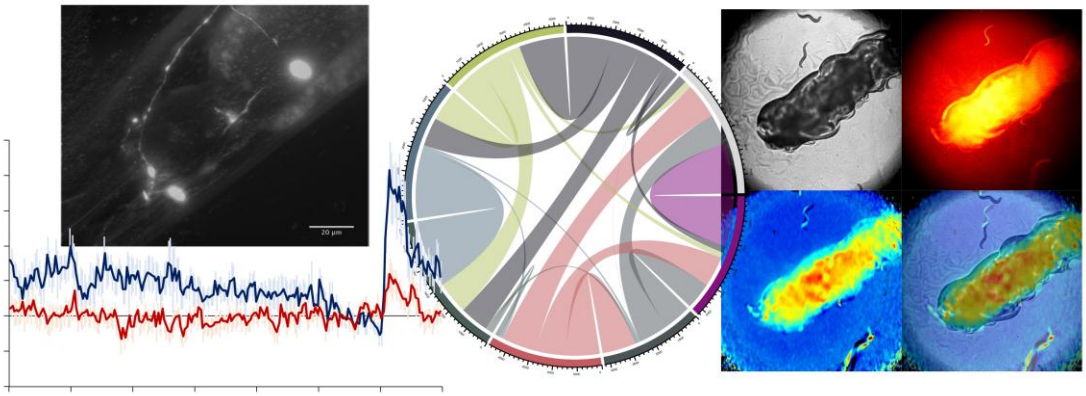
Busch Group – Research on Brain Ageing



Research Interests

One of the most feared aspects of ageing is that as we get older, our brain function declines.

The **overall goal of our research** is to gain an understanding of

1. the mechanisms that cause the decline of learning and neural plasticity with age

2. how the brain regulates ageing and longevity across the whole organism.

These processes are connected but poorly understood. Elucidating them can pave the way for a strategy to slow cognitive decline with age.

We use the nematode ***C. elegans* as an ideal and resilient model** to address these questions and have built a powerful arsenal of techniques from genetics and cell-specific transcriptomics, cellular and circuit dissection, to a systems-level analysis of behaviour and lifespan. We focus on the role of **Ca^{2+} homeostasis** and of **gap junction communication** in neuronal plasticity, cognitive decline and longevity.

Our **vision for the next years** is to aim to understand 1. the interplay of neural plasticity, resilience and age-dependent decline of cognitive function, and 2. how neural communication interfaces with the regulation of organismal ageing and longevity. We aim to elucidate the molecular and genetic factors underpinning these processes. Based on our unique findings, we will target the mechanisms that act downstream of Ca^{2+} in controlling cognitive decline with age, and to elucidate the mechanism of how communication by gap junctions regulates ageing.

Our research offers novel potential targets for future interventions in ageing and lifespan, one of the most important health issues of our time.

Our main, interlinked research directions are:

1. Targeting the molecular mechanisms governing early-stage cognitive decline

The ability to learn progressively declines with age. What causes this decline is one of the big unsolved questions in neuroscience. Neural hyperactivity has been implicated in impairing cognitive plasticity with age, but the molecular mechanisms are poorly understood.

We discovered that **chronic excitation of the *C. elegans* O_2-sensing neurons during ageing causes a rapid decline of experience-dependent plasticity**, whereas sustaining lower activity of these neurons retains plasticity with age. Chronic neural activity dysregulates neural calcium and alters the ageing trajectory in the transcriptome of O_2-sensing neurons, redirecting resources from maintaining plasticity to sustaining continuous firing.

Our research established a detailed model of how the control of Ca^{2+} homeostasis is a critical intermediary between neuronal activity and cognitive decline.

In the future, we will characterise how Ca^{2+}-dependent signalling pathways in chronically active neurons of *C. elegans* control the decline of memory and learning with age.

Dysregulation of Ca^{2+} plays a pivotal role in degeneration and death of brain cells after ischemic strokes and in long-term neurodegeneration such as Alzheimer's disease. Understanding the molecular processes regulating Ca^{2+} homeostasis in the ageing brain is critical for the development of therapeutic strategies targeting such disorders.

Our research throws light on key mechanisms that cause the loss of neuroplasticity and promote neurodegeneration, and offers the potential of early-stage treatment.

References:

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2. Gap junctions in excitable cells regulate ageing and longevity

Recent decades have seen intense research on the molecular and cellular mechanisms that determine ageing, senescence and lifespan. How they propagate through tissues and across

the whole organism to influence its longevity remains largely unknown, however. Gap junctions allow the direct transmission of signals across cellular networks and are important for sustaining cellular homeostasis in the nervous system. However, it was unknown whether they play a role in the regulation of aging and longevity.

We found that the **genes encoding gap junctions in *C. elegans* impact lifespan**. The loss of gap junctions in the nervous system or muscles promotes longevity by activating stress responses, and is a novel mechanism by which intercellular communication regulates the lifespan of the organism.

We will employ aging assays, optogenetics, chemogenetics, transcriptomics and metabolomics to investigate how gap junction uncoupling alters stress responses and metabolism, and identify candidate pathways to elucidate how gap junction communication underpins ageing at the organismal level.

Our research has the potential to reveal novel drug targets for the intervention in age-related diseases, cell death and to regulate longevity.

3. Mechanisms of neural and electrical synapse plasticity

To survive, animals dynamically adapt their behaviour to ever changing conditions. This is why, unlike the static circuits of microprocessors, neurons and neural circuits in the brain are highly plastic in their structure and function. Yet neural circuits have to produce reliable behavioural output to specific sensory input, and sustain these responses throughout the lifetime of an individual.

We found that O_2-evoked behavioural responses in C. elegans show extensive plasticity depending on experience, context or genotype. Taking advantage of this ideal *in vivo* model, we dissect the **molecular and cellular mechanisms that govern the plasticity of the neural circuit mediating O_2 homeostasis** in *C. elegans*.

The plasticity of gap junction coupling in neural circuits *in vivo* is little understood. We focus on examining the plasticity of electrical coupling in neural circuits of *C. elegans* and have identified environmental contexts that modify electrical coupling.

Current Members

- Emanuel Busch (PI)
- Daniel-Cosmin Marcu (academic staff)
- Rakesh Sharma (PhD student, together with Thorsten Pfirrmann)
- Frederic Schorcht (MD Student)
- Martin Oliver Schlak (MD Student)
- Rufus Mora (MD Student)
- Paulina Christ (student assistant)

Former Members

- Simon Warburton-Pitt (Postdoc)
- Elisabeth Fischer (Postdoc)
- Nathalie Vladis (PhD student)
- Qiaochu Li (PhD student)

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Academic positions

- Professor of Physiology (W3), Institute of Mind Brain and Behavior, Faculty of Medicine, HMU Health and Medical University, Potsdam, Germany

- Chancellor's Fellow, Centre for Discovery Brain Sciences, Edinburgh Medical School: Biomedical Sciences, The University of Edinburgh, UK

- Postdoctoral fellow with Mario de Bono in the Cell Biology Division, MRC Laboratory of Molecular Biology, Cambridge, UK

- Research Fellow, Darwin College, University of Cambridge, UK

- Postdoctoral fellow with Damian Brunner at EMBL Heidelberg, Germany

Education

- PhD in Cell Biology, European Molecular Biology Laboratory, Heidelberg, Germany and Biozentrum, University of Basel, Switzerland

- Diploma in Biology, University of Göttingen, Germany

Research Support

- Medical Research Council New Investigator Research Grant
- Wellcome Trust Seed Award in Science
- The Physiological Society Research Grant
- University of Edinburgh Principal's Career Development Award
- European Union Co-I on COST Grant
- Muir Maxwell Epilepsy Centre Seedcorn funding
- Wellcome Trust ISSF award
- The Royal Society Research Grant
- NC3Rs/Physiological Society Research Grant
- Moray Endowment Fund Equipment grant
- Swiss National Science Foundation Fellowship for Advanced Researchers
- Swiss National Science Foundation Postdoctoral Fellowship
- DAAD Postdoctoral Fellowship
- FEBS Postdoctoral Fellowship
- EU/Marie Curie Individual Postdoctoral Fellowship
- EMBO Long-term Postdoctoral Fellowship
- Roche Research Foundation PhD Fellowship

Publications

- F. Schildhauer, Petra SJ Ryl, Simon M Lauer, S. Lenz, Ayşe Berçin Barlas, Vasileios R Ouzounidis, K. Jeffrey, Daniel-Cosmin Marcu, Francis J O'Reilly, A. Graziadei, M. Stuiver, K. Schmidt, H. Ewers, Christian MT Spahn, E. Karaca, K. E. Busch, D. Cheerambathur, D. Schwefel, J. Rappsilber: An NADH-controlled gatekeeper of ATP synthase
  Molecular Cell, accepted in principle

- D.-C. Marcu, E. I. Berthold, K. E. Busch: Measuring Associative Learning in Chemotaxis of the Nematode *Caenorhabditis elegans.*
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Collaborators

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