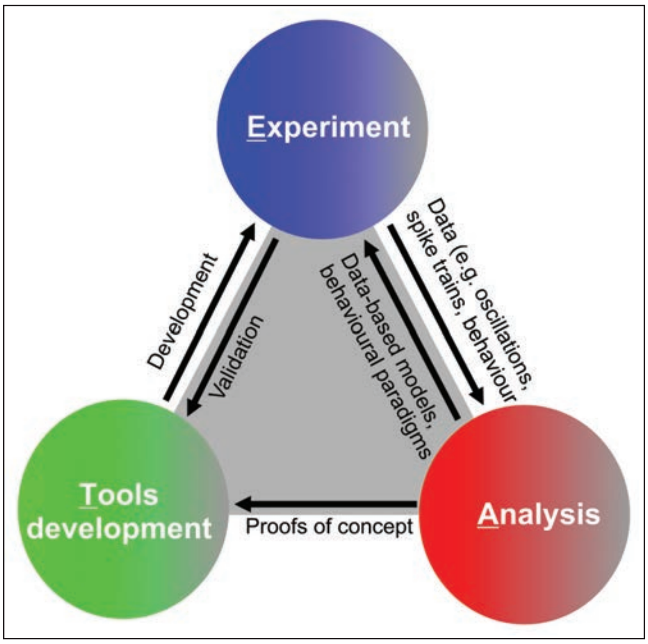
RESOLVING AND MANIPULATING NEURONAL NETWORKS

The Priority Program 1665 combines neuroengineering and biophysics with physiology and computational neuroscience to decipher the mechanisms of brain encoding

The day-to-day life of mammals relies on sensory perception, behavioural adaptation to an ever-changing environment, and on cognitive processing. These key abilities depend on neuronal networks of different complexity. Over the last decades an impressive effort has been made to understand the relationship between the neuronal and the behavioural/cognitive level.

Despite enormous amounts of detailed information about neurons and their assembling into small and large scale networks, a mechanistic explanation of how such groups or even single neurons account for a particular behaviour is still missing. This is due to three main drawbacks of past experimental approaches. First, the majority of studies investigated neuronal networks in isolation from the rest of the brain and their functional readout. Placing the knowledge gain of these studies back into a systemic context is a challenging task, which has been rarely achieved. As postulated by Donald Hebb more than 60 years ago in his functional cell assembly hypothesis, 'the problem of understanding behaviour is the problem of understanding the total action of the nervous system and *vice versa*' (Hebb, 1949).

Second, most past studies linking neuronal networks with their systemic functions were correlative rather than causal. Neuronal activity has been explored mainly by electrophysiological and imaging methods while the animal performed a specific task. This design allows the correlation of spatiotemporal network dynamics with the respective behavioural state. In this way, fundamental principles of cognitive function, e.g. formation of neuronal space representation in the hippocampus and entorhinal cortex or stimulus detection and sensory processing, have been elucidated. However, causal interactions between distributed networks and behaviour have only recently become accessible due to refined analysis methods and new techniques that allow highly specific manipulation at the cellular level.



Third, in recent decades the focus of the scientific community has shifted towards a molecular and biochemical perspective. It is now time to restore systems neuroscience in order to decode the function of neuronal networks in the living organism. All these facts justify the urgent need for strengthening research at the level of higher, integrated brain functions. The prerequisite for addressing this challenging issue in neuroscience – how behavioural abilities map onto neuronal networks – is the substantial technical progress and gain of knowledge over the last few years, to which German research groups have contributed significantly. The impressive development of new recording and imaging techniques, as well as of neuroengineering, optogenetic and analytical tools, in recent years had a profound impact on neuroscience. Thus the time has now come to bind experimental systems physiology with neurotechnology and analysis/modelling of network dynamics in an interdisciplinary and seminal collaborative endeavour.

Interdisciplinary collaboration

The Priority Program 1665 aims to identify causal relationships linking the activity of single neurons and networks to behaviour. This undertaking relies on the long and rich tradition of systemic neuroscience in Germany, pioneered by Otto Creutzfeldt, Bert Sakmann, Erwin Neher, Wolf Singer and Hans Dieter Lux. The interdisciplinary consortium initiated in 2013 brought together the available expertise in Germany. There is an emphasis on sensory-motor and cognitive processing, and investigations are performed at different levels of network complexity, ranging from single neurons and microcircuits to large scale cortico-subcortical neuronal networks, and both adult and developmental aspects are covered.

Specifically, the members of the consortium monitor and manipulate neuronal activity using new experimental tools, which are developed and validated in collaborative efforts centred on behavioural/functional readouts. Analysis of network dynamics and modelling allow the functional evaluation of mechanistic hypotheses and back up the links to behaviour. Practically, the working strategy of each project funded by the DFG within the Priority Program involves 'troika collaborations'. They include 'experimenters', i.e. groups resolving or manipulating neuronal activity, 'toolmakers', i.e. groups developing and validating the recording and manipulation methods, and 'analysts', i.e. groups analysing network dynamics, building data-constrained models or dissecting the functional readout. This general working strategy reinforces tight and coherent interactions by which well-established groups all over Germany form a truly interdisciplinary collaborative network.

Funding

The programme is funded by the DFG with a total budget of €13m for a period of six years with a second call for projects after the first three years. The first funding period (2013-2016) brought together 12 troikas and 42 research groups from 26 German universities and research centres. Their collaborative work led to almost 70 papers published in high-ranking journals. Important milestones have been reached including: 1) the engineering of new (micro)electrodes and optoelectrodes for high-resolution recordings and manipulation of neuronal networks; 2) the development of novel light-sensitive proteins for silencing neuronal activity; 3) the development of new technologies for transcranial stimulation; 4) the dissection of cortico-cortical and cortico-subcortical circuits; 5) the elucidation of wiring mechanisms and function of developing circuits; 6) the development of inter-lab workflows for increased reproducibility of findings; and 7) the elaboration of novel data-constrained models of network function. These achievements would not have been possible without an active exchange between troikas during meetings and workshops.

During the first funding period the focus of co-ordinated activities was laid on the development of tools and analytical strategies. For this, three workshops on the topics of 'optogenetics', 'analysis and management of electrophysiological activity data' and 'analysis and modulation of brain networks' have been organised in Bochum, Jülich and Hamburg respectively. Besides enabling intra and inter-troika collaborations they contributed to the development of professional skills of doctoral and postdoctoral researchers funded by the consortium.

Aims

From the beginning, the Priority Program was designed as a training centre for young researchers. During the first funding period 32 PhD students had been funded. Special attention was paid to the networking and professional development of doctoral and postdoctoral researchers. Each meeting of the consortium included an internal student meeting, during which their needs and expectations from the programme had been documented. The result of these fruitful discussions was a tailored support that included intense project-related training and measures for career development. Additionally, the programme supports female researchers and families with children by diverse measures (financial support for childcare, 'mother-child' offices, coaching, funding of female student assistants).

During the second funding period, which will be launched during autumn 2016, Priority Program 1665 aims to extend these initiatives and strengthen the interdisciplinarity of the consortium. For this, a particular focus will be on the development of common research strategies with complementary national and international consortia. On the one hand, the Priority Program 1926 entitled 'Next Generation Optogenetics: Tool Development and Application' has been launched this year and aims to design highly specific chemical photoswitches, implementing them in cells and animals and developing optogenetic therapies. The tight collaboration between the two Priority Programs will enable an efficient knowledge transfer, opening new perspectives for the applicability of light-sensitive proteins.

On the other hand, the International Program for the Advancement of Neurotechnology (IPAN) (www.eecs.umich.edu/ipan) has been funded by the US research programme PIRE since 2015 under the co-ordination of Euisik Yoon (University of Michigan). It aims to develop and deliver hardware and software systems that fundamentally simplify the ability of a neuroscientist to: 1) identify and classify a recorded neuron; 2) reconstruct a local neural circuit; and 3) deliver biomimetic or synthetic inputs in a cell-specific targeted manner. The co-ordinator of the Priority Program 1665, Ileana Hanganu-Opatz, who is an IPAN international partner, aims to foster the collaborations between the German and US consortia through a co-ordinated exchange of students and postdoctoral fellows.

The Priority Program 1665 has already pioneered a new direction of highly interdisciplinary research in Germany. On a medium to long-term scale, the programme: 1) will enable the development of innovative technologies in systems for neuroscience, for which young scientists will receive solid training; 2) will decipher the mechanisms by which the activation of single neurons or groups of neurons cause a specific behaviour; and 3) will set the course for understanding the contribution of neuronal networks to impaired behaviour in neurological and neuropsychiatric disorders.

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