University of Zurich[UZH]

URPP Adaptive Brain Circuits in Development and Learning (AdaBD)

Progress Report University Research Priority Program (URPP)

Adaptive Brain Circuits in Development and Learning (AdaBD)

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Scientific Report of the URPP AdaBD

1 Management Summary

The URPP AdaBD wants to understand behavioral changes during development and learning in terms of the underlying adaptations of brain circuits. Besides revealing physiological processes, we aim to establish causal links between learning deficits or developmental delay and impaired mechanisms of brain circuit adaptation. We aim to uncover molecular mechanisms underlying brain circuit development and to identify mutations affecting circuit formation and multi-sensory processing. Finally, we aim to translate new insights from our research to the clinic and to develop new diagnostic tools as well as innovative treatment strategies.

During the third year of existence of the URPP AdaBD, our collaborative research projects and platforms made major progress. Those projects that were started in 2021 begin to produce research output in form of publications (15 papers in 2023). In most cases, manuscripts are in preparation or submitted and available as pre-prints. Most importantly, the presentation of results in our regular seminar series, at lab visits and during networking events led to interesting discussion between members of the participating labs. This interdisciplinary exchange is highly appreciated and one of the main goals of the URPP.
Our four PLATFORMS and PLATFORM SEEDS keep supporting URPP researchers. The mesoSPIM Platform finalized its new portable "Benchtop" system, with a manuscript published as preprint and in final revision. The Developmental Delay Database (DD Database) has been used as a resource to recruit children with language disorders for our ChildBrainCircuits project.
During the last year, we started planning a new PLATFORM focusing on learning disorders, including both dyslexia and dyscalculia. It will foster collaboration in research, education, public outreach, and development of diagnostic and therapy tools. The goal is to help improve educational outcomes and well-being for individuals with learning disorders. We plan to launch the platform in 2024 and to expand it in the second four-year period (2025 – 2028).

In 2023, we held several events promoting networking within our community and beyond. We organized a symposium in January 2023 with invited guests from other research networks at the University of Zurich (URPP ITINERARE, NCCR Evolving Language, and Developmental Science Network Zurich (DSN-ZH)). We carried on with our well-attended online research seminars, as well as our series of informal lab visits. We organized educational events on open science and science communication. In July 2023, we organized a two-day retreat, with a focus on strategic planning. Our young researchers participated in the brainstorming activities, a unique opportunity for them to see the work behind such a research program and to contribute.

The URPP AdaBD continued its efforts to promote dialogue within and outside the scientific community. In 2023, we published a brochure describing our work, and we launched our AdaBD Newsletter with two issues per year. Furthermore, we had a booth at the Scientifica 2023 and were strongly involved in the organization of the BrainFair 2023 on 'Lernen bei Mensch und Maschine'. Several AdaBD members participated in outreach events, which are listed in Chapter 4.2. Finally, we strongly expanded our webpage with information on each research project.

2 Objectives

2.1 Scientific, structural and organizational objectives

2.1.1 Scientific objectives

The scientific objectives for 2023 have not changed compared to our original research plan. In this context, we planned to initiate additional collaborations also in 2023:

- Embedded in Path 1 (From molecules to behavior), a new project on brain circuit rewiring and its consequences on learning and memory. This project builds on the project "Molecular mechanisms of circuit wiring in the developing and adult brain" *(Földy, Helmchen, mesoSPIM Platform).*
- Embedded in Path 3 (From humans to animals and back), the project SMILE. The goal of this project is the development and the evaluation of interventions for adolescents and adults with dyscalculia *(collaboration Kucian, Ruff, Brem and external collaboration with E. Moser-Opitz from the Developmental Science Network Zurich (DSN-ZH)).*
- Embedded in Path 3 a collaborative effort towards a 3D mesoscale atlas of inhibitory interneurons in the human thalamus as basis for future projects *(Jakab, Helmchen, Karayannis, HDDA Platform)*.

Further, we planned to

- Continue development of our imaging technologies.
- Explore opportunities to jointly apply for external funding.

2.1.2 Structural and organizational objectives

- At the level of professorships, we had two major goals in 2023: the establishment of an ad personam professorship for Prof. Dr. Ruxandra Bachmann, and the establishment by 2024of a tenure-track assistant professorship in the area of "Modeling Neural Diseases using Stem Cell Technology".
- At the level of early career researchers, we planned to hire additional personnel.
- We wanted to continue our regular workshops, seminars and informal events. In addition, we planned to organize a two-day scientific retreat for URPP researchers and members of the Advisory Board, with the goal to network and brainstorm on future developments in the URPP.
- In educational workshops, we planned to train our PhD students and Postdocs in aspects of Open Science and in science communications.

2.1.3 Communication and outreach

- To ensure communication and outreach, we planned to publish a newsletter with announcements and information about our research.
- We wanted to expand our website with information on our research projects, partially targeted at the interested public, schools, and patient organizations. Further, we planned to create a brochure describing our research for non-experts.
- We wanted to continue our presence on X (formerly Twitter) and to collaborate with the UZH communication office. We planned to co-organize the BrainFair and participate in the Scientifica 2023.
- At the scientific level, we planned to maintain partnerships with McGill University and the University of Queensland (in collaboration with the ZNZ). We aimed for exchange with other research networks, such as other URPPs or the DSN-ZH.

2.2 Which objectives and milestones were achieved? Which not?

In 2023, we achieved almost all objectives listed in the annual report 2022:

2.2.1 Scientific objectives

- We successfully started planned new research projects and continued the ongoing ones (see Chapter 3).

- We could reach important milestones for further development of our imaging systems, e.g., releasing the Benchtop mesoSPIM system (see Research). For improvement of our MRI measurements, we purchased and established a new MRI phantom that allows quantitative comparisons between the MR scanners used for the different projects. This was an essential step for truly collaborative work between different MR research groups within our network.
- Some researchers and research consortia successfully acquired third-party funds for the running projects (See Chapter 8). Three of our young researchers were granted their own funds (Swiss Government Excellence Scholarship, UZH Candoc and UZH Postdoc Fellowships, respectively). We actively participated in the initial steps to apply for the next series of National Centres of Competence in Research (NCCR) of the Swiss National Science Foundation (SNSF). A consortium with members of the URPP AdaBD and members of the Hochschulmedizin Flagship project STRESS submitted a project sketch on the topic "Resilience: Adapting to a challenging world" for an internal UZH selection process. The UZH leadership decided on 24.1.2024 to support this proposal with UZH as leading house. The pre-proposal needs to be submitted to the SNSF by April 2024.

2.2.2 Structural and organizational objectives

- In agreement with the Faculty of Science, the URPP AdaBD will create an assistant professorship tenure-track for "Modeling Neural Diseases using Stem Cell Technology" at the Faculty of Science (double professorship with the Faculty of Medicine). The URPP AdaBD has committed financial support for this assistant professorship, supplementing a generous donation from the private bank Rahn & Bodmer. The position has been advertised with an application deadline on January, 20th, 2024. We got 42 applications.
- Prof. Dr. *Ruxandra Bachmann* has been appointed as associate professor ad personam for Developmental Genetics starting on October 1, 2023. This has been achieved thanks to an agreement with the Faculty of Science, which covers most of her general budget and states its commitment to support the professorship beyond the running time of our URPP. The URPP AdaBD covers some of the start-up costs as well as 70% of Prof. Bachmann's salary until the end of the program. The Faculty of Medicine covers 30% of her salary due to her clinical work in medical genetics.
- The URPP created four new PhD Positions in 2023. Additional researchers working on the projects were paid by other funds. Moreover, the URPP hired an additional staff scientist for the mesoSPIM Platform, who mainly supports the Platform manager in the optimization of clearing protocols for biological tissues and in user support and training.
- We continued our bi-weekly online seminar series and organized one on-site Symposium in January as well as a two-day Retreat in July 2023. In addition, we continued our lab visits, and PhD Students and Postdocs had the opportunity to meet at informal events (see Chapter 4)
- The URPP organized two workshops on Open Science (see Chapter 6.2) and an educational workshop for PhD Students and other researchers of the network on science communication (see Chapter 5.1)

2.2.3 Communication and outreach

- We launched our *AdaBD Newsletter* in January 2023. A second issue followed in August 2023.
- We organized a *networking symposium* in January 2023 with speakers from other research institutions in Zurich with common interests (see Chapter 4.1). Further, we started supporting the *DSN-ZH* for *public outreach events* (see Chapter 4.2.2).
- We rarely used the X Account (formerly Twitter), also because of concerns regarding the development of this platform. Instead, we recently opened a LinkedIn account and plan to expand our activities there. A *brochure* describing our research was printed in March 2023 and distributed at the BrainFair and the Scientifica.

- Our webpage has been further expanded with more information on our research projects. Because of the maternity leave of our scientific coordinator, the further expansion with more information for laypersons and schools is still pending and planned for the near future.
- We co-organized the *BrainFair 2023* on 'Lernen bei Mensch und Maschine' and contributed to the *Scientifica 2023*. In addition, we established further contacts with schools for pilot studies within our research project ChildBrainCircuits. Some URPP members participated in further outreach events and maintained contacts with patient organizations (see Chapter 4.2). We did not establish direct contacts as URPP, yet. This is planned for the second phase of the URPP.
- The communication office of the University published several articles on URPP AdaBD output on the portal *UZH News* (see Chapter 6.3). Our Managing Director *Sabina Huber* wrote one of these articles. The URPP participates in partnerships with the *McGill University* and the *University of Queensland.* Within this partnership, AdaBD member *Christian Ruff* received 2023 a grant financed by the ZNZ.

2.3 Updated project planning

2.3.1 Scientific objectives

- The research projects will be continued. We expect to publish additional results within the next year, as some manuscripts are currently in preparation and close to being submitted.
- We will start planning new and follow-up research projects as soon as the approval for the second phase is granted and the financial framework is clear. We present our ideas in the development plan.
- The imaging technologies and the data analysis tools will be further developed
- For the *NCCR Resilience*, plan to submit a pre-proposal to SNSF in spring 2024 with official UZH support.
- We plan to foster synergies and collaborate wherever possible with the new BioVisionCenter (BVC), dedicated to computational image analysis, which started its activity at UZH this fall. *Fritjof Helmchen* is member of the BVC's steering committee. In the long term, we envision the extension of our mesoSPIM Platform to a Center for Innovative Microscopy, which together with the BVC and the Center for Microscopy and Image Analysis (ZMB) would form a strong Imaging Technology hub at UZH.
- Next year, we plan to launch a new platform of the URPP AdaBD focusing on learning disorders. Our goal is to build up structures for efficient research, teaching and support regarding learning disorders.

2.3.2 Structural and organizational objectives

- Hiring of a staff member for coordination and formation of the new platform on learning disorders.
- Recruiting procedure for the advertised assistant professorship "Modeling Neural Diseases using Stem Cell Technology". The AdaBD co-directors and Sebastian Jessberger are members of the committee.
- Supporting the establishment of laboratories for Prof. Dr. Ruxandra Bachmann.
- Organizing the site visit of the URPP evaluation panel on April 16-17, 2024.
- Continuing organization of workshops, seminars, and informal events.
- Organizing a retreat for URPP researchers in autumn 2024.
- Organizing a scientific conference planned in 2025.
- Organizing educational workshops for PhD Students and other researchers of the network on topics to be defined according to the students' needs.

2.3.3 Communication and outreach

- Continuing our regular *AdaBD Newsletter.*
- Continuing partnerships with other universities in collaboration with the ZNZ.
- Establishing our collaboration with *DSN-ZH* by supporting public outreach events.
- Expanding our activities on *LinkedIn.*
- Continuing the collaboration with the *communication office* of the University.
- Expanding our *webpage* with more information for laypersons and schools.

3 Research

https://www.adabd.uzh.ch/en/research.html

During the third year, we further built up our PLATFORMS and PLATFORMS SEEDS (for simplicity called platforms in the following). We continued our research projects and started some new ones. Several cooperative projects are now in the process of finalizing their manuscripts. Major achievements are described below, more information can be found on our website (see also QR Code).

3.1 URPP PLATFORMS

3.1.1 Light-sheet microscopy PLATFORM (mesoSPIM PLATFORM)

During 2023, the new (Benchtop) mesoSPIM system design was finalized and a manuscript describing its advantages was published as preprint. It is currently in revision (minor edits) for a high-profile journal. The Benchtop design offers an increased magnification range, better resolution and higher throughput compared with older systems. Moreover, it is more compact, portable, easier to build, and affordable. We also upgraded the existing mesoSPIM system at the Center for Microscopy and Image Analysis (ZMB) to achieve higher resolution, magnification, and throughput. In September 2023, *Dr. Marco Garbelli* started as a staff scientist (0.5 FTE). He will specialize in tissue clearing and imaging, thus making our platform more accessible for new and existing users. In collaboration with the HDDA Platform image analysis workflows are scaled up, since these remain demanding. In this aspect, we plan to collaborate extensively with the new BioVisionCenter at UZH.

3.1.2 Developmental Delay Database PLATFORM (DD DB)

During 2023, we used the DD DB for selection and recruitment of families with children with a developmental language disorder (recruitment ongoing within the AdaBD Project ChildBrainCircuits). Further, the platform provided an anonymized test dataset to the HDDA Platform to test the software tool for applicability in these data. Additional collaborations with the aim to link clinical findings to genetic, cerebral imaging and electrophysiological findings remain challenging.

3.1.3 The iPSC PLATFORM SEED

The iPSC **PLATFORM** - which provides iPSC-derived material, expertise and support – currently focuses on neuronal differentiation protocols. We have successfully set up iPSC differentiation protocols for cortical, dopaminergic and neuron/microglia co-cultures. Collaborations with *Martin Müller (*for visualization of synapses), and *Ruxandra Bachmann* (for analysis of primary cilia in neural progenitors and different matured neurons) are ongoing. Currently, we are developing a reporter line where cilia are fluorescently tagged, and we are characterizing primary cilia in different iPSC-derived neuronal cells. The results will be important given that these key organelles have been little studied in human neurons, yet. We will publish a resource paper to help the scientific community plan human ciliopathy research in iPSC-derived neurons. A collaboration with *Esther Stoeckli* for transplantation of iPSC-derived commissural neurons to chicken embryos has been discontinued since the iPSC-derived neurons did not integrate well in the spinal cord of chicken embryos.

3.1.4 The High-Dimensional Data Analysis (HDDA) PLATFORM SEED

In 2023, we continued to improve structure and design of the software Dataspace (dspace), on which the HDDA data science platform is based. Several ongoing URPP AdaBD research groups make use of Dataspace. Based on knowledge gained in these collaborations, we have added tools for the analysis of unimodal and multimodal time series data (e.g., analysis of behavior and neural activity), evolved Dataspace's (meta-)data annotation capability, error reporting and usability, and integrated support

for the DataJoint format. Furthermore, our Dataspace expansion, enabling the analysis and exploration of light-sheet microscopy data (in particular data produced by the mesoSPIM platform), is now at beta stage and we are in the process of testing it with the mesoSPIM user base. An internal workshop for training Dataspace users was held on November 20th.

3.2 Research projects

3.2.1 PATH 1: From molecules to behavior

Workpackage leaders: Esther Stoeckli and Martin Müller
Following a bottom-up approach, in Path 1 we study molecular mechanisms underlying neural circuit development. In collaborative projects, we analyze the distribution of specific cell types in the developing brain, study the role of genes associated with developmental delay in neural circuit formation and function, and improve technologies to study neural circuit architecture across spatial scales from the subsynaptic to the circuit level. Furthermore, we follow up on mechanisms that allow for rewiring circuits in the adult mouse brain and want to investigate consequences on learning and memory. Neuronal rewiring may be a prerequisite for an eventual improvement of intellectual disabilities. Last, but not least, we are further characterizing our newly developed hippocampal organoids to study human brain development. Major achievements are described below, a description of the projects can be found on our website.

3.2.1.1 Revealing the cortical distribution of human Cajal-Retzius cells in a joint MRI + mesoSPIM reference space

Groups: T. Karayannis, A. Jakab. PhD Student: M. Karatsoli
Cajal-Retzius cells (CRs) are crucial coordinators of cortical lamination during development. Aberrant function and distribution of these cells have been found in neuropsychiatric disorders, such as autism and schizophrenia. By combining mouse genetics, novel 3D microscopic techniques and a new analysis pipeline based on dataspace (in collaboration with *Sepp Kollmorgen*), we revealed the age-dependent developmental distribution divergence amongst three groups of CRs. In particular, we found one population of CRs to be maintained for a prolonged period of time into adulthood in the frontal regions of the mouse brain. As a next step, we plan to assess if such a population exists in the human brain, by processing fixed adult human brain tissue. We already successfully cleared human brain tissues, to our knowledge for the first time in Zurich. Further, we are collecting mouse brains for MRI scans and mesoSPIM imaging, which will allow us to make further conclusions about the impact of CRs in the developing cortex at mesoscale level.

3.2.1.2 Molecular Mechanisms of Cerebellar Circuit Formation - Contribution of Genes Associated with ciliopathies

Groups: R. Bachmann, E. Stoeckli. PhD Student: A. Noble. Collaborators: Elkhan Yusifov. HDDA platform
Joubert Syndrome is a neurodevelopmental disorder in the ciliopathy spectrum, which includes developmental delay, and which is caused by dysfunction of the primary cilium. In this project, we study the role of genes associated with Joubert Syndrome in circuit formation in the zebrafish cerebellum. We had found that larval zebrafish *cc2d2a* and *talpid3* mutants have abnormal neuronal primary cilia, but that brain morphology is normal. This year, transcriptomic analyses of these two and four other ciliopathy mutants revealed dysregulated expression of genes involved in neuronal activity, paralleled by abnormal swimming behavior of mutant larvae. These findings support a role for primary cilia in neuronal function beyond proliferation, differentiation or patterning (Noble et al., 2024). Further, we plan to investigate the function of primary cilia in iPSC-derived neurons in collaboration with the

iPSC platform and in the chicken embryo. Our findings will ideally contribute both to a better understanding of the basic mechanisms of primary cilia-regulated neural circuit development and of the pathomechanisms underlying ciliopathies.

3.2.1.3 Expanding the dynamic range of light microscopy-based analysis of physiological and aberrant neural circuit development (EXPAND)

Groups: M. Müller, E. Stoeckli, A. Rauch. PhD Students: N. Bollmohr, M. Brasili, L. Kistler, H. Yeliseyeva. Collaborators: G. Saiz Castro, P. Muttathukunnel, G. Siegel, S. Thomasin. mesoSPIM platform

In this project, we further refined various Expansion Microscopy (ExM) protocols at the Drosophila neuromuscular junction, in the chicken cerebellum, and two human iPSC-derived neuronal culture systems. We also combined ExM with STED microscopy at the Drosophila neuromuscular junction, and in human iPSC-derived neuronal cultures. We are characterizing neuronal excitability and synaptic transmission in two human iPSC-derived neuronal culture systems: We observed increased neuronal excitability and decreased synaptic transmission in cultures carrying CADPS de novo mutations, which cause neurodevelopmental disorders. Furthermore, we are establishing a paradigm to study homeostatic synaptic plasticity in human iPSC-derived neuronal cultures.

We further analyzed the role of FoxP family genes – which have been associated with autism spectrum disorders - in axon guidance in the peripheral nervous system and extended the analysis to combinatorial knock-downs. For the analyses of the specific phenotypes, we are working on AI-based methods and are optimizing sample preparation and loading for imaging with mesoSPIM. The technologies developed in this project will allow AdaBD members to investigate neuronal circuits in different systems at increased resolution for characterization of candidate genes linked to developmental delay.

3.2.1.4 Molecular mechanisms of circuit wiring in the developing and adult brain

Groups: C. Földy, S. Jessberger. PhD Student: M. Egger (until 31.07.23). Collaborator: W. Luo

In this project, we investigated how the capacity of wiring can be reactivated and controlled in a specific group of adult hippocampal neurons, the dentate granule cells. This year, we published our discovery that a subpopulation of dentate granule cells in adult mice atypically project to the contralateral hippocampus (Egger at al., 2023). We also found that the number and contralateral axon length of commissural granule cells significantly increased in an experimental model of temporal lobe epilepsy, also highlighting the potential relevance of our findings to understanding seizure mechanisms.

3.2.1.5 Brain circuit rewiring and its consequences on learning and memory

Groups: C. Földy, F. Helmchen, mesoSPIM Platform. PhD Student: N. Cruz Ochoa

As a follow-up project, we started a new study aiming at enabling circuit rewiring in the adult mouse brain to investigate its consequences on circuit operations, learning and memory. First findings show that axonal wiring can be cell autonomously induced in adult hippocampal pyramidal neurons by molecular programing. Afterwards, synaptic weights are reconfigured both in the hippocampus and in target areas outside the hippocampus. Experiments characterizing the effect of rewiring on hippocampus-based learning and memory functions are ongoing. Recent advances in other areas of circuit research raise expectations that rewiring may be beneficial for a variety of brain disorders.

3.2.1.6 Using hippocampal organoids to study human brain development

Groups: S. Jessberger, C. Földy, F. Helmchen. PhD Students: D. Gonzalez (until 08.23), L. Brandi (from 01.24)

In the last years, we made substantial progress in developing organoids. Currently, we are still phenotyping them by extensive single cell RNA-sequencing experiments and conventional immunohistochemistry. In addition, we are using genetic approaches to induce formation of

hippocampus-like structures in human organoids. Establishing hippocampal organoids may be of substantial value for future research within the URPP that aims to bridge the current gap between experimental rodent work and human brain structure and function.

3.2.2 PATH 2: From behavior to molecules

Workpackage leaders: Fritjof Helmchen and Anita Rauch
Following a top-down approach, in Path 2 we investigate, mainly in animal models, multi-sensory learning and decision-making to reveal the underlying circuit mechanisms. We could track dendritic activity during learning in mice and are now further developing the tasks for quantification of multi-sensory learning in mice and for comparison with measurements in humans. Further, we could show a negative effect of reduced socialization on multi-sensory learning and maturation in adolescent mice. In a side-project, we investigated how death of a specific cell type after birth is key for development of somatosensory processing in mice. This work can pave the way for studies on somatosensory processing in children affected by neurodevelopmental diseases and in animal disease models. Finally, we are improving computational models of brain development that may help comparison between species. Major achievements are described below, more information can be found on our website.

3.2.2.1 Dendritic adaptations during learning

Groups: F. Helmchen, V. Mante. PhD Student: G. Schönfeld. HDDA platform
This work has been published as a preprint at the end of 2021 (see annual report 2022 for details) and was positively assessed by reviewers at *Nature*. We are currently addressing critical points of the reviews by including further experimental data and data analysis. A major addition to the manuscript will be the inclusion of modeling results based on an adapted reinforcement learning algorithm, developed in collaboration with *M. Tsai* and *W. Senn* (University of Bern). This model puts forward a novel interpretation of dendritic signals in terms of prediction errors and may provoke further hypotheses to be tested. The finalization of the revision is delayed, not least because *G. Schönfeld* finished her PhD and left the lab in 2022. Because she has now rejoined part-time as a postdoc, we are confident to be able to submit the revised manuscript early 2024. A follow-up project is described below.

3.2.2.2 Dendritic integration in neocortical pyramidal neurons as basis for multisensory learning

Groups: F. Helmchen, C. Ruff, S. Brem, V. Mante. PhD Student: J. Nieweler. Collaborating Postdoc: S. Han
Neocortical regions communicate with each other through long-range projections. In this project, we aim to understand learning-related changes of neuronal integration of converging projections from distinct sensory modalities (visual, auditory, tactile). We are applying and expanding approaches developed in the previous project. We implemented a two-alternative forced-choice behavioral paradigm for multi-sensory integration (Han and Helmchen, 2023), upon which we can further work towards establishing a multi-sensory behavioral paradigm closely related to the human behavioral paradigms used in other AdaBD projects (FuncMechanisms and ChildBrainCircuits). In the work by Han & Helmchen we also demonstrated feasibility of chronic measurements in the rostrolateral area of the posterior parietal cortex (PPC) of the mouse, where multi-sensory integration is known to occur. This paves the way for further measurements of dendritic activity and its learning-related changes using chronic two-photon calcium imaging during stimulus presentation as well as reward delivery periods. In the last year, we also implemented and tested a special technical add-on for two-photon microscopy (a Bessel beam module), which should allow to measure activity in nearly all branches of a dendritic tuft simultaneously.

3.2.2.3 The development of prefrontal cortex and executive functions in mice

Groups: C. Pryce, T. Karayannis, B. Grewe. PhD Students: S. Wicki, R. Missall, Ph. Eugster
During the reporting year, we demonstrated that, in terms of multi-sensory learning in the visual and somatosensory domains, adolescence in mice is a period of change, which ends with the onset of adult levels of behavior. We found that reduced socialization during adolescence increases adolescence-specific behaviors and delays onset of adult levels of behavior. To identify changes in specific neuronal populations in the prefrontal cortex we have established a method for quantification of immuno-histochemical images of synaptic puncta. Further, we are currently assessing how the visual and whisker-driven somatosensory stimuli are processed across the cortex and how they interact over development using in vivo wide-field calcium imaging and silicon probe recordings. We hired a PhD Student for computational modelling with the generated data to improve understanding of the inter-dependence between development, prefrontal cortex, and multi-sensory learning.

3.2.2.4 The impact of Cajal-Retzius (CR) cell death on the development of cortical circuits

Groups: T. Karayannis, F. Helmchen. PhD Student: A Damilou
In this project, we show that CR cell death contributes to the formation of the mature neocortical somatosensory circuit and is key for the development of somatosensory processing. This year, we finalized the manuscript (Damilou et al., currently in revision).

3.2.2.5 Linking brain-wide connectivity, function and dynamics with artificial neural networks

Groups: V. Mante, F. Helmchen. PhD Student: L. Pompe
In the past years, we have developed a novel machine learning approach for fitting artificial, recurrent neural networks to large-scale neural activity. In the reporting year, further validation and application to data from mice engaged in a decision-making task showed that neural activity resulting from internal brain processes largely accounts for the prominent variability apparent in individual task trials (Pompe et al., manuscript in preparation). The same approach could be used in the future to extract internal components from human functional imaging data. Such internally generated components have been difficult to model with past approaches and provide a novel window into possible differences between healthy and impaired brain function and development.

3.2.3 PATH 3: From humans to animals and back

Workpackage leaders: Christian Ruff and Bea Latal
In Path 3, we study human learning with the goal to relate findings from humans to animals and back. We eventually want to improve developmental delay diagnosis and treatment strategies. Our goal is to study the neuro-computational basis of learning and the differences between individuals with and without learning disorders. During the last three years, we especially focused on language and number processing disorders, which may relate to deficient multi-sensory learning. We developed tasks to assess multi-sensory learning in humans and combined them with fMRI measurements in adults and children. In a first clinical trial, we aim to apply our knowledge to evaluate an intervention. Further, we are establishing techniques to create novel 3D atlases of human brain combining meso- and macro-scale imaging, which will improve our understanding of the underlying neuroanatomical basis of developmental disorders. Impairments of brain connectivity likely play a role in developmental delay. In two of our studies, we found effects of clinical risks and environmental factors, incl. trauma, on brain connectivity and learning. Finally, we identified novel, likely causative genetic variants in a cohort of patients with congenital heart disease and developmental delay. These variants are promising candidates for future investigation in animal models or hiPSC-derived neurons. Major achievements are described below, more information can be found on our website.

3.2.3.1 Functional brain network mechanisms underlying multisensory learning (FuncMechanisms)

Groups: C. Ruff, F. Helmchen, S. Brem. PhD Students: E. Casimiro, S. Bedi. Collaborator: G. de Hollander
In the reporting year, we finished the collection of fMRI data of neurotypical adults to identify brain areas where neural activity tracks the learning of multi-sensory associations. We used our newly established task (see annual report 2022) and developed computational models that can be fit to data and provide us with parameters for the fMRI analyses. Variants of the task and model are currently also employed in children with learning disorders and are planned in mice. Our analysis confirmed that distinct neural networks underlie different types of learning computations (reward-based and statistical multisensory learning) and revealed connectivity patterns that specifically underlie audio-visual versus visuo-tactile learning (Bedi et al, manuscript in preparation). The focus of the ongoing analyses is on identifying whether distinct neural populations within these networks encode the different sensory modalities. We are also setting up non-invasive brain stimulation studies (TMS) to test whether activity disruptions in the identified cortical areas lead to problems with either reward-based or statistical multisensory learning, or both.

3.2.3.2 Neural basis of multisensory learning and processing during child development (ChildBrainCircuits)

Groups: S. Brem, N. Raschle, A. Rauch, C. Ruff, M. von Rhein. PhD Students: N. Raduner, C. Providoli. Postdoc: S. Di Pietro. Assistant: S Ismail. Collaborators: P. Dimanova, R. Borbás, I. Karipidis, M. Schneebeli, MSc students
During 2023, we finalized and evaluated in a fMRI pilot study our novel multisensory audiovisual and visuotactile learning tasks as well as the naturalistic audiovisual movie processing task. Further, we started collecting and analyzing behavioral, fMRI and genetic data in 35 healthy children, aged 6-13yrs. Further recruitment and data collection in healthy children and in children affected by developmental language disorders is ongoing. In addition, we published manuscripts related to learning trajectories and network connectivity analysis during print processing in development (see also report 2022). This research project lays the ground for longitudinally re-evaluating the study cohorts and implementing the developed evaluation tool in clinical assessments and next-generation interventions. Furthermore, specific patterns of neuronal circuit activation or genetic findings can be transferred to animal models to be further investigated by basic science techniques.

3.2.3.3 Neural origin of disrupted magnitude processing and risk taking in dyscalculia (NumRisk)

Groups: C. Ruff, K. Kucian, S. Brem. PhD Student: M. Renkert. Collaborator: G. de Hollander
In the reporting year, we developed a novel computational cognitive model of numerical processing to be used with our computerized task battery. Further, we developed an fMRI analysis method to probe the quality of neurocognitive representations of numbers in individual subjects (Barretto-Garcia et al, 2023). Currently, we are collecting and analyzing data in dyscalculic adolescents (several manuscripts in preparation). Our project will pave the way for novel diagnostic and therapeutic measures (behavioral assays and brain stimulation/training measures). A first randomized clinical trial (SMILE) has been started this year.

3.2.3.4 Development and evaluation of an intervention for adolescents and adults with dyscalculia (SMILE)

Groups: K. Kucian, C. Ruff, S. Brem. PhD Student: C. Biegel. External collaborators: Inst. of Education (UZH)
Although we know that dyscalculia persists into adulthood, no evaluated support for young adults exists. We aim to fill this gap by developing and evaluating interventions to improve numerical understanding in affected adolescents and adults. To evaluate the specific effects of the intervention, we will test the study participants behaviorally and by means of MRI before and after completion of the intervention, as well as after a waiting control period. We expect significant differences in brain

function, morphometry and connectivity between adolescents/adults with and without dyscalculia. We expect to see an improvement in numerical understanding and an adaptation of the neuronal network responsible for number processing after the intervention in affected individuals. For further analyses in a larger cohort, we plan to pool MRI data with the NumRisk project in a worldwide unique large MRI database of adolescents/adults with dyscalculia and matched controls.

3.2.3.5 A 3D mesoscale atlas of intrathalamic inhibitory interneurons in the human brain

Groups: A. Jakab, F. Helmchen, T. Karayannis, mesoSPIM and HDDA Platforms. PhD Student: M. Antonios. External collaborators: Preclinical Imaging Center (ETH/UZH), Inst. of Anatomy (UZH)

To understand the structure and function of the human brain, it is important to be able to create maps. We decided to join forces and start a new project, which focuses on the creation of a new open-source digital 3D atlas that characterizes the distribution of intrathalamic inhibitory interneurons (ITINs) in human brain tissue. These cells are sparsely distributed in the thalamus and their role is not well understood. We will focus on the thalamus, because it is crucial for control of sensory information flow to the cortex and for sensorimotor integration and learning. To enable imaging human brain tissues at high resolution in 3D with mesoSPIM and MRI, we are developing microscopy techniques, improving tissue processing protocols, and optimizing software algorithms for quantitative analysis. The methods developed in this project will first be applied to typical human brain tissue, but may then be tested on brains with a known developmental condition, or in animal models of developmental disorders.

3.2.3.6 Structural basis of mild developmental delay in the developing human brain connectome

Groups: A. Jakab, B. Latal, M. von Rhein, V. Mante. PhD Student: A. Speckert. Collaborator: H. Ji. External collaborators: Scalable Parallel Computing Laboratory (ETH)

We developed a comprehensive novel software pipeline to analyze structural neuronal network (connectome) data. This pipeline could already be used to analyze data of newborns with spina bifida (Ji H. et al, 2023 and 2024) and in an additional URPP project of a cohort of adolescents with congenital heart disease. To better reveal latent connectome features in relation to developmental delay and potentially predict cognitive outcomes, in the reporting year we worked on the development of a new, machine-learning based method in collaboration with the Scalable Parallel Computing Laboratory, ETH. Once established, the analysis could be applied to additional datasets, such as cases from the DD DB, as well as for cross-species comparisons.

3.2.3.7 The impact of clinical risk and environmental resilience factors on brain circuits & learning: A network connectivity analysis in adolescents with congenital heart disease

Groups: B. Latal, A. Jakab. PostDoc: M. Ehrler

In the reporting year, we adapted the analysis pipeline developed within our URPP to be applicable for adolescent and adult connectome data and then used it for structural brain connectome analysis in adolescents with congenital heart disease (CHD), who are at increased risk for learning impairments. We found altered structural brain connectomes in patients relative to controls: While network integration was preserved, patients showed lower network segregation and lower edge strength in a dense subnetwork. Further, we established a novel, clinically applicable measure of cumulative clinical risk score and found that more risk was associated with more alterations in the structural brain connectome and with poorer executive functioning. There was no association between structural brain connectome measures and social or environmental factors. These findings advance our understanding of the brain behavior connections in patients at risk for developmental impairments and learning disabilities. The manuscript is under review and published as a preprint (Ehrler et al., 2023). In a further set of experiments, we will investigate if similar alterations of the connectome can be detected in very preterm born patients, another clinical cohort with a risk for developmental impairments.

3.2.3.8 EarlyTrauma - The effect of early childhood and in utero trauma on brain development, educational outcomes, and professional attainment: Large-scale evidence from the UK Biobank

Groups: C. Ruff, V. Mante, HDDA Platform. PostDoc: G. Aydogan
We finalized our analysis of genetic, neural and behavioral data obtained in a prospective epidemiological study of 500,000 individuals (UKBiobank). We show that self-reported childhood trauma was associated with a reduction in grey matter substance across the whole brain, a significantly lower IQ, and reduced lifetime earnings. Further, we found that in utero trauma (specifically, World War 2 air-raids within a two km radius of self-reported birth location within the last trimester of pregnancy) exhibits a significant impact on grey matter volume, mostly in frontal brain areas and cerebellar structures, which in turn leads to a reduced IQ decades later. Our results provide direct (and partially causal) evidence for the harmful effects of in utero and early childhood trauma on brain development and life outcomes. Currently, two manuscripts are in preparation (Aydogan et al.).

3.2.3.9 The genetic contribution to mild neurodevelopmental impairments in congenital heart disease (CHD): direct or indirect effect

Groups: B. Latal, A. Rauch. Assistant: N. Braun
In this project, we used a cohort of patients with CHD and neurodevelopmental impairments to find potentially causative genetic variants and to correlate them with the clinical data. This year, we sequenced and analyzed a control cohort, which made it possible to compare the variants obtained from patients (see annual report 2022) with the control population (69 patient trios consisting of patients and their parents, vs 79 control trios). We identified 86 de novo and 99 homozygous rare variants in the patient cohort (Braun et al, manuscript in preparation). Literature research combined with bioinformatics analysis have shown that many of these variants are associated with CHD and developmental delay. We found not only genes that have already been implicated in disease in databases, but also novel, likely causative genes. These variants are promising candidates for future investigation in animal models, hiPSC-derived neurons or cardiomyocytes and collaborative projects planned for phase II of the URPP AdaBD.

4 Scientific Activities and Outreach

4.1 scientific activities

We organized an on-site **AdaBD symposium** on January 25th, which was open to all members of the AdaBD research groups. Topic of the symposium was "Networking at the University of Zurich". We invited representatives from the URPP ITINERARE (*Janine Reichenbach)*, from the NCCR Evolving Language (*Richard Hahnloser),* and from the Developmental Science Network ZH (DSN-ZH, *Moritz Daum*, *Elisabeth Moser, Alexandra Freund*): They presented their networks and gave guest lectures. In addition, our PhD students and postdocs presented their research projects either during short oral presentations (four presentations by *Lucas Pompe*, *Angeliki Damilou*, *Sarah Di Pietro*, and *Gökhan Aydogan*) or during a poster session.
In the reporting year, we organized our first **scientific retreat**, which took place with 50 participants in Flüeli-Ranft on July 3rd – 4th. It was open to all PIs, researchers and students involved in research projects of the URPP AdaBD. The aims of the retreat were to network and to discuss our strategies for the second phase of the URPP. The scientific program comprised:

- A series of short talks by our PIs summarizing current research
- Short talks by external PIs of the Children's Hospital (*Cornelia Hagmann*, *Reto Huber*, *Ruth O'Gorman Tuura*)

- A workshop on open science led by *Leonhard Held* (UZH Delegate for open science and member of our advisory board)
- A poster session
- Parallel brainstorming workshops on strategic planning 2025-2028 and beyond. The workshops covered the following topics: *sustainable measures, how to use the developmental delay database for research, new research topics and methods, outreach, third party funds and financial sources beyond 2028*. The workshops were followed by a plenary session where take-home messages were discussed. Minutes of all workshops and of the plenary session serve as the basis for the development plan of the URPP phase II.
- PhD/Postdoc meeting and steering committee meeting

The scientific program was followed by a nice walk on a circular route past various chapels. Informal exchange was also possible during breaks, apéros and meals. Seat assignments at the dinner table encouraged dialogue between generations and research areas. This intermingling was a success and was very well received. The retreat has been a great event in an inspiring and positive atmosphere.

We continued the well-established **bi-weekly online seminar series**, with the goal to present the AdaBD research groups and to discuss progress of research projects. The program of the online seminar series can be found on our website. Similarly, we followed up with mutual **lab visits** with the goal to learn more about the concrete work of the different research groups, to see the specialized experimental setups, and to foster networking. A new round of visits is planned for 2024.
One **Special Seminar** has been organized: *Dr. Sofie Valk*, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, presented on October 31st at the Irchel Campus (*How do genes and environment shape brain structure and function*).
Silvia Brem continued co-organization of the **Co_Air Webinar series**, 01.2023 - 09.2023, an online webinar three to four times a year. The webinar is an international forum on the current opinion on audiovisual integration and reading.
Activities related to open science are listed in chapter 6.2.

4.2 Outreach activities

4.2.1 Outreach in the science community

Several AdaBD PIs and PhD students presented research projects of the URPP AdaBD at international congresses and seminars. PIs and students have been asked to acknowledge funding by the URPP AdaBD as well as their affiliation to the network. This enables us to increase our visibility in the scientific community. Due to space limitations, we refrain from listing all oral and poster presentations. Below, we list invited talks and keynote lectures:

R. Bachmann gave a keynote lecture at the **French Cilia meeting**, Carry-le-Rouet, France, 16.-18-10.2023. *Presentation of data of the AdaBD project on primary cilia.*

S. Brem gave a keynote lecture at the **iWORD conference**, San Sebastian, Spain, 7.-9.6.2023, *Presentation of methods and data of the AdaBD project ChildBrainCircuits*

C. Földy was session chair at the **International Winter Neuroscience Conference**, Sölden, Austria, 12.-15.04.2023, and gave a talk on the rewiring AdaBD project.

F. Helmchen gave an invited talk at **OPTOGEN 2023,** Lecce, Italy, 10.-12.5.2023, with the title *"News about Light-sheets, Objectives, and Dendrites"*. Further, he gave an invited talk at the Neuroscience Network Basel, University of Basel, 10.02.2023, on *"Apical dendrites in neocortical layer 5 neurons enable task learning"* (AdaBD project).

S. Jessberger gave several invited talks on neural stem cells and neurogenesis (King's College London, LMU Munich, Biotech Research and Innovation Center in Copenhagen, Netherland Neuroscience

Institute). Further he gave a workshop at the **EMBO Workshop Gene regulatory mechanisms** Alicante, Spain, 7.-10.9.2023, on *"Molecular and functional heterogeneity of neural stem cells across lifespan"* and a keynote lecture at the **International Symposium on Neural Development and Diseases**, Kyoto, Japan, 15-17.3.2023, on *"Molecular and functional heterogeneity of hippocampal stem cells"*.

K. Kucian gave several invited talks and workshops on dyscalculia (related to the AdaBD projects NumRisk and SMILE) at several institutions and in the context of continued education courses: Schweizerischer Verband Lerntherapeuten (SVLT), Sozialpädiatrisches Zentrum des Kantonsspitals Winterthur, Kirchliche Pädagogische Hochschule Stams Austria, UMIT Tirol Austria, Österreichische Gesellschaft für Neuropsychologie (webinar).

Ch. Ruff gave an invited talk at the **RISLaB workshop Cognitive Economics (**program as PDF**)**, Gent University, Belgium, 14.06.2023 on *"Individual risk attitudes can arise from noise in neurocognitive magnitude representations"* (Presentation of data of the NumRisk project).

The *mesoSPIM Platform* participated in **several conferences and courses** in Switzerland and abroad with demos, talks and tutorials (e.g**. Focus on Microscopy Meeting**, April 2023, Porto; **"Image Analysis and Data Processing in Super-Resolution Microscopy" Workshop**, August 2023, Prague).

The *iPSC Platform* networked with other iPSC researchers in Zurich and participated at the annual **iPSZürich Symposium**, 14.04.2023. Further, the platform manager *W. Hänseler* gave an online talk at the **ISSCR Annual Meeting 2023** (Boston, 14.-17.06.2023)

4.2.2 Public Outreach

In the reporting year, the URPP AdaBD and its members engaged in several outreach events with the goal to increase visibility in the society and to inform the public on new insights from our research. Public events are also a great opportunity to feel the needs of society, which helps our strategic planning. For instance, the exchange with families affected by learning disorders motivates us to expand our research in this direction and to create structures for better support.

The URPP AdaBD co-organized the 2023 edition of the BrainFair (13.-18.03.2023), the annual event of the Neuroscience Center Zurich as part of the International Brain Awareness Week. The topic of the 2023 edition was "Lernen bei Mensch und Maschine". AdaBD members *M. Müller* and *K. Kucian*, our students representative *A. Speckert*, and our scientific coordinator *L. Zanetti* were members of the organizing committee. The main program consisted of five discussion forums in the evening (video recordings here, in German only), a series of short talks on Saturday, and live demonstrations (mesoSPIM platform, 3D reconstructions of neural networks in the human brain, neurocognitive game). Moreover, online talks and lab visits for schools have been organized. The whole program can be downloaded here (in German). Participating AdaBD researchers: *R. Bachmann, N. Raschle, E. Stoeckli* (Forum on the impact of genes and environment on learning); *S. Brem, K. Kucian* (Forum on learning disorders); *F. Helmchen, V. Mante, Ch. Ruff* (Forum on learning and decision taking in humans and animals); *B. Grewe* (Discussion on learning machines and consciousness); *M. Müller, M. von Rhein* (short talks); *mesoSPIM Platform, A. Jakab Lab, Ch. Ruff Lab* (live demonstrations).

Furthermore, the URPP AdaBD participated with a very successful exhibition booth at the **Scientifica 2023,** Switzerland's largest science festival. The following groups contributed to our booth:

1) The research groups of *R. Bachmann, M. Müller* und *E. Stoeckli* presented animal models (zebrafish larvae, fruit flies and chicken embryos) for research on formation and function of the nervous system.
2) The research group of *A. Jakab* gave the opportunity to explore a 3D reconstruction of the neural pathways in the human brain using virtual reality goggles. This was a major attraction with a constant waiting cue.

3) The research groups of *S. Brem* and *N. Raschle* prepared several games for children, with the goal to explain them how our brain develops and learns.

In the reporting year, we started financially supporting the **DSN-ZH** for the organization of events related to our research. We supported an online **panel discussion** on learning disorders (with the participation, of *Silvia Brem* and *Karin Kucian)*. The event has been recorded and can be seen here (in German).

Some AdaBD members and students participated to additional outreach activities:

S. Brem and *K. Kucian* participated in **several events related to learning disorders**: K. Kucian gave talks on dyscalculia for Kosmos Kind, Verband Dyslexie Schweiz, Fritz&Fränzi. Further, she organized lab visits for school classes on 20.09.2023. S.Brem gave a talk for the Schulpsychologie Affoltern on 1.02.2023.

S. Brem and *F. Helmchen* gave on an **online course** for the Zürcher Arbeitsgemeinschaft Lehrpersonenweiterbildung (ZAL) with the title «Hirnzellen beim Lesen und Lernen beobachten» (Flyer as PDF), 18.09.2023.

F. Helmchen participated as an expert and mentor to a high-school program of "Schweizer Jugend forscht". He also mentored a student from the Kantonsschule Baden, who visited his lab for her neuroscientific project. More information on the website of the program.

N. Raschle participated in several outreach events. A list of all events can be found here.

Ch. Ruff participated in the **SCNAT Biology Week 2023** by organizing lab visits for high school students and giving two talks on research in the context of the FuncMechanisms and NumRisk projects.

H. Yeliseyeva, AdaBD PhD Student, gave a public lecture on 30.03.2023 within the Series nanoTalks of the public outreach association "Reatch". Topic of her talk was her research within the AdaBD project EXPAND on molecular mechanisms of neurodevelopmental disorders such as autism.

D. Gonzalez, AdaBD PhD Student, co-produced the movies "The Beautiful Brain, which can be watched on YouTube.

Our **webpage** has been expanded with more information about our research projects. Currently, we are planning a subpage with information for the general public. We published two issues of our own **AdaBD Newsletter** for the science community and the interested general public. The newsletter can be downloaded from our website. In March 2023, we printed and published on our website a **brochure** that explains our work in simple words (in German). For a **Press review**, see Chapter 6.3.

5 Academic Career Development

5.1 Academic career development

AdaBD invested financial resources for a total of six PhD positions in 2021, 14 in 2022, and 16 in 2023. As of today, we financed – in some cases partially - a total of 20 PhD Students. Additional students are working on URPP research projects while being financed with UZH or third-party funds of their supervisors. One PhD Student had the opportunity to receive own funding through a UZH Candoc grant.

Young academics in our research groups can profit from an interdisciplinary environment, symposia, online seminars and support from the platform managers. This year, they had the opportunity to participate in our **URPP AdaBD Retreat**. They were involved in all program points, including workshops on the strategic development of the URPP. They actively participated and brought their own ideas. We believe that this was an outstanding opportunity to broaden horizons and learn about the work behind such a research program. Further, *A. Speckert* and *S. Kollmorgen* (students and platforms representatives) organized two informal networking events for PhD Students (28.02.2023 and 04.07.2023). As preparation for the retreat, our scientific coordinator, *L. Zanetti*, organized for PhD students and other young researchers of the network a **workshop on science communication** with

Adrian Ritter, science journalist and previous staff member of the UZH communication office (on 14.06.2023). The aim of the workshop was to learn how to discuss research results in an interdisciplinary environment such as our network. The participants especially learned how to create an informative poster, which is understandable for non-specialists.

Several members of the URPP (*R. Bachmann, F. Helmchen, M. Müller)* were co-organizers of a new version of a block course for bachelor and master students on "Modern microscopy in Life Science research". In this course, *N. Vladimirov,* manager of the mesoSPIM platform, demonstrated how to build a Benchtop mesoSPIM.

As of December 2023, three URPP members are young **group leaders and assistant professors** *(A. Jakab, K. Kucian, N. Raschle).* This is a smaller number than 2022 because *T. Karayannis* received tenure and was appointed as Associate Professor for Neuroscience starting 01.06.2023 and *R. Bachmann* was appointed as Associate Professor for Developmental Genetics starting 01.10.2023. The URPP AdaBD is supporting her professorship with 70% of the salary and with a contribution to her global budget. Further, the URPP is still financially supporting the assistant professorship for *A. Jakab* with 10% of the salary. We are in the process of filling the new tenure-track assistant professorship position in the field of "Modeling Neural Diseases using Stem Cell technology". We received 42 applications by the application deadline (January 20th, 2024).

5.2 Gender equality development

The URPP AdaBD commits to a favorable gender balance and has the goal to provide family friendly working conditions. In this reporting year, the AdaBD general manager *S. Huber-Reggi* acted as **representative for gender equality** in the steering committee. We mention our equal opportunity efforts in job advertisements. Further, when planning seminars and symposia, we always ensure gender balance. We believe that we achieved high standards regarding equal gender representation at all levels. Among the **PIs**, the proportion of women is 42%. Within the **steering committee**, the proportion of women is 56% and within the **advisory board** 40%. Eighty percent of the **PhD students** and 60% of the **Postdocs** financed by the URPP in the last three years are women. One platform manager out of four is a woman and works part-time (80%). Two PIs are working part-time due to family commitments. Two women working part-time due to family commitments run the coordinating office.

6 Publications

6.1 List of publications

The list contains only publications in which the URPP is mentioned in the acknowledgements. The URPP is mentioned if data collection and analysis has been possible thanks to the financial support of the URPP (salaries, running costs, method development). In addition, we asked our PIs to generally indicate the AdaBD affiliation in their publications. However, here we do not list publications that are not related to the URPP. URPP researchers are underlined. * *Shared Autorship;* # *Open Access*

Peer-reviewed publications

Barretto-García M., de Hollander G, Grueschow M, Polanía R, Woodford M, Ruff C.C. Individual risk attitudes arise from noise in neurocognitive magnitude representations. *Nat. Hum. Behav.* 1–17 (2023). doi:10.1038/s41562-023-01643-4.
doi.org/10.5167/uzh-239453doi.org/10.5167/uzh-239453 (accepted Version, embargo until 01.03.2024)

Baum S, …, Vladimirov N, Walsworth RL, Watanabe H, Mineral detection of neutrinos and dark matter. A whitepaper. *Physics of the Dark Universe* 41: 101245 (2023). doi.org/10.1016/j.dark.2023.101245.

Di Pietro SV, Karipidis II, Pleisch G, Brem S, Neurodevelopmental trajectories of letter and speech sound processing from preschool to the end of elementary school. *Developmental Cognitive Neuroscience* 61:101255 (2023). doi.org/10.1016/j.dcn.2023.101255

Di Pietro SV, Willinger D, Frei N, Lutz C, Coraj S, Schneider C, Stämpfli Ph, Brem S, Disentangling influences of dyslexia, development, and reading experience on effective brain connectivity in children. *NeuroImage* 268:119869 (2023). doi.org/10.1016/j.neuroimage.2023.119869

Egger M, Luo W, Cruz-Ochoa N, Lukacsovich D, Varga C, Que L, Maloveczky G, Winterer J, Kaur R, Lukacsovich T, Földy C, Commissural dentate granule cell projections and their rapid formation in the adult brain. *PNAS Nexus* 2(4):pgad088 (2023). doi.org/10.1093/pnasnexus/pgad088

Frey T, Ivanovski I, Bahr A, Zweier M, Laube J, Luchsinger I, Steindl K, Rauch A, A very mild phenotype in six individuals of a three-generation family with the novel HRAS variant c.176C > G p.(Ala59Gly): Emergence of a new HRAS-related RASopathy distinct from Costello syndrome, *American Journal of Medical Genetics* Part A, 191(8):2074-2082 (2023). doi.org/10.1002/ajmg.a.63240

Han S, Helmchen F, Behavior-relevant top-down cross-modal predictions in mouse neocortex, *Nature Neuroscience* (2024). doi.org/10.1038/s41593-023-01534-x

Ji H, Payette K, Speckert A, ..., Latal B, SPINA BIFIDA STUDY GROUP ZURICH, Jakab A, Thalamic connectivity topography in newborns with spina bifida: association with neurological functional level but not developmental outcome at 2 years. *Cerebral Cortex,* bhad438 (2024). doi.org/10.1093/cercor/bhad438

Ji H, Payette K, Speckert A, ..., Latal B, SPINA BIFIDA STUDY GROUP ZURICH, Jakab A, Thalamic connectivity topography in spina bifida newborns is linked to functional lesion level. *Cerebral Cortex*, bhad438 (2023). doi.org/10.1093/cercor/bhad438

Lewis CM, Hoffmann A, Helmchen F, Linking brain activity across scales with simultaneous opto- and electrophysiology, *Neurophotonics* 11(3):033403 (2023). doi.org/10.1117%2F1.NPh.11.3.033403 *Review*

Payette K, Hongwei L, de Dumast P, Licando E, Ji H, …, Jakab A, Fetal brain tissue annotation and segmentation challenge results. *Medical Image Analysis* 88: 102833 (2023). doi.org/10.1016/j.media.2023.102833

Royall LN, Machado D, Jessberger S, Denoth-Lippuner A. Asymmetric inheritance of centrosomes maintains stem cell properties in human neural progenitor cells. *eLife* 12:e83157 (2023). doi.org/10.7554/eLife.83157
[Comm.: This study used methods developed within the AdaBD project on organoids]

Voigt FV, Reuss AM, Naert T, Hildebrand S, Schaettin M, Hotz AL, Whitehead L, Bahl A, Neuhauss SCF, Roebroeck A, Stoeckli ET, Lienkamp SS, Aguzzi A, Helmchen F. Reflective multi-immersion microscope objectives inspired by the Schmidt telescope, *Nature Biotechnology* Online ahead of print (2023). doi.org/10.1038/s41587-023-01717-8

Hu, J., Konovalov, A., Ruff, C.C. A unified neural account of contextual and individual differences in altruism. *eLife* 12:e80667 (2023).
https://doi.org/10.7554/eLife.80667
[Comm.: This study used methods developed within the AdaBD project NumRisk]

# Wilhelm M*, Sych Y*, Fomins A, Alatorre Warren JL, Lewis CM, Serratosa Capdevila L, Boehringer R, Amadei EA, Grewe BF, O'Connor EC, Hall B, Helmchen F (2023) Striatum-projecting prefrontal cortex neurons support working memory maintenance. Nature Communications, 14: 7016. https://www.nature.com/articles/s41467-023-42777-3 (* equal contribution)
[Comm.: AdaBD supported this study with important equipment]

Preprints

Calangiu I, Kollmorgen S, Reppas J, Mante V, Primate pre-arcuate cortex actively maintains persistent representations of saccades from plans to outcomes, *bioRxiv* (2023).
doi.org/10.1101/2022.09.26.509463

Ehrler M, Speckert A, Kretschmar O, Tuura O'Gorman R, Latal B*, Jakab A*, The cumulative impact of clinical risk on brain networks and associations with executive function impairments in adolescents with congenital heart disease, *medRxiv* (2023).
doi.org/10.1101/2023.12.06.23299632
[In revision at Journal of American Heart Association]

Holfeld A, Schuster D, Sesterhenn F, Stalder P, Haenseler W, ..., Picotti P, Systematic identification of structure-specific protein–protein interactions, *bioRxiv* (2023).
doi.org/10.1101/2023.02.01.522707
[In revision at EMBO]

Noble A, Masek M, Hofmann C, Cuoco A, Kollmorgen S, Vladimirov N, Stoeckli E, Bachmann-Gagescu R, Shared and unique consequences of Joubert-gene loss-of-function in the zebrafish central nervous system, *bioRxiv* (2024)
[doi following soon]

Vladimirov N*, Voigt FF*, Naert T, Araujo GR, Cai R, Reuss AM, Zhao S, Schmid p, Hildebrand S, Schaettin M, Groos D, Mateos JM, Bethge Ph, Yamamoto T, Aerne V, Roebroeck A, Ertürk A, Aguzzi A, Ziegler U, Stoeckli E, Baudis L, Lienkamp SS, Helmchen F, The Benchtop mesoSPIM: a next-generation open-source light-sheet microscope for large cleared samples, *bioRxiv* (2023).
doi.org/10.1101/2023.06.16.545256
[In final revision at Nature Communications]

Submitted manuscripts

Damilou A, Cai L, Argunsah AÖ, Han S, Hanley O, Kanatouris G, Karatsoli M, Gesuita L, Kollmorgen S, Helmchen F, Karayannis T, Developmental Cajal-Retzius cell death contributes to the maturation of cortical inhibition and somatosensory processing.
[In revision at Nature Communications]

Stankovic A, Gonzalez-Bohorquez D, Mallona I, Quiniou M, Jaeger B, Korobeynyk V, Günther S, Rünker A, Garth A, Ochoa N, Földy C, Furlan SN, Kempermann G, Robinson M, Jessberger S, The histone variant CENP-A regulates activity-dependent gene expression and learning and memory.

Manuscripts in preparation (author lists and titles tentative)

We list here the expected output from running projects, which could not be published yet because of delays due to the pandemic (see Chapter 9). Several of these manuscripts are close to submission.

Antonios M, Ji H, Karayannis T, Jakab A, Charting the human thalamus: a review of open-source digital atlases and MRI imaging methods
Review

Aydogan G, Kollmorgen S, Mante V, Kleim B, Nave G, Ruff CC, In-utero trauma during World War II affects brain development and life outcomes.
[AdaBD Project EarlyTrauma]

Aydogan G, Kollmorgen S, Mante V, Kleim B, Ruff CC, The effect of early-childhood trauma on brain development and life outcomes: Large-scale evidence from the UK biobank. *[AdaBD Project EarlyTrauma]*

Bedi S*, Casimiro E*, Konovalov A, de Hollander G, Helmchen F, Brem S, Ruff CC, Separable neurocomputational mechanisms underlying multisensory learning. *[AdaBD Project FuncMechanisms]*

Braun NC, Ehrler M, Boonsawat P, Kraemer D, Ivanovski I, Cabello EM, Papik M, Bahr A, Zweier M, Latal B, Rauch A, The genetic contribution to mild neurodevelopmental impairments in congenital heart disease: Results from whole exome sequencing in patient- and control-trios. *[AdaBD Project on genetic contribution to neurodevelopmental impairments in CHD]*

Bürgi N, Aydogan G, Konovalov A, Ruff CC, A neural fingerprint of adaptive mentalization in strategic interactions. *[Pilot work for nnew AdaBD Project on Neural computations underlying learning and decision making in fronto-parietal networks, see research plan 2025-2028]*

Bürgi N, Aydogan G, Konovalov A, Ruff CC, Neurocomputational characterization of altered mentalization in autism. *[Pilot work for nnew AdaBD Project on Neural computations underlying learning and decision making in fronto-parietal networks, see research plan 2025-2028]*

de Hollander G, Grueschow M., Ruff CC, Rapid changes in risk attitude originate from Bayesian inference on noisy parietal magnitude representations. [AdaBD Project NumRisk]

de Hollander G, Moisa M, Ruff CC, Transcranial Magnetic Stimulation of parietal numerosity representations modulates risk appetite by increasing the noisiness of small magnitude representations. [AdaBD Project NumRisk]

Haenseler W, Figueiro da Silva J, Eschment M, Bachmann-Gagescu R, A guide to primary cilia in iPSC-derived neuronal models

Kollmorgen S, Karatsoli M, Noble A, Henley O, Bachmann R, Stoeckli E, Karayannis T, Vladimirov N, Helmchen F, Curation, fast exploration, and analysis of imaging data in Dataspace. [HDDA Platform]

Kollmorgen S, Calangiu I, Herbst J, Templier Th, Quiang X, Obermann V, Morina R, Zai A, Lorentz C, Schoenfeld G, Nambiar J, Panzeri M, Wahl AS, Helmchen F, Hahnloser R*, Mante V*, Multilevel hierachical datasets in Dataspace. [HDDA Platform]

Nair A, Bollmohr N, Muttathukunnel P, Müller M, A Dynamin-dependent increase in quantal size maintains synaptic transmission after tetanic stimulation. [AdaBD Project EXPAND]

Pompe L, Kollmorgen S, Gilad A, Helmchen F, Mante V, Inferring internally driven cortical dynamics with Sinkhorn recurrent neural networks. [AdaBD Project on artificial networks].

Renkert MF, de Hollander G, Aydogan G, Bedi S, Ruff CC, Acute stress induces risk-seeking via more optimistic beliefs. [AdaBD Project NumRisk]

Renkert MF, de Hollander G, Brem S, Kucian K, Ruff CC, A neurocomputational link between disrupted numerosity perception and risk-taking in dyscalculic adolescents. [AdaBD Project NumRisk]

Speckert A, Payette K, Knirsch W, von Rhein M, Grehten P, Kottke R, Hagmann C, Natalucci G, Moehrlen U, Mazzone L, Ochseinbein-Kölble N, Padden B, Meuli M, Spina bifida study group Zurich, Latal B, Jakab A, Altered connectome topology without an association to neurodevelopmental outcomes: a cross-etiologic study of newborns at risk for cognitive developmental delay.
[AdaBD Project on connectomes]

Wicki S, Canziani A, Argunsah AO, Karayannis T, Poggi G, Pryce CR, Development of sensory learning and orbital cortex neuronal synapses in mice: adolescent-to-adult changes and the effects of social isolation. [AdaBD Project on the development of the prefrontal cortex]

6.2 Activities to promote open science

Open Access publishing
Peer-reviewed publications marked with a # have been published open access (see Chapter 6.1).

Open research data
Data handling complies with the FAIR principle. In the reporting year, some measures have been implemented:

- The mesoSPIM Platform deposited all repositories, blueprints and code of the preprint on the Benchtop microscope on github:
    - Benchtop design files, list of parts, and building instructions (Wiki): https://github.com/mesoSPIM/benchtop-hardware

  - mesoSPIM control software: https://github.com/mesoSPIM/mesoSPIM-control
  - detection objective testing: https://github.com/nvladimus/lens-testing
  - PSF quantification: https://github.com/mesoSPIM/mesoSPIM-PSFanalysis
- The project SMILE implemented a mask in REDCAP of the entire study for demographic and behavioral data
- The project on trauma and brain development pre-registered the main analyses and the pre-processing code at OSF (https://osf.io/vpmhu)
- The project NumRisk made all the analysis code openly available on github (e.g. https://github.com/Gilles86/risk_experiment/). The computational cognitive model and the machine learning methods have been implemented as easy-to-use Python packages and can be used outside of the scope of this project, allowing for further collaboration within and outside UZH.

Most projects are still collecting data. Whenever possible, we will make data, codes and methods openly available.

Further Open Science measures
The mesoSPIM initiative further flourished this year. Meanwhile, 24 mesoSPIM instruments are in operation worldwide (see mesospim.org for details). Nikita Vladimirov delivered invited talks related to Open Science at the Royal Society Meeting (*Open, reproducible hardware for microscopy*, 22-23.05.2023) and at the EuroBioImaging Special Edition Virtual Pub (*Open Hardware in Imaging*, 22.09.2023)

Open Science awareness
An **Online Workshop on Open Science** for AdaBD researchers took place on 23.06.2023. *Leonhard Held*, Open Science Delegate of the UZH and member of the AdaBD Advisory Board, gave an overview of the Open Science Policy of UZH. *Melanie Röthlisberger*, responsible for Open Science Services of the University Library Zurich explained how the University Library can support us.
An additional **Workshop** took place during the AdaBD Retreat on 03.07.2023, in which we discussed opportunities and challenges of Open Science.

This year, the UZH launched a mentoring program for Data Management. *Marion Wenger* from the DD DB Platform participated to the program to become **Data Steward** of the UZH and will support AdaBD members regarding Data Management questions, including Open Science.

6.3 Articles on UZH News and press review

The list contains articles on topics related to the URPP and in which the URPP is mentioned.

«Die Qual der Zahl», UZH News, 07.03.2023
Interview with AdaBD-member Karin Kucian on one of the topics at the BrainFair 2023 (see Chapter 4.2.2)
«Den Ursachen von Lernstörungen auf der Spur», UZH News, 04.04.2023
Summary on two of the events at the BrainFair 2023 (see Chapter 4.2.2). Autor: AdaBD general manager S. Huber.

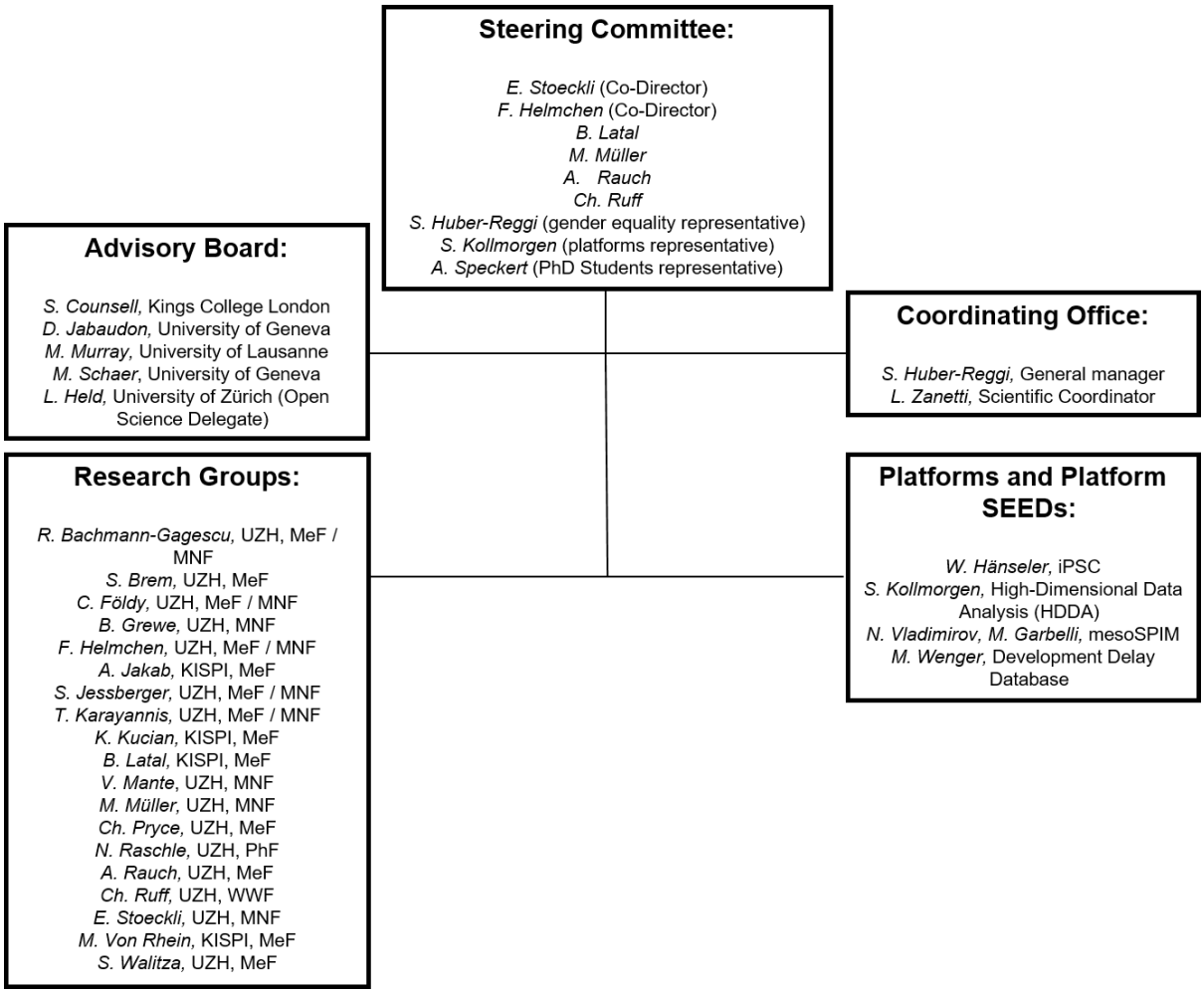
«Muschelaugen als Vorbild für neuartige Mikroskop-Objektive», UZH News, 31.03.2023
"Scallop Eyes as Inspiration for New Microscope Objectives", UZH News, 31.03.2023
On publication Voigt et al, 2023 (see Chapter 6.1)
Several additional articles in the scientific press.

«Bei einer Rechenstörung ist Abwarten die falsche Strategie», Fritz und Fränzi – Das Schweizer Elternmagazin, 26.04.2023
Interview with AdaBD-member Karin Kucian on dyscalculia

Wenn Silben und Zahlen zur Qual werden, Beobachter, 10.08.2023
With input from AdaBD-member Karin Kucian on dyscalculia

«Zwei Millionen für Gedächtnisforschung», UZH News, 29.08.2023
"Two Million for Memory Research", UZH News, 29.08.2023
On SNFS Advanced Grant for AdaBD-Co-Director Fritjof Helmchen

7 Structures



31.12.2023