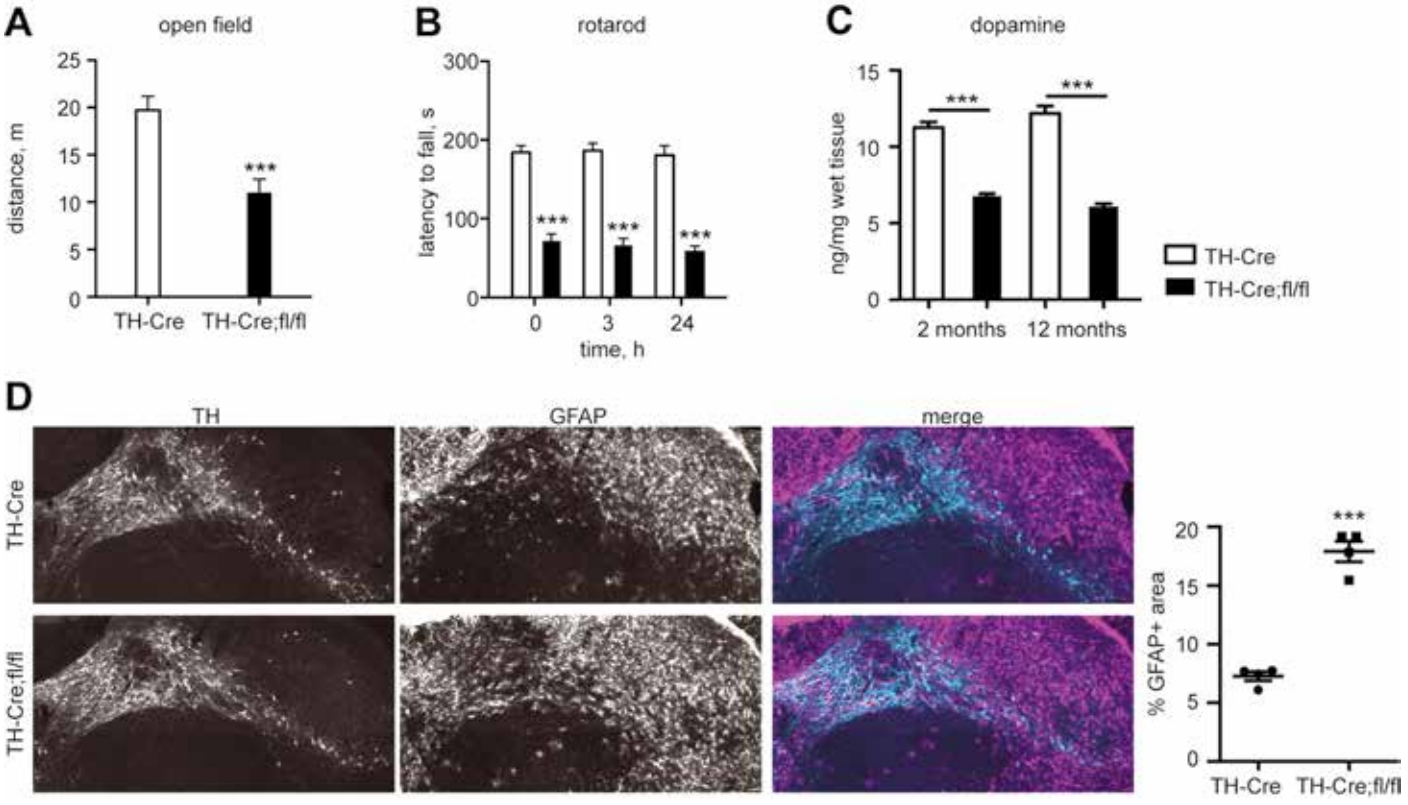

Fig. 1: TH-Cre mice show decline in open field activity at twelve months of age (A) and poor performance in the rota-rod test (B). TH-Cre;fl/fl mice show decreased levels of dopamine in the striatum both at two and twelve months (C) (HPLC experiment was conducted in collaboration with Dr. Tatenhorst in the Lingor lab). They also show increased levels of the astrocytic marker GFAP (magenta) in the substantia nigra (marked by TH, cyan) at twelve months (D). [1] Copyright © 2016 by John Wiley Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.

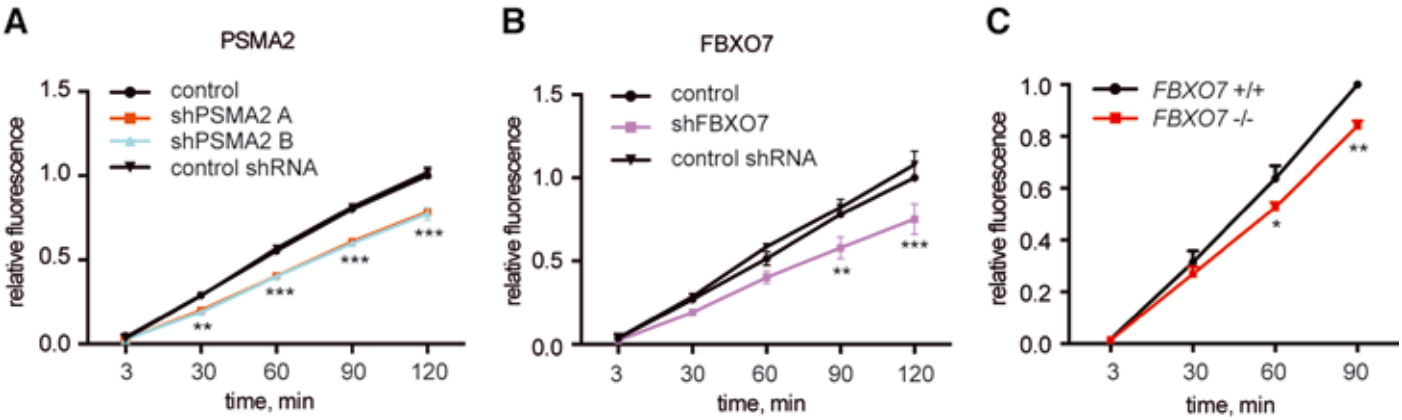

Fig. 3: PSMA2 was knocked down by siRNA in 293T HEK cells and proteasomal activity in the cells measured. Cells showed a lower activity of the proteasome upon knockdown of PSMA2 (A), as well as upon knock down of FBXO7 (B). Brain tissue from FBXO7 -/- conventional knock-out mice was lysed and subjected to the same assay. Also here loss of FBXO7 caused a lowered proteasomal activity (C).[1] Copyright © 2016 by John Wiley Sons, Inc. Reprinted by permission of John Wiley

clear hyperactivity already from two months of age (**Figure 2B**).

So what causes these behavioural disturbances? The strong phenotype of these mice suggested cellular dysfunction of the cells where we knocked-out FBXO7. However, we found no substantial cell death in the substantia nigra in the TH-Cre;fl/fl, or in the cortex of the NEX-Cre;fl/fl. We therefore investigated the output regions of these neurons and found clear differences compared to control mice. In the TH-Cre;fl/fl mice we found that the level of dopamine in the striatum was approximately half the level of their age-matched controls already at two months of age, which held true also at twelve months (**Figure 1C**). This matches current hypotheses suggesting that loss of terminals, and hence loss of dopamine, precede cellular loss in PD. In addition we saw increased levels of the astrocytic marker GFAP (**Figure 1D**), which suggests inflammation in the substantia nigra. Inflammation often accompanies neurodegeneration, and might be another early sign of poor cellular health.

As we had established that loss of FBXO7 caused dysfunction in the neuronal subtypes targeted, and that this led to specific symptoms resembling Parkinsonian-Pyramidal Syndrome, we started to investigate the cellular mechanisms causing the dysfunction. As an E3 ubiquitin ligase, FBXO7 is responsible for conferring the small signalling molecule ubiquitin onto proteins, to either target them for degradation by the proteasome or confer a functional modification. David Brockelt conducted a yeast-two hybrid screen and found FBXO7 to interact with PSMA2, a part of the core unit of the proteasome (**Figure 3A**). Through an elaborate row of experiments he could show that loss of FBXO7 causes structural changes in the proteasome. We further knocked down FBXO7 in 293T HEK cells and found that this reduction of FBXO7 protein levels reduced proteasomal activity to almost the same level as when we knocked down PSMA2 (**Figure 3B**). When we subsequently looked at brain tissue lysate from the FBXO7-/- mice we could see that they indeed had lowered proteasomal activity (**Figure 3C**).

FBXO7 has previously been linked to mitochondrial activity through its interaction with two other known PD genes, PINK and Parkin [10]. Mitochondrial function and proteasomal functions are closely linked and dysfunction in one pathway can cause disturbances in the other and vice versa. We show that FBXO7 in addition is involved in proteasomal function, which could link two vulnerable cellular pathways and explain why loss of FBXO7 has such severe consequences for neuronal function. We are using these models to further investigate how FBXO7 operates in neurons through a thorough molecular characterization. In the future we hope these models can be used to try to rescue

the phenotype seen and transfer the knowledge we have gained onto other models of PD.

Siv VINGILL did her doctoral thesis in Judith Stegmüller's department (Cellular and Molecular Neurobiology) at the Max Planck Institute for Experimental Medicine and defended her PhD thesis in May 2016. Right after that, Siv moved to England in order to take up a position at the University of Oxford, UK.

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References

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Students

Current

Master's class 2015/16

Heba Ali Syria, BSc from Tishreen University, Syria

Burak Bali Turkey, MSc from Bogazici University, Turkey

Allison Barry Canada, BSc from Dalhousie University, Canada

Tizibt Bogale Ethiopia, MD from Hawassa University College of Medicine and Health Sciences, Ethiopia

Tal Dankovich Israel, BSc from Tel Aviv University, Israel

Robert Epple Germany, MSc from Dresden University of Technology, Germany

Burak Gür Turkey, BSc from Sabanci University, Turkey

Alina Sophie Heukamp Germany, BSc from Georg August University Göttingen, Germany

Nehal Johri India, BSc from St. Xavier's College, Mumbai, India

Dimokratis Karamanlis Greece, MD from Aristotle University of Thessaloniki, Greece

Ronja Markworth Germany, BSc from University of Alberta, Canada

Sebastian Molina Obando Spain, BSc from Autonomous University of Barcelona, Spain

Helena Maria (Linda) Olsthoorn The Netherlands, BSc from University College Roosevelt, Utrecht University, The Netherlands

Carolina Piletti Chatain Brazil, BSc from Universidade Federal do Rio Grande do Sul, Brazil

Sonja Pribićević Serbia, BSc from University of Belgrade, Serbia

Alejandro Restrepo Arango Colombia, BSc from Universidad Nacional de Colombia, Bogotá, Colombia

Aditya Singh India, BS-MS Dual Degree from the Indian Institute of Science Education and Research (IISER) Trivandrum, India

Nikoloz Sirmpilatze Greece, MD from Aristotle University of Thessaloniki, Greece

Özge Uslu Turkey, BSc from Bogazici University, Turkey

Kwok Yui Reymond (Tony) Yip Hong Kong (SAR), BSc from Chinese University of Hong Kong (CUHK), Hong Kong

Applications 2015

In the year **2015**, the Neuroscience program received 363 applications from 59 countries.

Germany 35
other Western Europe 33
Eastern Europe 32
North America 17
Central/South America 19
North Africa 28
Central/South Africa 42
Asia / Near East 55
Central Asia / Far East 100
Australia 2

Master's class 2016/17

Theocharis Alvanos Greece, BSc from National and Kapodistrian University of Athens, Greece

Çağatay Aydın Turkey, BSc from Bogazici University, Turkey

Yunus Can Erol Turkey, BSc from Koç University, Turkey

Elisabeth Fritsch Germany, BSc from Georg August University Göttingen, Germany

Danai Katsere Zimbabwe, MedSc from University of Cape Town, South Africa

Henry Klemp Germany, BSc from Georg August University Göttingen, Germany

Ima Mansori Germany, MSc from University of Osnabrück, Germany

Vasyl Mykytiuk Ukraine, BSc from Taras Shevchenko National University of Kyiv, Ukraine

Juan Diego Prieto Ramírez Colombia, BSc from Universidad Nacional de Colombia, Colombia

Jenifer Rachel India, BTech from SRM University, India

Yasmine Shorafa Palestine, MD from Islamic University of Gaza

Elsa Steinfath Germany, BSc from Albert-Ludwigs-Universität Freiburg, Germany

Agnes Steixner Austria, Magister from Medical University Innsbruck & University of Innsbruck, Austria

Clara Tepohl Germany, BSc from Heidelberg University, Germany
Diana Toscano Tejeida Mexico, MD from Anahuac University, Mexico

Juan Felipe Vargas Fique Colombia, BSc from Universidad de los Andes, Colombia

Chrystalleni Vassiliou Cyprus, BSc from University of Edinburgh, UK

Deniz Yüzak Turkey, BSc from Bogazici University, Turkey

Yu Zhao China, BSc from Tongji University, China

Lin Zhou China, BSc from South University of Science and Technology of China (SUSTC), China

Applications 2016

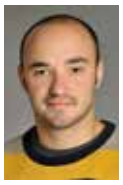
In the year 2016, the Neuroscience program received 581 applications from 81 countries.

Germany 42
other Western Europe 35
Eastern Europe 48
North America 31
Central/South America 37
North Africa 38
Central/South Africa 58
Asia / Near East 79
Central Asia / Far East 213

New Students

PhD projects started in 2015 and 2016

Reham Abdelaziz
Structural determinants of voltage dependant gating of K^+ channels
Luis Pardo,
Ralf Heinrich,
Andreas Neef



Carlos Duque Afonso
Characterization of optogenetic stimulation of cochlear spiral ganglion neurons
Tobias Moser,
Alexander Flügel,
Katrin Willig

Md. Rezaul Islam
Role of non-coding RNA in brain function
André Fischer,
Camin Dean,
Tiago Outeiro

Burak Bali
Optogenetic Manipulation of the Auditory System
Tobias Moser,
Jens Gruber,
Manuela Schmidt

Robert Epple
RNA-depdendent mechanisms in neuronal plasticity
André Fischer,
Camin Dean,
Tiago Outeiro

Sebastian Jähne
The physical basis of neuronal communiation: a quantitative view of the average neuron
Silvio Rizzoli,
Manfred Lindau,
Nils Brose

Lucas Caldi Gomes
Analysis of microRNA expression in Parkinson's disease - from human tissue to animal models
Paul Lingor,
André Fischer,
Silvio Rizzoli

Michael Feyerabend
Subcortical Input onto Inhibitory Interneuons in Mouse Vibrissal Somatosensory Cortex
Jochen Staiger,
Camin Dean,
Tobias Moser

Lina María Jaime Tobón
The physical basis of neuronal communiation: a quantitative view of the average neuron
Tobias Moser,
Erwin Neher,
Manfred Lindau

Alexander Dieter
Optogenetic Activation of the Auditory System
Tobias Moser,
Tim Gollisch,
Stefan Treue

Georg Hafner
Comparing the brain wide afferent connectome of PV, SOM and VIP expressing interneurons in the mouse barrel cortex using retrograde rabies virus tracing
Jochen Staiger,
Silvio Rizzoli,
Camin Dean

Students New

Albert Lehr
Modulation of neuronal excitability in deep brain areas by electric stimulation
Andrea Antal,
Arezoo Pooresmaeili,
Susann Boretius

Luis Giorgano Ramos
Traslosheros López Microcircuits and receptive field organization in the Drosophila visual system
Marion Silies,
Tim Gollisch,
Fred Wolf

Aditya Singh
Investigation of brain networks with TMS for treatment optimization in mood disorders
Andrea Antal,
André Fischer,
Peter Dechent

Thomas Offner
Wiring and information processing in the olfactory bulb of Xenopus laevis
Ivan Manzini,
Thomas Dresbach,
Silvio Rizzoli

Rafael Rinaldi Ferreira
Development of Optogenetic Tool for Induction of Reversible Genome Editing in Specific Subpopulation of Neurons in Non-human Primates
Jens Gruber,
Camin Dean,
Tobias Moser

Rebecca Wallrafen
Assembling a dopaminergic synapse: The role of cell adhesion and scaffolding molecules
Thomas Dresbach,
Nils Brose,
Paul Lingor

Özge Demet Özçete
Studying synaptic sound encoding by fluorescence imaging of single synapses
Tobias Moser,
Camin Dean,
Erwin Neher

M. Sadman Sakib
Role of non-canonical histone varients in cognitive function and aging and neurodegeneration
André Fischer,
Camin Dean,
Tiago Outeiro

Lukas Weiss
Information processing in the olfactory system of different amphibian species
Ivan Manzini,
Ralf Heinrich,
Michael Hörner

Myrto Panopoulou
Behavioral alterations and underlying synaptic plasticity mechanisms in response to cocaine exposure
Oliver Schlüter,
André Fischer,
Siegrid Löwel

Sinem Sertel
Cellular and Synaptic Biology of Daily Cycle
Silvio Rizzoli,
Henrik Bringmann,
Hannelore Ehrenreich

Rashad Yusifov
Structural and functional correlates of neuronal plasticity in the mouse visual cortex
Siegrid Löwel,
Oliver Schlüter,
Marion Silies

Graduated Students

The Masters of 2015 and 2016

Reham Abdelaziz
(*M. Schmidt*) Functional characterization of TRPV1 modulation by protein-protein interactions in somatosensory neurons

Martina Arends
(*M. Simons*) Comparing two vector-based CRISPR/Cas9-systems for Targeting Myelinating Proteins in Zebrafish

Mar Bosch Queralt
(*M. Simons*) Stimulation of the LXR pathway improves remyelination in aged mice after lysolecithin-induced demyelination

Lucas Caldi Gomes
(*M. Bähr*) The effect of increased levels of miR-132 on dopaminergic primary midbrain neurons

Monika Chanu Chongtham
(*G. Eichele*) Stroke induces gene profile changes in adult primate subventricular zone

Alexander Dieter
(*J. Staiger*) Optogenetic Dissection of Cortical Circuits

Carlos Javier Duque Afonso
(*T. Moser*) The role of harmonin for the synaptic heterogeneity of the inner hair cells

Leonard Frederik Engels
(*W. Paulus*) Evaluation of a Novel Feedback System for Myoelectric Hand Prostheses in a Clinically Relevant Setting

Rajaram Ezhilarasan
(*O. Schlüter*) Dissociation of neural circuitry in PSD-95-dependent cocaine-associated memories

Michael Daan Feyerabend
(*J. Staiger*) Characterizing Cell Type Specific Inhibitory Inputs onto Martinotti Cells in Mouse Vibrissal Somatosensory Cortex

Oli Abate Fulas
((*M. Schmidt*) Characterization of protein-protein interactions relevant for TRPA1 mediated nociception

Georg Hafner
(*J. Staiger*) The layer- and column-specific afferent connectome of VIP expressing GABAergic interneurons in the mouse barrel cortex: a brain-wide atlas using retrograde rabies virus tracing

Md. Rezaul Islam
(*A. Fischer*) Small noncoding RNAs as marker for age-associated memory decline

Sebastian Jähne
(*S. Rizzoli*) The Anatomy of the Average Hippocampal Neuron

Lina María Jaime Tobón
(*T. Moser*) Role of endophilin in exocytosis and endocytosis at cochlear inner hair cells

Madhura Ketkar
(*S. Treue*) Combined fMRI- and Eye Movement-based Decoding of Bistacle Plaid Motion Perception

Albert Lehr
(*M. Wilke*) Development of no-report readouts for conscious visibility

Yi-An Liao
(*M. Wilke*) Confidence in Visual Decision-Making

Noam Nitzan
(*N. Brose*) Electrophysiological investigation of the calcium-dependent regulation of Munc13-1 by calmodulin and its involvement in short- and long-term plasticity

Thomas Offner
(*D. Schild*) Calcium response profiles of glomerular regions innervated by a bifurcating olfactory receptor neuron in Xenopus laevis tadpoles

Students Graduated

Özge Demet Özçete
(*T. Marquardt*) The non-canonical Notch ligands Dlk1 and Dlk2 in motor neurogenesis

Myrto Panopoulou
(*O. Schlüter*) Brain region requirements for long-term drug-associated memory retention and Silent synapses protein markers

Foteini Paraskevopoulou
(*E. Neher*) The Developmental Regulation and Localization of Frizzled Family Receptors in the Hippocampus: Screening for Roles in Axon Guidance

Luis Giordano Ramos Traslosheros López
(*S. Treue*) Lentiviral re-targeting for in vivo neuro-optogenetics applications

M. Sadman Sakib
(*A. Fischer*) Role Of Non-Canonical Histone Variant H2A.Z And Its Modification In Cognitive Function

Sura Saleh
(*E. Neher*) RhoA and Cdc42 activity at the Axonal Growth Cone

Erik Schäffner
(*K.-A. Nave*) The effect of PLP overexpression on murine experimental autoimmune encephalomyelitis

Francesca Schönsberg
(*T. Geisel*) Information routing by rate fluctuations in structured neural circuits

Paromita Sen
(*M. Simons*) The role LXR alpha in myelin debris clearance during demyelinating conditions

Sinem Meleknur Sertel
(*S. Rizzoli*) The Patterns of Neuronal Activity in Daily Cycle

Jiyun Shin
(*J. Rhee*) The Novel Functions of Synaptogmin-1 C2 Domains

Michael Siebrecht
(*T. Gollisch*) Effects of Light Adaptation on Stimulus Encoding in Mouse Retinal Ganglion Cells

Sebastian Sydlik
(*A. Fiala*) Analysis of Potential Effects of pH on Vesicle Release in Neuromuscular Junctions of Drosophila Third Instar Larvae

Lenka Vaculčiaková
(*F. Wolf*) The influence of cellular morphology and sub-threshold conductances on the neuronal transfer function

Dennis Vollweiter
(*S. Rizzoli*) Formin-mediated actin assembly regulates endocytosis in hippocampal neurons

Kanishka Waghmare
(*S. Löwel*) Effect of PSD-95 KO on the orientation selectivity in the primary visual cortex of mice: an electrophysiological study

Rebecca Wallrafen
(*T. Dresbach*) Studying Dopaminergic Synapses in Brain Tissue and Cell Culture: Molecular Composition of Tyrosine Hydroxylase-Containing Varicosities

Lukas Weiss
(*I. Manzini*) Plasticity of mitral-tufted cell dendrites after olfactory nerve transection in larval Xenopus laevis

Rashad Yusifov
(*S. Löwel)* Morphological characterization of dendritic spines in the visual cortex of PSD-95 knockout mice

The Doctors of 2015 and 2016

Bekir Altas
Roles of the Nedd4 Family E3 Ligases in Glial Function and Nerve Cell Development
Nils Brose,
Judith Stegmüller,
Dirk Görlich

Mateusz Ambrozkiewicz
HECT-type Ubiquitin Ligases in the Nerve Cell Development
Nils Brose,
Judith Stegmüller,
Ahmed Mansouri

Vinita Bharat
Phosphorylation of Synaptotagmin 4 captures transiting dense core vesicle at active synapses
Camin Dean,
Nils Brose,
Reinhard Jahn

David Brockelt
The role of the E3 ubiquitin ligase FBXO7-SCF in early-onset Parkinson's disease
Judith Stegmüller,
Tiago Outeiro,
Klaus-Armin Nave

Hugo Cruces Solís
Neuronal correlates of implicit learning in the mammalian midbrain
Klaus-Armin Nave,
Tobias Moser,
Stefan Treue

Zohreh Farsi
A Single Vesicle Assay to Study the Electrochemical Gradient Regulation in Glutamatergic and GABAergic Synaptic Vesicles
Reinhard Jahn,
Silvio Rizzoli,
Tobias Moser

Ricardo Merino
Determination of the dynamic gain function of cortical interneurons with distinct electrical types
Fred Wolf,
Walter Stühmer,
Andreas Neef

Chaitali Mukherjee
Functional analysis of the CNS-specific F-box protein FBXO41 in cerebellar development
Judith Stegmüller,
Mikael Simons,
Michael Hörner

Markus Stahlberg
Nanoscale probing of single synapse function and BDNF Cell-to-Cell transfer
Camin Dean,
Stefan Hell,
Detlev Schild

Nidhi Subhashini
Dlk1 Membrane-to-Nuclear Signalling During Motor Neuron Functional Diversification
Till Marquardt,
André Fischer,
Judith Stegmüller

Adam Tomczak
Voltage-gating and assembly of split Kv10.1 channels
Luis Pardo,
Tobias Moser,
Silvio Rizzoli

Siv Vingill
Characterization of FBXO7 (PARK15) knockout mice modeling Parkinsonian-Pyramidal Syndrome
Judith Stegmüller,
Thomas Bayer,
Tiago Outeiro

Learning to do science ...

and being a good mentor in Goettingen *by Jin Bao*

Since 2014 I am working as an associate professor at the University of Science and Technology of China in Hefei, which is my former hometown. Returning from my postdoctoral studies in Paris, and taking over a position at USTC Hefei truely marked a new stage in my accademic career. Besides further developing my own scientific career, I also carry much more responsibilitiy for others ever since. This feeling starts when talking to my first student, who joined the lab. When mentoring students, very often I tried to recall what my PhD supervisor would do in a similar situation. My supervisor in Goettingen was Dr. Takeshi Sakaba, a Japanese scientist who worked in Prof. Erwin Neher's department for 12 years.

I came to Goettingen in 2005 from the despair of not finding a good mentor even in the best Chinese university. Our ancestors told us 'Misfortune may be a blessing in disguise'. I was certainly blessed during the period in Goettingen being part of the Neuroscience Program. Lectures were difficult for me at the beginning, not only because of the language barrier, but also due to my comparably weak background in biology. Then I got a lot of help from colleagues in the study group. The close interaction with colleagues and faculty members during the first year was a great experience for me. Our discussions were not restricted to science, and in fact discussions on broad topics, debates and culture exchanges were also important. Since I am back to China, I see an increasing number of foreign researchers and students working in China, and many Chinese researchers returning from abroad. The Chinese scientific community is growing and is getting more and more international. International collaborations, co-funded joint projects and student exchanges are encouraged and for the students it is practically easy to apply. My international experience in Goettingen, especially in our Neuroscience program, certainly prepared me for this international scientific environment with knowledge and ability for communication, network for collaboration and most importantly an open mind.

Starting a lab is a complicated project. I took an easy path by joining a group of another two young scientists. Close collaboration brings our knowledge and experience together to tackle problems in Neuroscience. It is especially important to collaborate for neuroscientists because the techniques and knowledge are expanding so quickly. China is a quickly developing country as I barely recognised my hometown upon returning from Europe. In the scientific community young scientists are outernumbered. The good side is young people are more ambitious and ready to try on new things, open new research fields. The drawback is lack of senior scientists nearby as mentors for the young ones. The way to solve this problem is turning to your former supervisors or collaborators abroad to get advice. I often consult Takeshi and also my collaborators during my time as a postdoctoral fellow in Paris in situations that require more experience.

I like to work side by side with students, which I myself experienced as very helpful when working with Takeshi Sakaba, my PhD supervisor and Drs. Alain Marty, Isabel Llano, Phillipe Ascher, whom I worked with in Paris. They are fantastic scientists and mentors. They share one similar style of working, which is working

side by side with students and discussing openly all issues of a given project and beyond. So I adopted this mentoring style and I do experiments together with students especially at the beginning of a project. Sometimes

I purposely create small contests with them, and of course, most of the time I win. Experience counts! My students do enjoy this way of working and I can tell by their growing motivation that they enjoy this way of personal training and mentoring. I believe this is a good way for a student to learn. As all experimental scientists know, sometimes new trials and approaches do not work as expected, take more time and don't bring the expected results and projects get stuck. In these situations it is quite a challenge to convince and motivate students to continue or, alternatively, to develop other experimental approaches, if technical problems just can't be solved. In some cases it is also needed to develop criteria to decide to stop and not further continue a project. Luckily I learnt many skills of motivating students and cheering up collaborators from my peers in Goettingen. In fact, I already started supervising students during my time in Goettingen, when I trained lab rotation students from our program. This was an important experience. Solving problems together and giving feedback immediately without much of a delay is very important. I remember whenever I needed help or feedback from Prof. Erwin Neher, I usually got it within a day.

After working on target-dependent synaptic plasticity in Goettingen and mGluR signaling *in vivo* in Paris, I wanted to work on the function of synapses in the context of large neuronal circuits and behavior. An ideal system for this kind of study would be a circuit with well-defined synaptic connections receiving input by an ensemble of identifiable synapses. I started to look for a suitable system already during my postdoc time in Paris. One day I got to know that a new faculty member just joined USTC and I became interested in joining his group. My colleague is working on a special type of retinal ganglion cells named intrinsic photosensitive retinal ganglion cells. As the name indicates, this type of ganglion cell could sense light independent of rod and cones in the retina. After talking to my new colleague, I learnt that these newly discovered ganglion cells project to many regions of the brain and mediate various light-dependent functions. Light-dependent behaviors show differences in how light is driving these behaviors. For example, pupillary light reflex responds to light immediately, while photo-entrained circadian system needs a longer time to sample the ambient light intensities. It has been demonstrated that the same type of intrinsic photosensitive retinal ganglion cells are involved in both types of behaviors. I was very happy that I could collaborate with this group and use the genetic tools available in the lab to look for the properties that determined the circuit response to different light stimuli. We hypothesized that differences in synaptic properties must be involved. Luckily, we were able to provide evidences to prove this hypothesis. During the last years, many new techniques for neuronal circuit studies have been developed and widely used, for example, optogenetic tools, trans-synaptic viral systems and *in vivo* population ima-

ging which allow characterization of functional variations in synaptic transmission and modulation.

We do research mostly based on our own interests and ideas, but teaching and mentoring are responsibilities that involve training of young scholars which should be taken very seriously. Maybe that is the reason why Goettingen has embraced so many great scientists!

Jin BAO did her doctoral thesis on the functional role of short-term synaptic plasticity in neuronal circuits in Takeshi Sakaba's group, department of Membrane Biophysics, Max-Planck Institute for Biophysical Chemistry. After graduation in 2010 in Göttingen she went on working on synaptic transmission *in vivo* as a Marie-Curie IntraEuropean postdoctoral fellow in Paris.

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Remembering: On the Fly

by David Owald

As a high school student I visited the University of Göttingen to find out what the best subject for me to study would be. I had an equally strong interest in history and the sciences; I was told that there were no jobs in archaeology, so I decided to opt for molecular biology.

Before I moved to Göttingen in 2005, I lived in Heidelberg for three years. The Bachelor's course I studied there, Molecular Biotechnology, was quite intense – I learnt a lot about molecular pathways and state-of–the-art methods in the life sciences. But I also realized that my real passion had always been to understand what goes on in one's brain – a daunting task that may or may not be feasible. I really liked Heidelberg, so at the time when I applied for the Neuroscience Master's program in Göttingen, I was rather sure that I'd stay in Heidelberg no matter what comes. After the interviews in Göttingen, I changed my mind. I think the main reason for this was that some of the interviews were tough and that helped me to understand my own limitations.

The first year of courses in Göttingen was great fun and truly educational. I was lucky enough to have the opportunity to do fantastic lab rotations, learning methods including imaging, electrophysiology and electron microscopy. The wide variety of methods again helped to open my eyes just a bit further. A neuroscientist, as far as I believe and have come to learn, needs to understand the basics of a cell, of a synapse – and it helps to see a synaptic vesicle on an electron micrograph, see a quantum of neurotransmitters in an electrophysiological recording, see the molecular composite of individual active zones and postsynaptic densities – but a neuroscientist also needs to tackle the logics of neural circuits: one needs the road map. I was extremely fortunate to join labs where I was taken seriously from the start and integrated immediately. That not only gave me a massive boost of confidence but set free extra energy and motivation that, as an experimental scientist, I think one needs for keeping up perseverance, often the key to progress.

I decided to join Stephan Sigrist's lab to do my PhD. I had done a rotation in his lab and it was then that I fell in love with a model organism – *Drosophila melanogaster*. This was not planned. When I started my Master's studies

I had limited interest in, what some people and me at that time, would consider a simple organism. But I got to learn the power of simplicity (in reality this system is of course far from simple). Joining Stephan's lab meant leaving Göttingen because he had accepted a professorship in Würzburg. However, I was fortunate enough to stay in the Göttingen Neuroscience program with a great PhD committee consisting of Stephan, Erwin Neher and Evgeni Ponimaskin. This meant going to Göttingen a couple of times a year either for committee meetings or seminars and it also meant that I was able to meet up with my friends from the Master's course.

During my PhD, I focused on studying a model synapse in a model system – the glutamatergic neuromuscular junction of *Drosophila* larvae. What was especially appealing about this synaptic junction was the variety of approaches that one could take. Methods used included live imaging of synaptic proteins, super-resolution imaging, two-electrode voltage clamp and mass spectrometry, just to name a few. My projects went reasonably well and we were able to tackle synapse assembly and rearrangement processes at a molecular as well as high-resolution spatio-temporal level. I have a lot to owe to fantastic colleagues – it was down to the truly collaborative nature of the lab that we were able to make significant progress.

After two years in Würzburg, the lab moved to Berlin. I graduated after another one and a half years and stayed on for another 18 months to finish my last project. For later grant applications I did get criticism for staying on and not moving to a different post-doc lab straight away – but what can I say, it was the only thing that made sense scientifically.

After graduating, I looked nonetheless into changing fields and was considering switching to an even simpler system. I had applied to labs in the US and went on an interview tour. As part of my trip, I also spent three weeks in Cold Spring Harbor as a technical assistant at the 'Neurobiology of *Drosophila*' course. It was there that I got into scientific discussions with Scott Waddell. I decided that the time for me was right to move into the (more complex!) fly brain and work on the circuit underpinnings of learning and memory. My aim was to identify a synaptic junction at cellular resolution that would directly underlie a defined behavior. Scott's lab was just about to move from the US to Oxford and we found that the timing of his move would fit well with finishing my work in Stephan's lab.

I applied for post-doc grants and got lucky. I received an EMBO log-term fellowship and a Sir Henry Wellcome post-doctoral fellowship from the Wellcome Trust. Obviously I had to put a lot of effort into applying for that funding and preparing for interviews; I had great support from Scott Waddell and also Gero Miesenböck, the director of the Centre for Neural Circuits and Behaviour in Oxford: both discussed my proposals with me on the phone from a very early point on. So my time in Oxford was funded for 5 years from the start (1 year EMBO + 4 years Wellcome Trust) and that gave me a good degree of independence. It was that freedom, the job certainty (for a junior scientist) for an extended period of time, together with a thrilling scientific environment that allowed me to thoroughly enjoy my time in Oxford.

That said, arriving in Oxford from a capital city, Berlin, was quite a change and I initially took the bus (that runs more or less 24 hours) into London quite regularly. But the urge to leave Oxford gradually subsided; I learnt to appreciate the calmness of the town and the fantastic countryside on my doorstep. I soon became integrated as a Junior Research Fellow at Wolfson College which turned out – especially considering prices and housing difficulties in Oxford - to be quite important for my young family, as it came with access to family housing and an in-house nursery.

Scientifically, I was again fortunate to work in an outstanding team. We tackled positive dopaminergic reinforcement learning in *Drosophila*, investigated the neurochemistry of memory-storage synapses in the fly, looked into disinhibition pathways underlying aversive memory retrieval and hunger-mediated gating of positive memories and finally identified a synaptic junction that upon appetitive learning turned default avoidance into approach behavior.

We found that the learning and memory center of the fly, the mushroom bodies, has default approach and avoidance pathways that are zonally organized and anatomically distinguisha-

ble. Each of these zones is innervated by a specific set of mushroom body-extrinsic dopaminergic neurons, some

are activated for instance by a sugar, others by a water reward and others by aversive stimuli. It is the coincident activity of subsets of dopaminergic neurons with that of mushroom body-intrinsic odor-coding neurons that leads to olfactory memory formation. We found that this is accompanied by depression or potentiation of the activity of the output from specific zones. We were able to mimic this finding using a simple behavioral assay. Naïve flies that would normally avoid an odor would start to approach it if we blocked the output of a default aversive zone thermogenetically – just as if the fly had learnt that the odor was associated with something positive. Likewise, naïve flies would avoid optogenetic activation of this pathway by choosing a dark over an illuminated side while control flies would be indifferent as to which side to choose. Our model thus predicts that in the naïve fly the mushroom body output from avoidance and approach zones is balanced, and learning changes this balance to trigger a certain behavior. Again, I was able to use an extended set of techniques, including genetics, anatomy, behavioral assays, optogenetics and optophysiology.

In 2016, I moved back to Berlin to start an Emmy Noether Nachwuchsgruppe at the Charité. We are surrounded by many great neuroscientists and have found ourselves in a highly collaborative environment right in the center of Berlin. My group now uses combined two photon, optogenetic, genetic, electrophysiological, molecular and behavioral approaches to focus on the computational rules that shape the synapses we identified to play a direct role during learning and memory in the behaving animal. Likewise we interfere with the molecular composite of these sites using, for example, single cell RNA interference combined with pharmacology. Finally, we look into the cell biological properties that allow single neurons to integrate and compute information and how these properties change in response to network activity.

David OWALD did his PhD in Stephan Sigrist's lab at the European Neuroscience Institute Göttingen (ENI-G) in Göttingen, the Rudolf-Virchow-Zentrum in Würzburg and at the Freie Universität Berlin. He defended his PhD in Göttingen in 2010. David then joined the Centre for Neural Circuits and Behaviour in Oxford, UK as a postdoctoral fellow funded by an EMBO long-term and a Sir Henry Wellcome Post-Doctoral Fellowship. He received the 2013 Otto Creutzfeldt PhD Award and the 2017 Schilling Award of the Neurowissenschaftliche Gesellschaft. Since 2016 he heads an Emmy Noether Junior Group at the Institute of Neurophysiology, Charité – Universitätsmedizin Berlin (Owald-lab.de).

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Academia inside out –

at the interface of science and society

With one foot back in Göttingen, but in a new shoe *by Roman Stilling*

When I talk to former colleagues and friends about the new job I started in September 2016 I often earn a concerned, but affirmative look: "*Oh, that sounds challenging… but good to hear that this is addressed!*", this look seems to say. I always wanted to be a scientist but at the same time always felt science and society are way too often way too far apart and wanted to help bridging the gap. As for all of us, I had to make a tough decision, but I may have found the perfect role to combine these two interests.

Becoming a scientist

It was during my third year of PhD work (2012) at the ENI Göttingen with Prof. André Fischer (now DZNE Göttingen), when I became interested in how neuronal circuits can be manipulated from the outside. I am not talking about our senses or optogenetics, transcranial stimulation or other man-made tools, but rather about some terrifying parasites that can influence the behaviour of their animal hosts in their own interest. I did some research on existing literature and, combining this interest with my PhD topic of epigenetic regulation of cognition, a naïve hypothesis was forming in my head: Could some of these mysterious parasite effects be mediated by host epigenetics? This interest also led me to my first encounter with science communication: I presented the topic and my ideas to the public in an entertaining way during my first science slam in Göttingen (actually, a really rewarding thing to do, I highly recommend participating!).

They say if you want to pursue the academic career, do something that you are really into. But of course it also helps if you look for your own little scientific niche. Thus, I was looking for postdoc opportunities to test my hypothesis. While investigating labs in this area a related topic gained traction that has now become one of the most influential fields in modern biomedicine: The influence of the throng of microbes living in and on our bodies on our health, physiology and even behaviour. Influences of omnipresent symbiotic microbes are obviously a lot more common than those of a few exotic parasites, but the mechanisms for such "bacteria-brain interaction" might be very similar and were (and largely still are!) completely elusive.
I focused my search for a good postdoc lab on not-to-distant European countries, since my partner had to stay in Germany for a job offer she couldn't refuse. This turned out to be a great choice, as I found a world-leading institute in this research area in Cork, Ireland: the APC Microbiome Institute. Prof. John Cryan and Prof. Ted Dinan were enthusiastic about my ideas and took me in. It was the right time and the right place: The field was young and up for grabs and we successfully published some influential papers and reviews to advance the field. I had a wonderful time in Cork and found many new friends.

However, staying not too far away from home also turned out to be useful for another reason, as things changed quite dramatically when I learned I was going to be father in a few months.

Becoming a science advocate

I was lucky: My supervisors were extremely supportive and understanding. Still, it did put some pressure on me to answer the questions that every (PhD) student and postdoctoral fellow has to ask at some point: Do I *really* want to be a professor? Do I *really* have everything that it takes to achieve this long-term goal? What are feasible alternatives? These are very important questions that cannot be answered for you by others and thus need some serious thinking. For me,

this was a recurring process and the answer changed several times. What helped me in this process was deliberately limiting possible alternatives: If I would not work in "hands-on academic research" I wanted to be as close as possible. So I had interviews and offers both inside and outside of performing my own research, but always within the wider sphere of academia.

Finally, in spring 2016 I found a job advertisement that promised to be close enough to actually performing (literature-based) research but the predominant part would be communicating research to the public. A role perfectly situated at the interface of science and society, just the way I had in mind. Interestingly, the work would be for the "Alliance of Science Organisations in Germany"* – a massive and powerful consortium of key players in science in Germany and Europe. The cherry on top: I would be employed at the German Primate Center in Göttingen (my "scientific hometown"), but physical presence would be required in Münster (my "real-life hometown"). In short: I applied, got lucky and accepted the offer without (additional) second thoughts.

So what is this job all about? In essence, I support the science organisations in Germany in publicly showing what animal research is all about and why we need it to guarantee progress in biomedicine. In September 2016, the Alliance has launched an initiative to offer transparency and reliable information about all aspects of animals used in research in a fact-based manner. It is called "Tierversuche verstehen" (translates to "understanding animal experiments") and its flagship part is the web platform www.tierversuche-verstehen.de.

For my new role it certainly helps that I have performed experiments using animals (mice and rats) myself and have made up my mind about this emotional topic since the very beginning of my PhD studies. I also knew some of the young researchers that became organised in 2015 to promote this topic in the German public (www.pro-test-deutschland.de/en/) and signed the Basel Declaration (http://www.basel-declaration.org/) - by the way: you should definitely consider supporting/joining Pro-Test and sign the declaration! A large part of my work now is to research topics suitable for our website, to make sure all our information is scientifically sound and to support the steering committee of the initiative, chaired by Prof. Stefan Treue. I also work closely with a team of editors within the communication/PR agency that was contracted to provide infrastructure, editorial work and communications expertise for the initiative. This agency is based in Münster, hence the loca-

tion of my office. I also participate in public debates about animal research offline and on the internet (follow @TVVde on Twitter!), often to discuss common misconceptions that are promoted by animal rights activists.

Initiatives similar to "Tierversuche verstehen" have been very successful in other European countries such as the UK (e.g. www.understandinganimalresearch.org.uk), France or Switzerland but also in the USA (e.g. www.speakingofresearch.com). All these are based on the idea that proactive communication, i.e. taking initiative and continuously provide first-hand, evidence-based information, is the only effective way to achieve better public understanding of research using animals and improve trust in science and researchers. Unfortunately, much of my daily work is to convince institutions, their leaders and PR offices as well as individual researchers, that there is no reasonable alternative to this kind of communication. In fact, "Tierversuche verstehen" can only work, if we all together foster a culture of openness. If you want to learn more and how you can contribute, don't hesitate to contact me.

Finally, it is worth mentioning that working for the Alliance offers the opportunity to getting in touch with the "who-is-who" of the German research system. This will certainly come in handy one day, when I have to think about the next steps on my career path.

Leaving the path of a hands-on researcher was no easy decision, but until now I don't entertain any doubts it has been the right one. "*Oh, I thought you wanted to be a professor? I always pictured you as one.*", I still get to hear a lot. "*Me, too*", I have to agree, but opportunities are to be seized when they hit you, right?

Roman STILLING did his doctoral thesis in André Fischer's department at the European Neuroscience Institute Göttingen (ENI-G). He graduated in April 2013 and held a postdoc position at the University College Cork, Ireland before he returned to Germany as a science advocate in 2016.

Wissenschaftlicher Referent
Informationsinitiative „Tierversuche verstehen"
der Allianz der Wissenschaftsorganisationen
c/o Cyrano Kommunikation GmbH
Hohenzollernring 49-51
48155 Münster

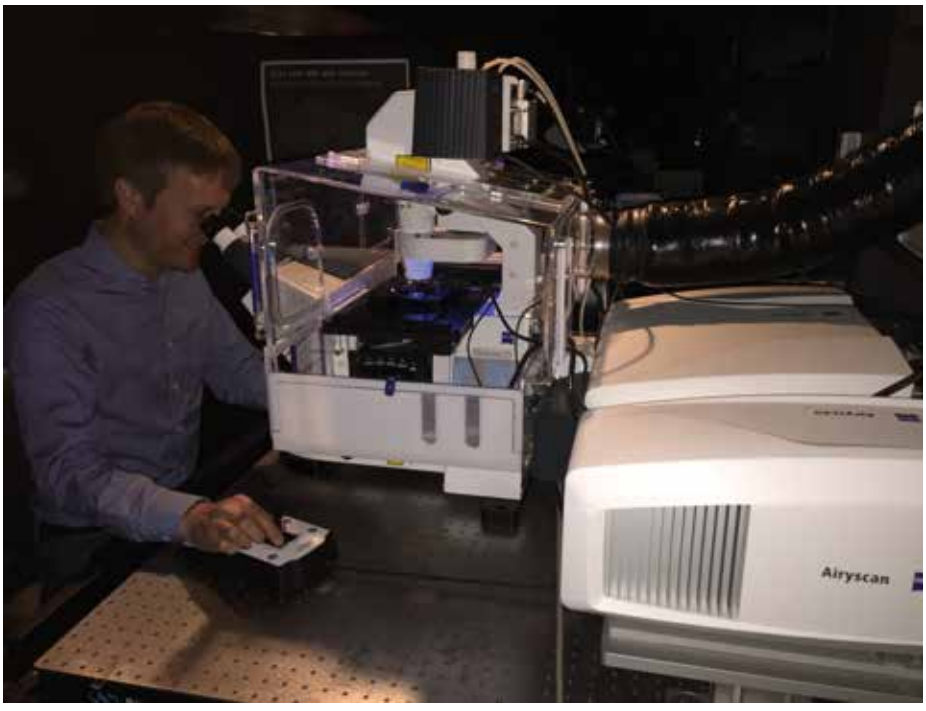
* The Alliance of Science Organisations in Germany is a union of the most important German research organisations. It issues statements relating to research policy and funding and the structural development of the German research system.
Members of the Alliance include the Alexander von Humboldt Foundation, the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), the Fraunhofer-Gesellschaft, the German Academic Exchange Service, the German Council of Science and Humanities (Wissenschaftsrat), the German National Academy of Sciences Leopoldina, the German Rectors' Conference, the Helmholtz Association of German Research Centres, the Leibniz Association, and the Max Planck Society.

Quo vadis? “Where do you go?”

by Sebastian Gliem

Johann Wolfgang von Goethe once wrote: “Die beste Bildung findet ein gescheiter Mensch auf Reisen.” which could be translated to “A prudant (hu) man receives the best education while traveling.” When I think back to my travel experiences, when traveling through China/Tibet more than 10 years ago and standing in front of the Mount Everest with two former Neuro colleagues (Jin and Andrea); I absolutely agree with good old Goethe: Traveling the world provided me the opportunity to experience different cultures, mentalities, foods and architecture. As of today, I´ve traveled to more than 60 countries. Aside from marvelous landscapes, nature scenery, a variety of mind-sets or e.g. an unimaginable high degree of amity that I found in India, the greatest awareness was that humans all around the world are not so different as we often think even when our politics and media sometimes states otherwise. I assume that Goethe must have made similar experiences already more than 200 years ago. His thirst for more impressions probably became the main driver for him to continue his journeys within Europe and become one of the most famous travelers of his time.

My thirst for traveling the world intensified while standing on the top of the world. Once back, I wondered whether there actually would be a job where I could integrate my passion for travel, science and teaching. At first glance a combination of the three was unlikely to be realized in one job. While on deck of a boat drinking wine near the island to the Galapagos Islands, I coincidentally spoke to a person whose profession included all three of my passion (travel, science and teaching). In describing the position the job title would be: Application Specialist. After significant consideration and the realization that an academic career is not what I wanted, and in general hard to be realized nowadays, I set out to seek jobs to become an ‘Application Specialist’. Two years of specific search and five applications later, I got my current job as an Application Specialist for Light Microscopy at ZEISS. There, my responsibilities are divided into four areas: 1) After-sales support of researchers. I train researchers on their new equipment and answer questions by mail or phone regarding how to use hard- and software best to answer certain research questions. 2) Pre-sales activities. I help organizing and conducting microscope workshops and support our sales crew with technical and application arguments during sales projects. 3) Support of product management and marketing. I join strategy as well as problem solving meetings and provide feedback that I get from researchers and sales colleagues. 4) Support of development. I test new microscope systems and provide feedback to our developers.



On average, I am out of our headquarters in Göttingen/Jena for about 40% of my working time and travel to many different places all around the globe. By the way, yes, I am still living in Göttingen. I really appreciate this beloved town, low rents and the easy access to Berlin, Hamburg and Frankfurt. At any rate, as a kind of exception from

Outside Academia

this rule of thumb regarding traveling, I went on an external assignment to Harvard University in 2016 and co-supervised our ZEISS imaging facility for 8 months. I trained researchers on our equipment and helped them to optimize imaging for their applications and samples. Revisiting my time at Harvard, I have to confess that it was a really great experience. I was challenged by a multitude of cool and intricate projects that you´ll probably only find there. Still, despite the interesting projects, I decided not to stay in the US and extend my assignment because I honestly missed my life, my friends, my family, the food, and the way of living in Germany. But I am very grateful for this opportunity and the experiences that I made during my work as well for the impressions that I collected! I am even more grateful for the finding of awareness about valued aspects of my own culture and country. Despite uncounted positive experiences and enviable cultural aspects in the US and different other countries, I now appreciate my own roots, certain cultural aspects as well as social achievements here in Germany much more. Since I am back in Germany, I often smile when I hear about problems that German people or politicians discuss. I now believe that we Germans actually must have it imprinted in our cultural genes to complain even about situations that 95% of all other cultures on our earth would like to achieve. Contrary, I am also sadly convinced about that the German culture unfortunately possess an enzyme that degrades high levels of mRNA encoding for such positive life attitude as Americans express or such strong friendliness and kindness as people in India. In conclusion, having a job that allows you to explore the world can not only be mind-opening towards differences and similarities between cultures; but also towards a stronger appreciation of values and aspects from your own culture. That`s also why one of my trips has become more and more important over time: Going home to friends and family :-)

Sebastan GLIEM did his doctoral thesis in Detlev Schild's department (Neurophysiology and Cellular Biophysics) and defended his doctoral thesis in October 2010. He continued his projects in Prof. Schild's department until he joined the ZEISS Company as an Application Specialist.

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Creutzfeldt Award

Creutzfeldt PhD Prize
The Creutzfeldt PhD Prize is awarded for the best PhD thesis in memoriam of Prof. Dr. Otto Detlev Creutzfeldt, founding director of the department of Neurobiology at the Max Planck Institute for Biophysical Chemistry in Göttingen. The prize is awarded since 2007 to PhD graduates of the Neuroscience program based on excellent achievements during the PhD and the grading of the written dissertation and the oral defense. In 2011 for the first time 2 winners have been selected for the Creutzfeldt Prize.

Traditionally, the award ceremony is part of the official opening of the NEURIZONS Symposium and takes place in the presence of the spokespersons of the MSc/PhD/MD-PhD Program & International Max Planck Research School for Neurosciences, a representative of Sartorius stedim AG and Mary Creutzfeldt.

The award includes the book present 'Cortex Cerebri' written by Otto Creutzfeldt and a gift of 500,-€ sponsored by the Göttingen company Sartorius stedim biotech AG, which has generously supported the Neuroscience program since its foundation.

The next Creutzfeldt PhD Prize for the best PhD thesis of the graduates of 2016 and 2017 will be awarded during the next NEURIZONS symposium scheduled from 29. May until 01. June 2018.

2007 Prize winner:
Dr. Irina Dudanova
Max Planck Institute of Neurobiology
Department of Molecular Neurobiology
Am Klopferspitz 18
82152 Martinsried

2009 Prize winner:
Dr. Henry Lütcke
Brain Research Institute
University of Zurich
Winterthurerstr. 190
8057 Zurich, Switzerland

2011 Prize winners:
Dr. Ioanna Bethani
Goethe-Universität Frankfurt
Institute of Cell Biology and Neuroscience Cluster of Excellence
Molecular and Cellular Neuroscience
Macromolecular Complexes (CEF)
Max-von-Laue-Str. 9
60438 Frankfurt am Main

Dr. Stephan Junek
Max Planck Institute for Brain Research
Neural Systems and Coding Group
Deutschordenstr. 46
60528 Frankfurt am Main

2013 Prize winners:
Sadim Jawhar, Ph.D.
Biomedical Research Institute,
Doha, Qatar

Dr. David Owald
Center for Neural Circuits and Behavior,
Oxford University, United Kingdom

2015 Prize winners:
Dr. Natalia Revelo Nuncira
Radboud umc, Institute for Molecular Life Sciences
Tumour Immunology Lab
Geert Grooteplein 26/28
6525 GA Nijmegen, Netherlands

Nicolas Snaidero, Ph.D.
Institute of Neuronal Cell Biology
Technical University München
Biedersteiner Str. 29
80802 München

Institute of Clinical Neuroimmunology
Ludwig-Maximilians University Munich
Marchioninistr. 17
81373 München

Creutzfeldt Award Ceremony 2015: Gregor Eichele, Natalia Revelo Nuncira, Nicolas Snaidero, Denise van Rossum, Margret Creutzfeldt, Michael Hörner

New Faculty

Joining the program in 2015 and 2016

Andrea Antal
habilitated in the Medical Faculty in 2005 and was appointed extraordinary professor at the Georg August University Göttingen in 2010. Ever since she contributes to teaching in the Neuroscience program in the field of brain stimulation and imaging techniques. The primary aim of Prof. Antal's and her group's recent work is to develop and establish new non-invasive brain stimulation methods to study physiological changes in the central nervous system in order to investigate cognition and complex information processing, and eventual later clinical use.
Further information: http://www.uni-goettingen.de/en/88816.html

Susann Boretius
obtained both a doctoral degree as veterinarian and a diploma in physics. Prof. Boretius joined the Biomedical NMR Research Group at the Max Planck Institute for Biophysical Chemistry in 2003. In 2011 she was appointed as a Professor of Biomedical Imaging at the University of Kiel. In the year 2015 Prof. Boretius returned to Göttingen to take over the position as a Professor of Functional Imaging at the University of Göttingen and head of the Functional Imaging Laboratory at the German Primate Center. She joined the Neuroscience program in the study year 2016 and offers introductory lectures and courses in high-resolution imaging techniques.
Further information: http://www.uni-goettingen.de/en/551221.html

Peter Dechent
earned his doctoral degree in biology in Göttingen and was appointed Head of the Research Group MR-Research in Neurology and Psychiatry in the Medical Faculty in Göttingen in 2011. Dr. Dechent joined the Neuroscience program in 2016 and offers -together with his colleague Dr. Renate Schweizer- theoretical and practical courses in the field of MR research. His group aims to bring modern magnetic resonance techniques from basic neuroscientific research into the clinical research and practice. He runs the facility „MR research in neurology and psychiatry" developing innovative structural and functional imaging solutions including methods for structural MR imaging (MRI), quantitative MR spectroscopy (MRS), diffusion-weighted and diffusion tensor imaging (DWI/DTI) and functional MRI (fMRI).
Further information: http://www.uni-goettingen.de/en/57929.html

Alexander Gail
studied physics in Marburg and earned his doctoral degree in 2002. From 2003 to 2006 he worked as a postdoctoral fellow in Pasadena/USA. He was then appointed Head of the Sensorimotor Group at the German Primate Center in 2006. His research focusses on principles of sensorimotor integration, cognitive movement planning and the development of neuroprosthetics. He has established various in-vivo recording techniques in human and non-human primates in his laboratory. Prof. Gail is also member of the Bernstein Center for Computational Neuroscience and offers training opportunities in the Neuroscience program since 2011.
Further information: http://www.uni-goettingen.de/en/57950.html

Tiago Outeiro
studied biochemistry and cell biology and earned his PhD degree at the Whitehead Institute for Biomedical Research at the University of Chicago in 2004. After taking over a postdoctoral fellow position at Harvard University he moved to Lisbon and joined the Instituto de Medicina Molecular as a group leader in 2007. He was appointed as Professor of Aggregopathies and Director of the department of Neurodegeneration and Restaurative Research at the University Medical Center Göttingen in 2010. His research interests are focused on the understanding of the molecular mechanisms which lead to neurodegeneration in diseases such as Parkinson's, Huntington's, or Alzheimer's disease, which are associated with protein misfolding and aggregation in specific regions of the brain.
Further information: http://www.uni-goettingen.de/en/216914.html

Arezoo Pooresmaeili
earned her MD degree at the University of Tehran School of Medicine in 2001 and later her PhD in 2009 exploring mechanisms of visual attention. She took over a postdoctoral fellow position at the Pisa Vision Laboratory in 2009. In

2011 she joined the Berlin School of Mind and Brain. She became group leader in the European Neuroscience Institute in 2015 and joined the Neuroscience program right from the start of her position at the ENI. She took over an introductory lecture and a course on psychophysical methods and has offered several lab rotation projects. Dr. Pooresmaeili works on perception and cognition using functional imaging techniques and psychophysics in humans to obtain behavioral and neuronal data, which is being analyzed in order to make sense of the brain-behavior relationship.
Further information: http://www.uni-goettingen.de/en/550502.html

Annekathrin Schacht
earned her doctoral degree in the field of psychophysiology at the Humboldt University Berlin in 2008. After postdoctoral positions at the Universities of Potsdam and Geneva she was habilitated and appointed visiting Professor of Cognitive Neuroscience at the Humboldt University Berlin in 2011. She took over a position as a Junior Professor and became Head of the Courant Research Centre 'Text Structures' at the University of Göttingen. In 2016 she became Professor of Affective Neuroscience and Psychophysiology in Göttingen and joined the Neuroscience program in the same year. Her main research deals with questions on the interplay of cognition and emotion in several domains of human information processing.
Further information: http://www.uni-goettingen.de/en/515512.html

Hansjörg Scherberger
studied mathematics and medicine in Freiburg and earned his MD degree in 1996. After postdoctoral research stays at the University of Zürich and the California Institute of Technology he was appointed as a group leader at the Institute for Neuroinformatics at the University Zürich in 2004. He was appointed Professor of Primate Neurobiology at the German Primate Center in 2008 and is associated with the Department of Biology at the University of Göttingen. He and his team investigate how hand movements are generated in the primate brain and how intentions to grasp objects can be decoded for controlling a neural prosthesis and brain-machine interfaces to control robotic devices. In the teaching courses he introduces various in-vivo recording techniques and physiological approaches relevant for studies in primates.
Further information: http://www.uni-goettingen.de/en/212824.html

Melanie Wilke
studied psycholinguistics, neuropsychology and neurobiology and earned her doctoral degree at the University of Tübingen in 2005. She then joined the Laboratory of Neuropsychology at Bethesda as a postdoctoral fellow and took over another postdoctoral position at Caltech in Pasadena in 2008. She was appointed Co-Investigator in the Decision and Awareness group at the German Primate Center in Göttingen in 2011. She was awarded the Schilling Foundation Professorship in 2011 and became Director of the Department of Cognitive Neurology and Head of the MR-Research Unit at the University Medical Center Göttingen. The goal of her research is to understand how neural activity gives rise to spatial awareness and how distributed information is integrated to guide the selection of movement goals from monkey models of cognitive disorders to human patients by means of imaging and stimulation methods. Prof. Wilke offers lectures and courses in the field of higher cognitive function.
Further information: http://www.uni-goettingen.de/en/359148.html

Sonja Wojcik
studied biology in Aachen and earned her PhD degree in medicine at the Baylor College in 2000. After taking over a postdoctoral fellow position at the Max Planck Institute for Experimental Medicine in the department of Molecular Neurobiology in Göttingen in 2001, she was appointed as a group leader at the same institute in 2008. She was habilitated at the Medical Faculty in Göttingen in 2014. Dr. Wojcik's research concentrates on the characterization of neurotransmitter systems and vesicular transporters to elucidate the molecular processes underlying neurotransmitter release and the functional consequences of alterations in these processes at the cellular and network levels. She supervises lab rotation students since 2013 and offers lectures and courses in the field of modern molecular techniques.
Further information: http://www.uni-goettingen.de/en/216914.html

Faculty

Leaving

Left the program since 2015

Theo Geisel
is Professor of Theoretical Physics and Director, Max Planck Institute for Dynamics and Self-Organization Göttingen and Founder of the Bernstein Center for Computational Neuroscience. He joined the Neuroscience program in 2004. He developed models and mathematical approaches to better understand neuronal network behavior typically characterized by a high degree of flexibility and able to adapt to permanently changing tasks from the level of single cells to the level of cell assemblies and large cortical networks, and from the time scales of action potentials to the time scales of learning and long-term memory. He established the teaching module modelling and theoretical neuroscience in the Neuroscience program.

Hubertus Jarry
is Professor of Clinical and Experimental Endocrinology at the University Medical Center Göttingen. His research focuses on understanding mechanisms of hormone release controlling proper pituitary gonadotropin release and how interaction with catecholamine and other transmitter systems and peptides leads to regular hormonal release cycles, which in turn regulate specific gene expression during development and ageing. He joined the Neuroscience program in 2002 and provided comprehensive lecture series and practical training courses in classical and molecular hormone physiology.

Hiroshi Kawabe
held the position of a group leader in the department of Molecular Neurobiology at the Max Planck Institute of Experimental Medicine in Göttingen since 2008. He was appointed as full professor at the University of Kobe in Japan in 2017. As a biochemist he studies the function of synaptic scaffolding proteins their homeostasis and role in development. He is especially interested in elucidating possible functions of E3 ubiquitin ligases on shaping neurite morphology and outgrowth during development. He offered lectures and courses including cell culture techniques and molecular and biochemical methodologies to students of the Neuroscience program.

Ivan Manzini
was the first graduate of the Neuroscience program and obtained his doctoral degree from the University of Göttingen in 2003. He continued his studies in Göttingen as a postdoctoral fellow and later became a faculty member of the program. In 2011 he took over a group leader position at the Center for Nanoscale Microscopy and Molecular Physiology of the Brain. In 2016 he was appointed as Professor for Animal Physiology and Molecular Biomedicine at the University of Giessen. His research is directed towards a better understanding of how olfactory networks are formed during development and maintained in the adult to elucidate molecular and cellular mechanisms of olfactory coding. He contributed to the teaching curriculum with lectures and courses in the field of comparative developmental biology.

Till Marquardt
took over research group leader and principal investigator position at the European Neuroscience Institute, Göttingen in 2007 as an Emmy Noether young investigator fellow. He was appointed Professor for Neurobiological Research at the department of Neurology at the Medical Clinics of the University of Aachen in 2016. His research touches upon the question on how the functional architecture of the nervous system assembles during development and how the properties of its cellular components are tuned to proper neural network function including protective functions after injury and disease. He joined the Neuroscience program in 2007 and contributed to teaching offering lectures and practical courses in the field of molecular developmental neurosciences.

Detlev Schild
was appointed Professor of Physiology and Head of the Department of Molecular Neurophysiology in the Center of Physiology and Pathophysiology, Medical School, University of Göttingen in 1997. He was one of the founders of the Neuroscience program back in in the year 2000 and was a member ever since. As the program speaker, he has led the program over almost 2 decades and considerably contributed to the development and

success of the program. His research focusses on coding mechanisms in the olfactory system and the transduction processes from chemical to electrical signaling and on olfactory information processing in the central nervous system. As a physicist and medical doctor he offered lecture series on basic cellular physiology, electrophysiological processing in central and sensory systems, electrophysiological techniques in combination with high resolution imaging approaches with respect to basic research and clinical applications. This theoretical canon was complemented by introductory and advanced practical courses on the techniques discussed in the lectures.

Judith Stegmüller
was appointed as group leader at the Max-Planck-Institute of Experimental Medicine in Göttingen in 2008. Two years later she joined the Neuroscience program and offered practical courses and lectures in the field of molecular and developmental biology. She took over an independent senior postdoctoral fellow position at the department of Neurology at the Medical Clinics of the University of Aachen in 2016. Her research work focusses on the role of intrinsic mechanisms such as the ubiquitin proteasome systems in brain development and disease. Particular interest lies in the question as to how E3 ubiquitin ligases regulate axon growth and regeneration and various aspects of neuronal development by using molecular and cell biological and biochemical techniques in combination with various mouse models. She contributed to teaching in the field of molecular developmental biology.

Walter Stühmer
was appointed as Professor of Neurophysiology and Director of the department Molecular Biology of Neuronal Signals at the Max Planck Institute for Experimental Medicine in Göttingen in 1992. He belongs to the founding generation of the Neuroscience program and was a program member since the year 2000 until he resigned in 2016. He and his group investigated the structure-function relationships of native and genetically modified ion channels, their genetic and physiological regulation and mechanisms how expression of different ion channels and membrane proteins are accomplished. By a combination of high resolution imaging and electrophysiological techniques the team studied neuronal interactions during development and cancerogenesis. He continuously offered theoretical and practical courses in the field of electrophysiology and electrophysiological techniques and actively participated in several summer schools offered in Göttingen.

Current Faculty Members

Andrea Antal
Matthias Bähr
Thomas Bayer
Susann Boretius
Nils Brose
Wolfgang Brück
Camin Dean
Peter Dechent
Thomas Dresbach
Hannelore Ehrenreich
Gregor Eichele
André Fiala
André Fischer
Alexander Flügel
Jens Frahm
Tim Friede
Alexander Gail
Tim Gollisch
Martin Göpfert
Robert Gütig
Ralf Heinrich
Stefan Hell
Michael Hörner
Swen Hülsmann
Reinhard Jahn
Siegrid Löwel
Ira Milosevic
Tobias Moser
Klaus-Armin Nave
Tiago Outeiro
Luis Pardo
Walter Paulus
Arezoo Pooresmaeili
Jeong Seop Rhee
Michael Rickmann
Silvio Rizzoli
Annekathrin Schacht
Hansjörg Scherberger
Oliver Schlüter
Manuela Schmidt
Michael Sereda
Marion Silies
Jochen Staiger
Anastassia Stoykova
Stefan Treue
Melanie Wilke
Sonja Wojcik
Fred Wolf
Fred Wouters

For details regarding the research of all faculty members, please see www.gpneuro.uni-goettingen.de/content/c_faculty.php

Neurizons 2016 –

speak your mind *by Georg Hafner*

A PhD student sits relaxed in the lecture hall of the Max Planck Institute for Biophysical Chemistry in Göttingen. Her head rests comfortably on the soft back of the chair. Her eyes are fixed at the stage where an enthusiastic lady tells about her idea to restore vision of humans using a light sensitive ion channel. The student is alert because she just had coffee and cookies. She is fascinated and entertained. She enjoys her life. She is a participant of the Neurizons conference 2016.

Two floors down a creature in a green shirt runs frantically through the narrow basement corridors. Sweat is pouring down his face. Fear projects out of his widely torn open eyes. His ear is attached to a mobile phone. He is desperately looking for the stock of plates and forks his colleagues were supposed to buy while he is arguing into the phone that the delivery for the cheese buffet was scheduled 15 minutes before current time. He is stressed. He curses his life. He is an organizer of the Neurizons conference 2016.

Neurizons is a biennial conference organized by the students of the MSc/PhD/MD-PhD Program and International Max Planck Research School (IMPRS) for Neurosciences. In 2016 Neurizons gathered an audience from all around the globe for informative talks in multiple areas of neuroscience. Participants could hear about the exciting progress in fields like cortical microcircuits, Alzheimer's disease, sleep circuits or human volition and get a broad but still in-depth update about the progress in brain research. For the first time, Neurizons reserved a whole session just for talks about methodological advances, for example light-sheet imaging in living animals or engineering of single molecule fluorescence tools. As always, Neurizons also included speakers who work in very interesting fields outside of the main stream fields of neuroscience. How radio waves influence migration of birds, how the mantis shrimp sees the world with 12 different color photoreceptors or how bacteria in the gut affect brain function were topics with high level of both entertainment and information. Prof. Stuart Firestein from Columbia University, USA, gave a highly amusing and instructive keynote lecture about

his work on the olfactory system, signal transduction and neuronal regeneration. Exactly this diverse mix of topics attracted more than 300 participants from different fields of neuroscience, at different stages of their career and from countries all over the world. As for the previous Neurizons symposia again 2 doctoral students from the Weizmann Institute of Science in Israel joined the meeting continuing the long standing co-operation and scientific exchange with the Neuroscience program.

However, Neurizons was not just about lectures. It was about interaction. Apart from talks, Neurizons offered a lot of events. The Coach Me was a one on one mentoring session allowing students to ask the speakers what they always wanted to know from successful scientist. Workshops in STED microscopy, transcranial magnetic stimulation and in-vivo electrophysiology provided a hands-on opportunity to get to know new techniques. Poster sessions, student talks, a career fair, an open panel discussion and an exhibition about art in science provided ample room for exchange of ideas in a stimulating environment and fostered the networking spirit of this conference. A city tour and an exuberant party broke the last floes of ice. In addition, Neurizons 2016 was preceded by the 15th anniversary symposium of the European Neuroscience Institute (ENI). So, this year the audience of two conferences

came together in these joint events. Therefore, many participants were pleased by the multi-faceted program, collected many impressions and built new connections. The impression of a seemingly flawless conference required a lot of work and preparation. The organizers in the green shirts had not only the role of the helpful guides at the registration desk but pulled strings in the background and shadowed the events only appearing in anticipation of a problem. All planning had already started ten month before the actual conference by inviting speakers, designing posters and flyers, making the website and advertising the conference. In regular meetings throughout the following months, the framework of Neurizons had been sculptured with the chisel of creativity and the sledge of diligence. Although it was laborious for the organizing team, everyone was rewarded by the positive feedback of both the participants and the speakers. Furthermore, the process of preparation allowed them to meet the person behind their favorite scientist, taught them about teamwork and how to solve problems,

for example how to organize plates last minute. Especially memorable was the personal dinner with the speakers. In the end, all the small mishaps were forgotten and just the memory of a successful conference remained.

The organization of Neurizons 2018 has already been launched. The eager IMPRS students have set out once again to administer a conference in which young researches can interact with renowned scientist, present their ideas, gain insight into new techniques, seek out job opportunities, forge co-operations and learn about the most recent advances in neuroscience.

Journeys of Science

PhD-retreats of the IMPRS Neuroscience *by Alexander Dieter*

Since the last issue of this newsletter two PhD retreats of the IMPRS Neuroscience took place - one was held in Goslar (December 2015), a cozy city in the Harz mountains, and the second one took place in Spiekeroog (April 2016), a small but beautiful island in the northern sea. Given the local infrastructure our travel to Goslar was quite unspectacular compared to the journey to Spiekeroog, starting in the early morning and involving several train and bus trips as well as a ride with the ferry across the northern sea, before the students - accompanied by Sandra, Mirja and Michael - finally arrived at their dorms on the lonely island. The scientific exchange between students during the seminars was on a high level, given not only the critical scientific supervision by Michael Hörner but also by Detlev Schild in Goslar and by Martin Göpfert in Spiekeroog. In Goslar, the first scientific sessions, dealing with modeling and development, were held in the afternoon of the day of arrival. The next day started with a session dealing with a variety of behavioral topics, while neuroanatomy and –degeneration were discussed in the afternoon. Last but not least, PhD-projects dealing with synapses and senses were presented on the last day of the retreat, before heading back to Göttingen. During our Spiekeroog retreat, four different sessions were held. The scientific program started on the day after arrival. In the morning, a session of clinical neuroscience was held, followed by a developmental symposium in the afternoon. On the second day, a synaptic session took place in the morning, while the time after lunch was dedicated to sensory neuroscience. All in all, during both retreats almost all of the participants had the opportunity to present their PhD-projects. Breaks between the sessions were filled with stimulating debates about the research being done by IMPRS students, questions were answered and even possible collaborations were discussed. Besides the scientific program, the framework of both trips also incorporated the exploration of local sights. Of course a hike in the mudflats is a must whenever you travel to the northern sea, just as bird watching - and even the occasional rough weather could not hold us back. In Goslar we visited the old mining shaft of the Rammelsberg, where silver, copper and lead were mined before it has been declared world cultural heritage in 1992. Also, thanks to the date of the retreat, we had the opportunity to visit the famous Christmas market of Goslar and warm ourselves with a cup of red 'Glühwein'. As in the previous years, our retreats offered great opportunities to network within the IMPRS, discuss your own and your fellow's research and form new as well as strengthen existing friendships. Opportunities which I personally do not want to miss.

ELECTRAIN courses ...

at the European Neuroscience Institute again supported by FENS

The ELECTRAIN courses in electrophysiology are held in the ENI teaching labs since 2009. Started as one of the training initiatives of the Graduate School GGNB, the course is meant to train local PhD students and postdocs in advanced electrophysiological techniques. Meanwhile, ELECTRAIN increasingly also attracts external participants, who take the course together with local doctoral students. In 2015 and 2017 participants from Florida Atlantic University in Jupiter joined the course held at the European Neuroscience Institute Göttingen (ENI-G). This brings again life to the partnership with the Florida campus, which also hosts the Max Planck Florida Institute, the only MPI in the US.

This extended methods course provides both theoretical and practical knowledge and skills of modern electrophysiology, with lectures in the morning and hands-on lab work in the afternoons. The ELECTRAIN course concept was awarded by the Federation of European Neuroscience Societies (FENS) following worldwide yearly calls launched by FENS since 2013. The GGNB course was selected for FENS funding since 2014 and funding was continuously renewed ever since. ELECTRAIN 2017, thus, hosted again 4 FENS participants, who receive financial support to cover their living and travel costs.

3MT:

The three-minute thesis competition *by Tanvi Butola*

On 2nd of February 2017, the University of Göttingen hosted the first round of the 'three-minute thesis competition', being organized across the Coimbra Group Universities. Out of the 39 universities in this cluster, 20 participated this year. Each university held the first round within its campus. A video recording of the presentation of the winners from the first round was judged by a jury, which then selected three finalists. These three people will now present their work at the Coimbra Group Annual Assembly in Edinburg.

Amidst the commotion of thesis submission and initial hesitance to participate, I am proud to report that I made it to the final round and will represent the University of Göttingen at the annual meeting in Edinburgh. As I prepare for the final lap, here is my perspective on this unusual yet fascinating format of scientific communication. I say unusual because this presentation involved condensing three years' worth of work into just three minutes. The trick was to reflect on your years of labour, and bring out not just the significant result but a significant story of what you do and why you do it. This experience was a crash course in perspective. My years as a graduate student have prepared

me to talk about my work for hours, discuss my research in extensive detail, and debate over its outcome and shortcomings. However, here I needed to break it down to its core and extract from it the essence that is meaningful to others. I had to project it out from the perspective of a person who does not care about a protein that may reduce the vesicle numbers at a neuronal synapse, but would be excited about learning how the brain functions, and why one needs to study individual, seemingly insignificant, proteins to know more about it.

This format provides an efficient way of public outreach and bridging the gap between academia and the taxpayers, whose support we rely on. Regardless

of what science one does, it does not help if it does not reach people. The public needs to know why it is important to invest in science and how it helps, and how a thesis on a single protein fits in the 'bigger picture'. Yes, it is a cliché, but it is so for good reason; because perspective matters.

At the end of it all, it is an incredible training as a graduate student to really dig deep into your mounds of indecipherable data and present something that is exciting even for people, who care not about a whimsical p-value. Albert Einstein once said, 'if you can't explain it simply, you don't understand it well enough'. In the quest to put forward the simplest version of my thesis, these three minutes forced me to better understand my work and regain some of the meaning in it, that one loses along the way of a gruelling PhD.

Joint Information Booth

'Neuroscience in Germany' at the SfN Meeting 2016

Neuroscience in Germany

The Society for Neuroscience Annual Meeting was held 13.-16. November 2016 in San Diego

Based on the experience of the existing network of international graduate programs in the neurosciences in Germany 'Neuro Schools Germany', now comprising 15 German universities (http://www.neuroschools-germany.com), the idea of joining forces with other German institutions in the field of neuroscientific research has been realized in fall 2014 during the Society for Neuroscience (SFN) Meeting in Washington for the first time. Due to the great success, the 'Neuroscience in Germany' booth was continued ever since. The common landmark German platform at the SFN meeting now includes the Excellence Clusters in the neurosciences, the national Bernstein network (http://www.nncn.de/de) and the organization 'Research in Germany' (http://www.research-in-germany.org/en; Alexander von Humboldt Foundation, the German Academic Exchange Service, the German Research Foundation) and the German Research Council (DFG). The common booth 'Neuroscience in Germany' was also supported by the local office of the German Research Foundation based in Washington.

Traditionally, the German Research Institution Consortium present at the SFN also hosts the Leibniz Lecture held by recent Leibniz awardees. This time Prof. Dr. Tobias Moser from Göttingen, Leibniz awardee in 2015, gave a lecture entitled "How hearing happens – molecular physiology and optogenetic restoration". After this scientific highlight the participants of the Leibniz lecture and other guests gathered for the 'German Social', an informal get together hosted by the DFG Office in North America and the 'Research in Germany' Initiative.

The joint information booth provided comprehensive information on the German research landscape, training options, funding opportunities, and open positions in the neurosciences at German research institutions. Compared to similar marketing efforts in previous years with all partners running their own booths separately, the joint booth keeps on attracting increasing numbers of visitors. The joint financial support by the above mentioned partners allowed setting up one of the largest booth areas in the non-commercial exhibition area directly at the main poster passage. More than 700 visitors discussed in detail with the representatives of the different research organizations research and funding opportunities in Germany. The main advantage turned out to be the fact that visitors with very different specific interests could directly be guided to the suitable partners of teaching programs, research institutions or funding agencies at the very same booth.

After successfully establishing the 'Neuroscience in Germany' booth the organizing team has already started to plan for a joint outreach stand at the next SFN in Chicago in fall 2018.

NEUROMUNDUS:

New EU-Funding granted for Training of Master Students within the European Neuroscience Network

The ENC-Network is the organization that hosts both the Erasmus Mundus Master Course (EMMC) and the Erasmus Mundus Joint Doctorate (EMJD) program, in addition to two ITN (Brain-Train and SymBad). The ENC-Network (ENC: http://www.enc-network.eu) was founded in 2009 with EU funding granted in 2010 (doctoral positions, overhead of 1.3Mio€/year).

In conjunction with the establishment of the European Neuroscience Campus training network for doctoral candidates the European Master Neuroscience program 'NEURASMUS' has been launched in 2010 with the aim to extend exchange and training opportunities also for MSc students. Since 2011 three to five NEURASMUS MSc students join the Göttingen Neuroscience Program per year. They are trained in at least two home institutes of the ENC Network and have the option to enroll in existing and established PhD courses in each of the participating home institutes after successful graduating from the MSc program.

A new proposal to further develop and extend the joint MSc training scheme called 'NEUROMUNDUS' has meanwhile been approved by the EU authorities. Starting from the 1st of September 2016 and until the 31st of August 2021 a total funding of 2.9 million € was granted to the NEUROMUNDUS consortium. The NEUROMUNDUS proposal was selected from a total of 89 grant applications from which 27 were chosen for funding.

Between desert, beach and mountains –

9 months at the Weizmann Institute

External Master Thesis project at the Weizmann Institute of Science in Israel *by Alina Heukamp*

Over the past 10 years the Göttingen Neuroscience Program has an active partnership with the Weizman Institute of Science in Israel – promoting scientific and intercultural exchange, and regular visits of students both ways. When I was presented with the opportunity of spending six months at the Weizmann Institute to work on my master's thesis project, I was immediately intrigued by the idea – not only, because the Weizmann Institute is an excellent research institute, but also because I have so far not yet spent time abroad, unlike most of my international classmates. I looked into the labs in the department of Neurobiology and immediately liked the work of Dr. Michal Rivlin, a young group leader who started her lab around two years ago and works on neural computations in the retina, a field I had previously explored in a lab rotation and wished investigate in more detail. After I talked to her, she offered to host my master's thesis: It all went very quickly – we discussed a project, I took care of the visa and formalities, and a few months later in September 2016 I joined our delegation to visit the Life Science Open Day at the Weizmann Institute, where I had a chance to meet my future lab members. Another month later, I found myself at Ben Gurion airport in Tel Aviv with a big suitcase, surrounded by cab drivers who offered me the best deal to the Weizmann Institute – in Hebrew, of course, and each one trying to be louder than the other!

My master's thesis project focuses on the role of the neurotransmitter acetylcholine in shaping the response properties of subtypes of retinal ganglion cells – the output cells of the retina that send information about the visual world to higher order brain areas. We are currently building a new setup in the lab, equipped with a two-photon laser microscope, that allows for calcium imaging of a large population of retinal ganglion cells, while at the same time projecting various visual stimuli onto the retina. Moreover, we can target single cells electrophysiologically to record spiking activity or their inputs, and fill these cells to characterize them based on their morphology. After months of fixing and adjusting the system, we are finally able to record our first data.

Since my first day at the Weizmann Institute I felt very welcome, both in my lab and the institute itself. Our lab consists of only five people and we all work on different projects, yet everyone is there to help and discuss problems or results. People in my lab are very open and friendly and offered me help in every imaginary way starting from the first day, even giving me small Hebrew lessons of useful (and less useful) words and phrases. The department of neurobiology (Fig. 1B) consists of 20 research groups working in all fields of neuroscience. A weekly happy hour where the labs take turn in preparing food and drinks brings the whole department together and people can stay in touch, even across labs, so that one knows what other people are working on right now (or can simply meet new people). In December 2016, we went for a two-day lab trip to the Negev desert – every lab receives money to go on a trip once a year. We went for day hikes, spent the evening around the campfire and slept in a Bedouin camp in the middle of the desert (see Fig. 1A). Furthermore, two of us went to the annual meeting of the Israeli Society for Neuroscience, held in Eilat at the Red Sea, with neuroscientists from all over Israel and

Fig. 1: (Scientific) life at the Weizmann Institute of Science. A. Group photo of my lab during a two-day lab trip to the Negev desert. B. The department of neurobiology shown in October sunlight. C. Holi celebration, a festival organized for all international students and postdocs at the Weizmann Institute in March 2017.

abroad presenting their work in interesting talks and posters.

There are many international students and postdocs at the Weizmann Institute, and people here are doing their very best to make sure they have a great time at the institute and in Israel itself. The Institute offers monthly subsidized day trips for international scientists across Israel and several other events to promote a lively atmosphere, friendships and scientific exchange (see Fig. 1C). This way I found myself with friends not only from my field, but also from theoretical physics, mathematics, computer science, chemistry or stem cell research, which definitely provides ground for interesting discussions.

My project focuses on how retinal ganglion cells' outputs are shaped by the neurotransmitter acetylcholine. Acetylcholine is known to be involved in shaping the responses of one particular type of retinal ganglion cells, namely direction-selective ganglion cells, which respond to motion in only one direction. We built a setup that combines two-photon calcium imaging of a population of retinal ganglion cells expressing GCaMP, a calcium indicator protein that increases its fluorescence upon neural activation and hence increased intracellular calcium concentration (Fig. 2B). At the same time we can project visual stimuli onto the retina to activate the photoreceptors. The challenge here was to ensure that the visual stimulus does not interfere with the fluorescence of the calcium indicator. After facing many problems, ranging from broken parts over wrong or delayed deliveries to antibodies and virus that are not working the way they should, we are finally reporting first successful experiments (see Fig. 2).

When projecting various light stimuli onto the retina, we are able to extract the responses of retinal ganglion cells from the fluorescence of the GCaMP protein as the change in fluorescence, and we can characterize the cells based on their responses, for example into an ON-OFF cell (Fig. 2C) or a cell that prefers motion into one direction (Fig. 2D). Future experiments will hopefully reveal interesting effects of acetylcholine in the retina.

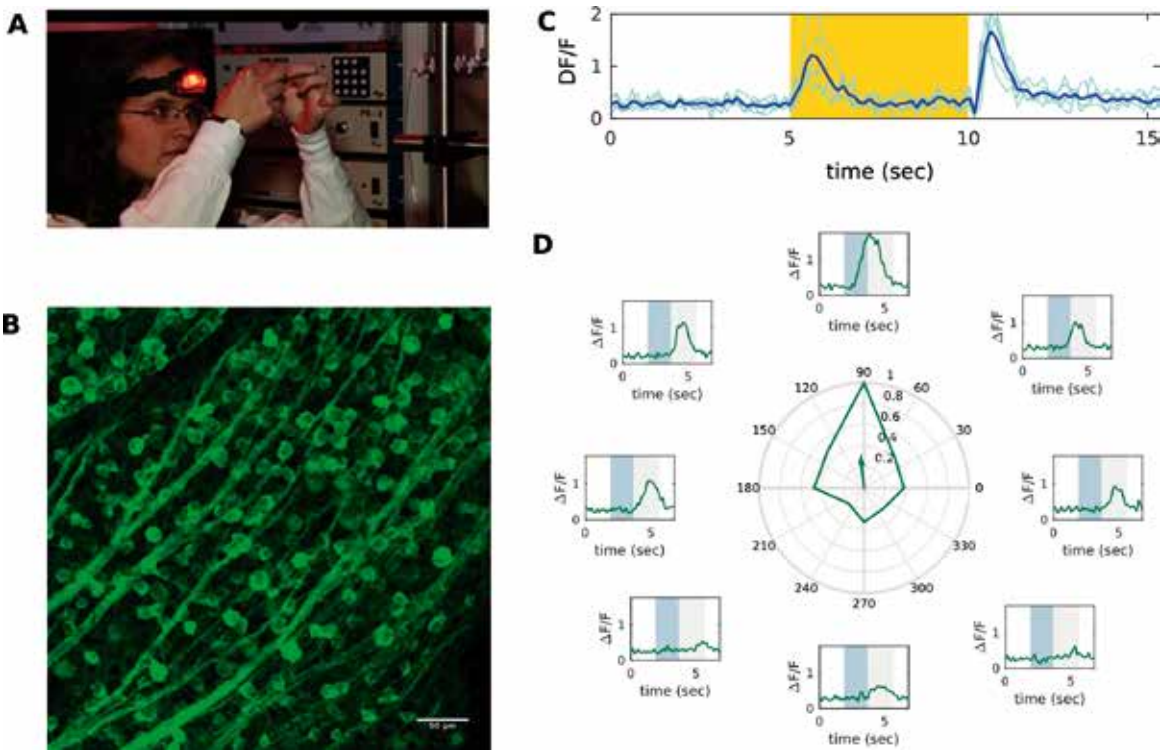

Fig. 2: Calcium imaging from retinal ganglion cells. A. During work in the lab. B. Retinal ganglion cells of a mouse retina expressing GCaMP, a calcium indicator to reflect neuronal activity. (Scalebar: 50µm). C. Response of an ON-OFF retinal ganglion cell that responds to both the onset and offset of light (yellow area represents light on). D. Responses of a retinal ganglion cell to moving bars presented in eight different directions. This cell prefers bars moving upward.

Israel is a country full of opposites – dry desert (Fig. 3A) vs. lush, green mountains (Fig. 3B), Jews vs. Arabs, religious vs. secular life, – the list goes on (see Fig. c). The Weizmann Institute is

located in Rehovot, a small city close to Tel Aviv, which offers a good base for travelling all over the country. Tel Aviv with its night life, beaches and young population is a bustling city (Fig. 3D), very open and liberal, and is a big contrast to the ultra-orthodox parts one might find in Jerusalem or other small towns throughout the country. Jerusalem offers a huge amount of history, from visiting holy places that are already mentioned in the bible or walking on old streets built by the Romans (see Fig. 3C). The country offers everything from desert landscapes, craters, beaches, the Dead Sea, up to green mountains, and even snow in the winter on Mt. Hermon, the highest mountain in Israel. Over the past few months I had the opportunity to discover the country on the weekends bit by bit, meet people all over the country and realize that there are still thousands of places left to discover.

Fig. 3: Life in Israel. A. The endless vastness of the Judaen desert in the Westbank, south-east of Jerusalem. B. Lush green hills, rivers and lakes in the Golan Heights in the north of the country. C. In front of the Dome of the Rock in Jerusalem. D. The skyline of Tel Aviv at night.

This study aimed at investigating the effect of working in a lab at the Weizmann Institute in Israel, and overall revealed an amazing working atmosphere, friendly and helpful people and significantly more sunlight in March than one might find in Germany's peak summer. My time here so far has been great and, and I believe that I profited from it both academically and personally – learning new techniques in neuroscience, establishing a new experimental setup, learning bits of Hebrew, making new friends from all over the world and learning more about the history of this country and the wider region. I am very grateful for this opportunity and will make the most of it, and I am looking forward to many more exchanges between our programs and the Weizmann Institute.

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Neurofaces

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