Forschungsgruppe (FOR5159) Resolving the prefrontal circuits of cognitive flexibility

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Albert Einstein once claimed that “The measure of intelligence is the ability to change”. We painfully experienced the practical relevance of this fact during the last pandemic years, when we suddenly had to change our time management, implement new ways of interactions and reevaluate the importance of previously barely relevant items, e.g. face masks, test kits, and disinfectants, to name just a few examples. Our successful survival in a permanently changing environment would not be possible without the ability to store and update new evidence, (re)-evaluate the choices and take adaptive decisions. This amazing ability to easily change according to the situation defines the cognitive flexibility of our minds. It implies that low-level sensory and motor processes are internally coordinated to endow the brain with the capacity to develop and adapt internal goals and act accordingly. It is obvious that such processes involve a neural circuitry that extends over much of the brain, yet it is commonly held that the prefrontal cortex (PFC) is a critical hub (Miller and Cohen, 2001; Chini and Hanganu-Opatz, 2021). Despite the relevance of cognitive flexibility for day-to-day life, a mechanistic understanding of prefrontal coding of behavioral flexibility is still lacking, mainly due to the ethical concerns and technical limitations of human research, on the one hand, and the absence of a translational consensus regarding the prefrontal region, on the other hand (Carlen, 2017).

To fill this knowledge gap, the German Research Foundation (DFG) funds a new Research Unit FOR5159 “Resolving the prefrontal circuits of cognitive flexibility” with 4.1 million Euro for 4 years. FOR 5159 is a consortium integrating the universities Hamburg, Freiburg, Tübingen, Munich, Frankfurt, Mannheim, and Vienna and complements local initiatives, strengthening the Neuroscience research at national level. The FOR5159 aims to elucidate the mechanisms that enable neuronal populations in PFC to code for cognitive flexibility. For addressing this, the novel technical developments of recent years, which enable targeting, monitoring, and manipulating individual neurons and neuronal populations, are combined with data-constrained computational models that offer an integrative view embedding species-relevant similarities and differences. To enable in-depth investigations and comparisons between species, the focus of the FOR5159 will be laid on two complementary processes within the large spectrum of cognitive flexibility: working memory (WM, i.e. the short-term memory for quick access) and decision making (DM, i.e. the ability to act according to an anticipated outcome). Investigating mice, rats, primates, and humans, the consortium tests the hypothesis, that cognitive flexibility relies on temporally coordinated prefrontal ensembles defined by their outputs and inputs.

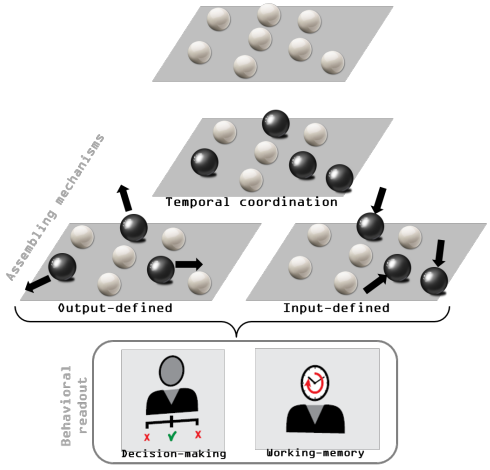


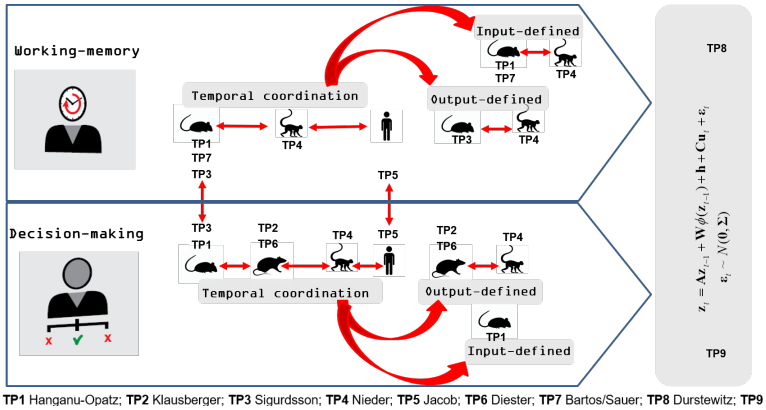
Figure 1. Proposed prefrontal mechanisms of cognitive flexibility. Depending on the context, prefrontal neurons build temporally coordinated ensembles defined by outputs or inputs that account for behavioral performance (WM and DM).

A major aim of the consortium is to elucidate how temporal coordination enables the binding of neuronal populations in PFC in a task-dependent manner. The following key questions will be addressed: (i) Which patterns of neuronal firing in PFC do code for the same task component across species and which ones are common across tasks in one species? (ii)

Which neuronal subtypes are activated during specific tasks? (iii) How are different types of neurons interconnected across and within cortical layers to build functional microcircuits in a task-dependent manner or across tasks? (iv) Do these neurons causally control behavioral performance? (v) How do frequency-specific oscillatory synchrony temporally coordinate the firing of neuronal populations during a specific task? To address these questions, the task-related activity patterns of identified individual prefrontal neurons during WM (TP1, TP3, TP4, TP5, TP7) and DM (TP1, TP2, TP3, TP4, TP5, TP6) will be assessed. In rodents, the identified task-related neuronal populations will be manipulated and their contribution to behavioral performance during distinct phases of the task will be monitored. A particular strong point of the consortium is the ability to monitor these patterns during the same task across species and developmental stages as well as across tasks in the same subject. For example, coordinated firing and network activity during different phases of WM or DM tasks will be recorded in the PFC of rats (TP2, TP6) and mice (TP1, TP3, TP7) as well as monkeys (TP4) and humans (TP5). This approach will enable us to identify computations within prefrontal microcircuits common across species. TP9 will test whether these computations strongly depend on the network state prior to the task.

TP7 will elucidate to which extent the prefrontal ensembles dynamically coding for working memory overlap with those dedicated to stable representations. Moreover, TP1 will identify the developmental time windows of critical relevance for the emergence of task-related prefrontal ensembles. Recordings from the same prefrontal neurons during multiple tasks in mice (TP3) and humans (TP5) will be performed to examine to what extent independent or overlapping neuronal populations in PFC are flexibly recruited. Using recurrent neural network (RNN) models inferred directly from physiological and behavioral data by deep learning methods, the features of task-related prefrontal activation and processing will be integrated across cell types, layers, ages, and species (TP8).

A second major aim of the consortium is to uncover how the projection-defined organization of PFC controls the formation of functional ensembles in WM and DM. Using recently developed tools for targeting projection-defined neuronal subpopulations, the prefrontal ensembles organized through communication with thalamic nuclei (TP6), ventral tegmental area (TP3), as well as parietal and premotor areas (TP4) will be investigated.



TP1 Hanganu-Opatz; **TP2** Klausberger; **TP3** Sigurdsson; **TP4** Nieder; **TP5** Jacob; **TP6** Diester; **TP7** Bartos/Sauer; **TP8** Durstewitz; **TP9** Lei

Figure 2. Schematic diagram of the research program. The interactions between the projects addressing the main hypotheses in different species (mouse, rat, primate, human) are schematically displayed for and across behavioral tasks. The resulting data will be integrated into models to extract the general rules of ensemble formation.

The implementation of all these data into computational models (TP8) might uncover fundamental principles of how the PFC interacts with other brain areas to implement flexibility-related computations.

Finally, the FOR5159 will assess the role of hippocampal and thalamic inputs for the development (TP1) and function (TP7) of neuronal ensembles during WM and DM in relationship with the network state prior to the task (TP9).

The FOR5159 will provide comprehensive knowledge about the mechanisms of prefrontal processing underlying aspects of cognitive flexibility through life in mammalian species. Using cutting-edge technologies of recent years and truly translational approaches (i.e. same experimental paradigms in rodents, non-human primates and humans integrated within a modelling framework), we will identify species-independent strategies that rest on dynamic formation of neuronal ensembles coding for a specific behavior as well as specializations accounting for species-characteristic complexity of cognitive demands. In the long run, achieving these goals is the pre-requisite for understanding the mechanisms of disease-related loss of cognitive flexibility. For neuropsychiatric disorders, such as schizophrenia and autism, it represents one of the major burdens with dramatic consequnces for the daily life.

The FOR5159 will be launched in January 2022. The research Unit 5159 will highlight the topic and research of the consortium in a symposium at the FENS 2022 in Paris.

Homepage FOR5159: www.FOR5159.de.

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