Name	ANDREAS SCHAEFER
Position	Group Leader (2nd 6) Assistant Research Director
Year joined *(Crick or founder institute)*	2013

Career History

2004: Ph.D. Max-Planck Institute for Medical Research
2004- 2007: Postdoc, Department of Physiology, University College London
2007- 2008: BBSRC David Philips Fellow, University College London
2008- 2013: Independent group leader ("SNWG") at the Max-Planck Institute for Medical Research, Heidelberg, Germany
2010: Research Professor of Neuroscience at the Institute of Anatomy and Cell Biology; Univ. Heidelberg
2013-3/2015: MRC - National Institute for Medical Research: Francis Crick institute
2013- present: Professor of Neuroscience, Department of Neuroscience, Physiology, and Pharmacology, University College London
2015- present: Group Leader, Francis Crick Institute, London
2019- present: Assistant Research Director, Francis Crick Institute, London

Major Awards, Honours and Prizes

2019: Fellow of the Royal Society of Biologists

Membership of external committees, editorial boards, review panels, SABs etc

eLife (since 2019)
PLoS One, Scientific Reports (Since 2014)
SAB for ID16A Beamline ESRF (Since 2020)
NC3Rs rodent behaviour working group (since 2019)
NIH BRAIN initiative review panel (since 2016)

Lab Name	***Sensory Circuits and Neurotechnology Laboratory***

Research programme and achievements

My lab's central ambition is to elucidate how information is processed in the mammalian brain, and to investigate the cellular and circuit mechanisms by which neurons represent and process information. We employ the mouse olfactory system as a tractable, anatomically compact model system of high ethological relevance in a highly genetically accessible mammalian model species. In the past, we have recorded activity from projection neurons in different states – anaesthetised, awake passive and awake actively behaving. We have found that the two projection neuron classes represent odour inputs differently and that these differences are set up by the local interneuron network.

Moreover, we found that using unbiased whole-cell recordings differences between awake and anesthetised state are subtle but that there are learning induced changes that can in part be traced back to changes in sampling behaviour.

In order to in the future further dissect the circuit mechanisms underlying odour processing, we have developed new technical approaches: first, we have developed a home-cage based training system that allows efficient operant conditioning of group-housed mice over periods of months, allowing us now to broadly sample the psychophysical limits of odour representation; second, we have started to dissect the cellular and anatomical basis of local processing in the olfactory bulb combining physiology and anatomy, providing the basis for comprehensive, volume EM based analysis of local information processing; third, to enable sampling information from a significant fraction of all projection neurons in the OB, we have developed scalable electrophysiology that allows recording from 10^2-10^3 of neurons arranged in 3D in a minimally invasive manner.

In the future, we will follow three intertwined lines of research. First, we will assess how the mammalian olfactory system extracts information from temporal structure in odours to gain insight into the spatial structure of the olfactory landscape. This is based on the observation that natural odours are transported by turbulent air flow that imposes rich dynamics on odour concentrations. In ongoing work we have demonstrated that mice can detect concentration fluctuations with frequencies exceeding 40 Hz and that they can use this information to perform a source separation task. In the future we will assess which features of turbulent odour plumes are used to gauge distance or direction of odours, how these are represented in the early olfactory system and how the local interneuron networks enable extraction of this information.

Second, we will explore the topology of neural activity in the OB by combining high-dimensional temporally structured odour stimuli with large-scale electrical recording and local perturbation of the circuitry. By recording from increasing ensembles of neurons in the olfactory bulb and more and more cortical areas in response to high dimensional sensory stimuli and by stimulating large numbers of sites independently we will gain insight into the complex topology of sensory representation. Technical improvements will further increase the number of sites, recording density and 3D distribution and allow us and others to perform chronic recordings to both increase accessible stimulus space and enable us to assess stability of neural representation.

Third, we will directly link outputs and inputs in the OB and dissect the circuits underlying this transformation by combining *in vivo* imaging with detailed circuit reconstructions using electron microscopy and synchrotron X-ray tomography. Based on ongoing work we will further improve synchrotron X-ray tomography to allow us to capture subcellular detail over mm^3 volumes.

Together, this research programme will provide mechanistic insight into how the mouse olfactory bulb neural circuitry structures neural activity and extracts information about the odour landscape.

Research outputs

Obaid, A.M.*, Hanna, M-E.S.*, Wu Y-E.*, Kollo M.*, Racz R.R., Angle M.R., Muller J., Brackbill N., Wray W., Franke F., Chichilinisky E.J., Hierlemann A., Ding J.B., Schaefer A.T., Melosh N.A., (2020) *Massively Parallel Microwire Arrays Integrated with CMOS chips for Neural Recording*. Science Advances 12:eaay2789 DOI: 10.1126/sciadv.aay2789
Neuroprosthetics and neuroscience research alike are limited by the bandwidth of neural recording. At the same time, ever-more powerful silicon-based technology is ubiquitous in our phones, tablets and computers. Here we showed that progress in neural recording can be coupled to this by fusing bundles of microwires to pixel array chips, lifting silicon technology to the third dimension for deep brain recording.

Erskine A, Bus T, Herb J.T., Schaefer A.T., (2019) *AutonoMouse: High throughput operant conditioning reveals progressive impairment with graded olfactory bulb lesions.* PLoS One e0211571. DOI: 10.1371/journal.pone.0211571
Operant conditioning is a crucial tool in neuroscience research for probing brain function. Here we described a fully automated, high-throughput system for self-initiated conditioning of group-housed mice over periods of several months and >106 trials. We used this "AutonoMouse" system to systematically probe the impact of graded olfactory bulb lesions on olfactory behaviour, demonstrating that while odour discrimination in general is robust to even the most extensive disruptions, small olfactory bulb lesions already impair odour detection. The modular nature and open-source design of AutonoMouse makes it a versatile platform for efficiently and systematically assessing behaviour in mice.

Koldaeva A., Schaefer A.T., Fukunaga I. (2019) *Rapid task-dependent tuning of the mouse olfactory bulb.* eLife e43558. DOI: 10.7554/eLife.43558
Adapting neural representation to rapidly changing behavioural demands is a key challenge for the nervous system. Here, we demonstrated that the output of the primary olfactory area of the mouse, the olfactory bulb, is already a target of dynamic and reproducible modulation. The modulation depends on the stimulus tuning of a given neuron, making olfactory responses more discriminable through selective amplification in a demand-specific way.

Jordan R., Fukunaga I., Kollo M., and Schaefer A.T. (2018) *Active Sampling State Dynamically Enhances Olfactory Bulb Odor Representation.* Neuron 98:1214-1228. DOI: 10.1016/j.neuron.2018.05.016
Animals engage actively with their environment, yet how active sampling strategies impact neural activity was unknown. We showed that mice adapt sniffing during learning in a way that enhances neuronal representation. Furthermore, this work resolves a long-standing conundrum that seemingly non-olfactory information is prominently represented in the OB: context influences sniffing, which in turn changes neural activity.

Schwarz D., M. Kollo, C. Bosch, C. Feinauer, I. Whiteley, T. W. Margrie, T. Cutforth and Schaefer A.T. (2018) *Architecture of a mammalian glomerular domain revealed by novel volume electroporation using nanoengineered microelectrodes.* Nature Communications 9:183. DOI: 10.1038/s41467-017-02560-7
Mechanistic understanding of neural circuit function requires a wiring diagram. Electron microscopy is, however, limited to small volumes, such that generally only parts of

neurites are captured. Here we developed a new technique that allows comprehensive labelling of cells that extend neurites into a defined volume, adding context to local circuits. We apply this to for the first time register all projection neurons of a genetically identified glomerulus.