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Monoaminergic IMPACT on neuronal circuits - a Leibniz postdoctoral network

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Inhalt

1. Zielerreichung und Umsetzung der Meilensteine

The aim of the project was the establishment of a postdoctoral network at the Leibniz Institute for Neurobiology (LIN) in Magdeburg, Germany, fostering research on the impact of monoamines, an important class of neurotransmitters and neuromodulators, on neuronal networks of the brain. Thus, the project had both a ***scientific mission*** and a ***career-support mission*** with respect to postgraduate career development. The latter mission reflected the fact that in Germany currently postgraduate career support is far less developed than graduate career support. Both missions were accomplished successfully and in accordance with the planned milestones.

2. Aktivitäten und Hindernisse

During the project, a network of postdocs was successfully established that implemented research strategies to unravel monoaminergic modulation of brain activity at various different levels of brain organization (from molecular, via circuit-level to behavioral levels). This ensured sufficient independence of each postdoctoral project while at the same time providing unique opportunities for interaction and gain of international visibility. The project worked out as planned with the additional challenge of career dynamics: two postdocs who had received offers from outside (a measure of success in itself) could quickly be replaced ensuring continuity of the scientific mission (see sections 1. and 3.). It was also possible to achieve a cost-neutral prolongation of the support by one year.

3. Ergebnisse und Erfolge

3.1. Overview

With respect to the ***scientific mission*** of the project, new fundamental insights into the neuronal mechanisms by which monoamines impact neuronal activity in several brain regions have been obtained. Collaborations within and across subprojects have led to a number of publications in peer-reviewed journals (see below). A result obtained in one postdoctoral project has received particular public attention by being rewarded with the first price of the Hugo-Junkers Award in the category "Most innovative project in fundamental research".
With respect to the ***career-development mission*** the project was successful in identifying and serving the needs that are special to postgraduate career development and differ from those of graduate career support, namely the mechanisms by which young researches can increase the impact of their own research within relevant scientific communities (we chose the term "IMPACT" in the title of the project to reflect this double function of impact as both a *neuronal operational principle* and a *career development strategy*). The supported postdocs have been individually successful in gaining international visibility and establishing their own networks and have received and accepted long-term invitations for collaborative work in international laboratories.

3.2. Monoaminergic impact on neuronal networks of the brain

The project has allowed investigating the monoaminergic impact on brain systems at several levels, from the molecular level, via circuit-level systems analyses to behavioral outputs.
In collaborative work across the network we demonstrated the role of the locus coeruleus not only for attentional set shifting behavior, but cognitive flexibility in general (Janitzky, Lippert, et al. 2015). We further established microendoscopic calcium imaging of genetically defined neurons in the network and created a novel analysis tool for such data (Tegtmeier et al, 2018). We also addressed the often neglected issue of thermal artifacts accompanying optogenetic experiments by quantifying theoretically and experimentally the temperature rise of widely-used stimulation paradigm (Arias-Gil et al. 2016) and created an open access

online-app supporting experimenters to calculate the thermal impact for custom imaging or stimulation experiments. To gain a larger picture of the impact of monoaminergic on brain-wide circuits we used fMRI and SPECT in combination with dopamine-specific optogenetic stimulation (Brocka et al. 2018, Helbing et al. 2016). These experiments resulted in a surprising finding: dopamine release itself was insufficient to induce canonical BOLD or cerebral blood flow responses. This finding raises questions about the origin of these signals, which are clearly observable in human fMRI studies on reward. Based on pharmacological evidence and less dopamine specific optogenetic stimulation, we conclude that the driver of these signals is more likely glutamatergic activity. As a result, striatal BOLD responses should not be interpreted as markers of reward-related dopamine release but simply striatal synaptic and spiking activity.

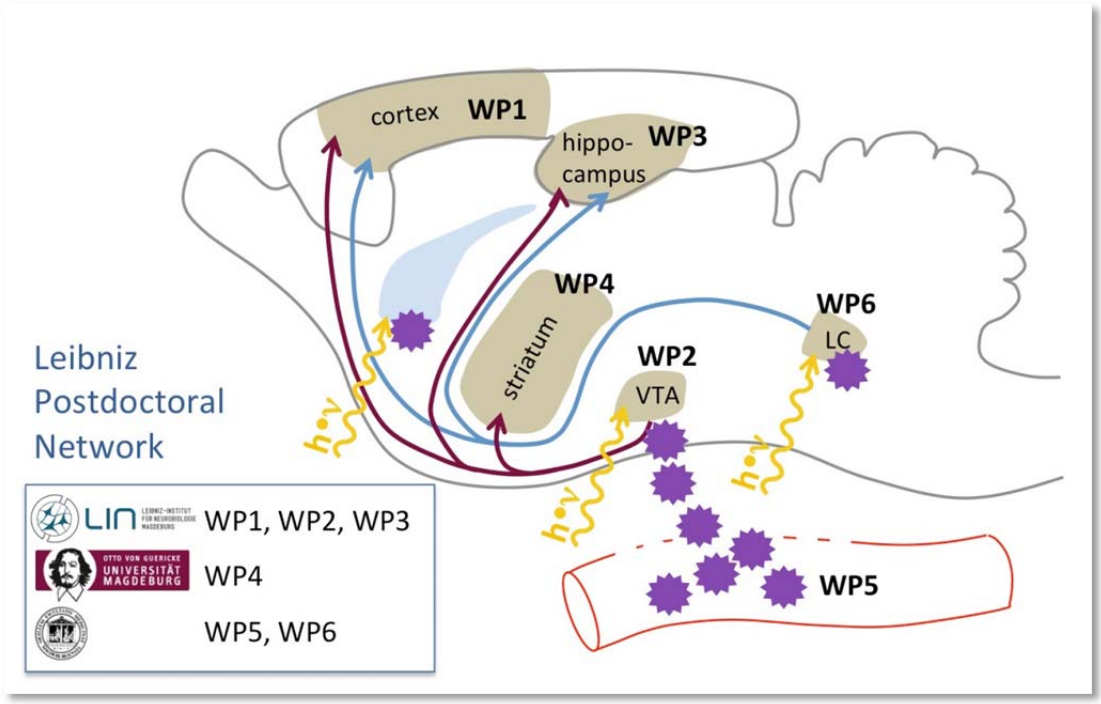

Figure. The Leibniz Postdoctoral Network (LPN). The network includes members from the Leibniz Institute for Neurobiology, the University of Magdeburg (Faculty for Natural Sciences) and the University Clinic. Work packages (WP) focus at target brain areas (beige) connected by two major monoaminergic projection systems (dark red: dopaminergic, blue: noradrenergic). Yellow waves indicate primary target sites for optical stimulation.

Using optogenetic stimulation of the ventral tegmental area (VTA) in combination with cortical current-source density analysis (Happel 2016, Happel and Ohl 2017) we showed that VTA-based dopamine modulates a cortico-thalamocortical positive feedback loop. While such feedback loops form important functions in sensory processing (e.g. Homma et al. 2017) their modulation is an important aspect of learning-associated neuronal plasticity. We specifically showed that dopamine modulates thalamocortical oscillations and alters phase-locking of cortical responses to sensory stimuli (Deliano et al. 2018).
Dopamine release from the VTA is regulated in a circadian fashion, thereby modulating striatal, cortical and hippocampal brain. Indeed, the formation and retrieval of hippocampus-dependent contextual fear memory underlies a circadian regulation (Albrecht and Stork 2017). We further found circadian effects on learning and memory retrieval in a task that allows assessing striatum- vs. hippocampus-dependent processes in one paradigm, the dual solution task. Here, mice learn to locate a reward within an open field by either utilizing a spatial configuration (hippocampus) or by relying on a proximal cue (striatum). By providing the cue separated from the reinforced spatial position during the memory test, the strategy choice to locate a reward can be assessed. Since performance in this task was strongly related to circadian effects on anxiety levels, we utilized a genetic model of increased anxiety, the GAD65 knock out mouse (Müller et al. 2015). In Gad65 ko mice, learning is not impaired, but they preferably choose a cue-based retrieval strategy. IEG-based mapping revealed a shift in the co-activation of the hippocampal dorsal dentate gyrus (dDG) and the

anterior cingulate cortex (ACC), a region relevant for decision making. The local knock down of GAD65 in the dDG was sufficient to reproduce the phenotype of the total knock out mouse and furthermore resulted in a reduced IEG-activation in the ACC. At the moment, we are investigating the potential role of local GABAergic interneuron populations in this task using interneuron subtype-specific Cre-Driver lines and acute chemogenetic interventions. This study will provide novel insights into the control of the ACC-hippocampal-striatal network in strategy decisions under emotional and circadian modulation.
On the neuronal level we have focussed on the roles of voltage-gated ion channels in the dendrites for computational processes within neurons (Bikbaev et al. 2016, Dumenieu et al. 2017). Early observations suggested that mature granule cell dendrites lacked active properties with no significant contribution of voltage-dependent sodium or potassium conductances to granule cell dendritic integration. But recent findings challenge this view (Lopez-Rojas and Kreutz 2016). Indeed, we found (Lopez-Rojas et al. 2016) that mature granule cells can increase their ability to fire action potentials in response to synaptic stimulation after weak but physiologically relevant conditioning protocols that did not even elicit any synaptic potentiation. Those excitability changes are related to modifications in the intrinsic properties of dendritic A-type channels. More recently we found that Kv4.2 A-type channel subtype plays a more prominent role than Kv4.3 in regulating the excitability of medial dendrites of mature granule cells. Moreover we observed that animals lacking the Kv4.2 channels are significantly impaired in their ability to discriminate similar spatial patterns, pointing to an improper processing of medial perforant path inputs. Another interesting feature of mature granule cells is their capability to fire *in vivo* action potentials preferentially in bursts. It is believed that the particularly pronounced short-term facilitation of mossy fiber synapses makes granule cell bursting a very effective means of properly transferring information to CA3. We recently showed that Cav3.2 T-type channels at the axon initial segment are responsible for burst firing of mature granule cells in rats and mice. Accordingly, Cav3.2 knockout mice fire tonic spikes and exhibit impaired bursting, synaptic plasticity and dentate-to-CA3 communication. Thus, the Cav3.2 channels are strong modulators of bursting and can be considered a critical molecular switch that enables effective information transfer from mature granule cells to the CA3 pyramids (Dumenieu et al. 2018).

3.3. References

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3.4. Further disseminination

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4. Chancengleichheit

The Leibniz Postdoctoral Network (LPN) was established at the Leibniz Institute of Neurobiology (LIN), Magdeburg, and therefore implemented the institute's general policy for equal-career management. Equal opportunities were already guaranteed during the recruitment process. Consequently, for the six workpackages of the network, three male postdocs and three female postdocs were recruited and coached during the project. In the last year of the project, the network was additionally supported by the newly established Office for Equal Opportunities and Career Development at the LIN, founded by the FemPower Project of the State of Saxony-Anhalt.

5. Qualitätssicherung

As an organizational unit of the Leibniz Institute for Neurobiology (LIN) the Leibniz Postdoctoral Network (LPN) is committed to following the rules of good scientific practice. The postdocs supported by the LPN have been specifically coached in the corresponding rule set. This coaching included individual project-related coaching by the respective PI of the subproject, participation at workshops dedicated to general aspects of good scientific practice. Quality control was also a major topic of several task force meetings held at the LIN in the context of the institute's management that were attended by the LPN members. The scientific results obtained in the network were published (and further results await publication in the future) in peer-reviewed scientific journals providing (1) independent critical review of scientific content and quality of the work, (2) independent review of the proper implementation of rules of good scientific conduct, and (3) access to results and data for the scientific community.

6. Zusätzliche eigene Ressourcen

The establishment of the Leibniz Postdoctoral Network (LPN) was based on hosting postdoctoral researchers in already existing, highly established laboratories. Thus, the postdocs could take full advantage of a developed infrastructure. The postdocs of the network were hosted by experienced PIs in established laboratories at the LIN and the OVGU. Postdocs had full access to all resources provided by their host laboratories, with respect to human resources (technical assistance, student assistance), investments (large experimental setup devices), and consumables and participation at laboratory-held technologies (molecular, electrophysiological and optic laboratories).

7. Strukturen und Kooperation

It has been a primary aim of the Leibniz Postdoctoral Network (LPN) to support the postdocs forming their own structural units and networks of international cooperations. Several postdocs have established their own working groups within the departments of their hosts that feature them as head personnel with individual research profiles and responsibilities. These new structures have greatly enhanced the postdocs international visibility. In addition, the LPN postdocs have all established their own international cooperations which have already led to short and long-time invitations in laboratories abroad.

8. Ausblick

The project has opened interesting vistas on future development, both with respect to the scientific mission of the network, and the structure of postgraduate support. First, with respect to the scientific aims, research on the impact of monoamines in various brain circuits is still on the rise and profits from the availability of new technologies targeting defined brain circuits. The focus on one particular class of neurotransmitters, here monoamines, in the research agenda has allowed to combine several different levels of brain organization, form molecular, via circuit-level to the whole brain, under a common scientific umbrella. We believe that this level of interdisciplinarity will be a key feature of future successful research programs on brain functionality. Another important aspect of research will be, of course, to put here obtained insights in the mechanisms of monoaminergic activity into relation with other neurotransmitters and modulators. Second, with respect to the structure of postgraduate training the results of our approach have confirmed our view that, in addition to the establishment of suitable networks among partners with complementary expertise, postdocs greatly profit from combining expertise in different, traditionally disjunct, fields in themselves, enabling them to pursue new original research paths and developing highly competitive skill profiles.