NEURONEX: The fabric of the primate neocortex and the origin of mental representations

NXWM

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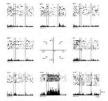
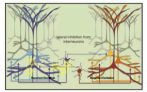
Background

Mental representations liberated from sensory experience and motor actions are the foundation of abstract thought. How such representations arose during primate evolution is a question of paramount importance to science and is the focus of this NEURONEX project. The ability to use mental representations to guide behavior is often probed using working memory tasks in which information must be briefly remembered (on the scale of seconds) to guide a subsequent behavioral response. Mental representations may be a step up in brain evolution, they exist in a virtual space. Current evidence indicates that representations of this kind arose in anthropoid primates, with the development and expansion of the granular prefrontal cortex in the frontal lobe. We hypothesize that there is a gradient of complexity of working memory representations from early sensory to association areas and from new world (marmosets) to old world (macaques) monkeys. The substrate of this gradient could include changes in receptor composition, abundances of neurons of specific types, gene-expression programs within these neurons, microcircuit motifs, and network level interactions across areas and species.

Some landmarks in working memory research in monkeys relevant to the objectives of our NEURONEX:

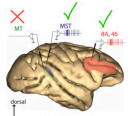
Seminal studies by Fuster and Alexander (1971) and Goldman-Rakic and others (1980-) reported neurons in the macaque lateral prefrontal cortex show persistent firing encoding remember locations in the absence of sensory stimulation. Persistent activity or persistent firing has been known as the most widely reported correlate of working memory in neurphysiological studies.





Goldman-Rakic, Wang and colleagues proposed a model of working memory in which pyramidal cells produce persistent firing in the absence of inputs via recurrent excitatory connections. Recurrent network activity is shaped by the activity of inhibitory interneurons, the parvalbumin positive basquet cells. These cells establish horizontal connections between columns of pyramidal cells with opposite tuning.

Several studies over decades have reported persistent firing representing the contents of working memory is found in the lateral prefrontal cortex and other association cortices but not in early sensory cortices. This persistent firing is not ubiquitous to all cortical circuits. There must be features that change across circuits that allow persistent firing representing working memory to emerge.



Several features have been proposed

-Changes in the abundance of recurrent connections from low in sensory areas to higher in association areas. Example: more dendritic spines in PFC with complex molecular regulation.
-Changes in the proportion of different neuronal types. Increase in the proportion of VIP/CR positive interneurons that facilitate activation of pyramidal cells.
-Changes in receptor composition from sensory areas to association areas. Eg. AMPA receptors with short time contants predominate in early sensory areas while NMDA receptors with longer time constants predominate in association areas.

NEURONEX feature search space

Our feature search takes place along three main axes. The species (marmoset and macaque), the brain areas (V1, LIP and LPFC) from early sensory to the high order association areas of the PFC, and the different scales, from molecules and receptors to networks of neurons. The International Research Groups (IRG) map the entire space. Cartoon and labels indicate the species and levels.

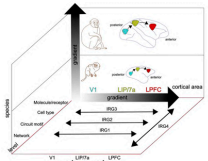


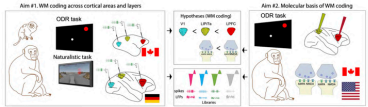
Figure 1. Central hypothesis and International Research Groups (IRG).

NSF
CIHR IRSC
DFG Deutsche Forschungsgemeinschaft
German Research Foundation

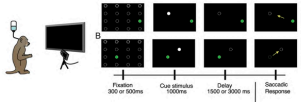
IRG1: Behavior and ePhys

Amy Arnsten Stefan Treue Julio Martinez-Trujillo Stefan Everling

IRG1: In vivo experiments (Arnsten: USA, Martinez-Trujillo and Everling: Canada, Treue: Germany). IRG1 will observe the evolution of persistent firing across species, cortical areas and layers by recording from cognitively engaged macaques vs. marmosets, comparing LPFC to LIP/7a to V1. These experiments are motivated by predictions generated by computational models of working memory circuits proposed in IRG4. The collected data will serve for the planning of stimulation in vitro experiments in IRG2. Arnsten and Everling are experts in iontophoretic manipulation of task-related neurons for molecular characterization and comparison to molecular signatures in vitro in IRG2 and IRG3. The figure bellow shows the general goals and methods of IRG1 (**Fig. 1 IRG1**).



Example results:
The modified Oculomotor Delayed responsed (ODR) task and the virtual reality task.
In the modified ODR we seek to examine whether neurons have retinotopic or spatiotoptic memory fields (**Fig. 2 IRG1** below).



In this variant of the ODR task the fixation point can change position in every trial as well as the target. This allows the dissociation between retinal and spatial reference frames.

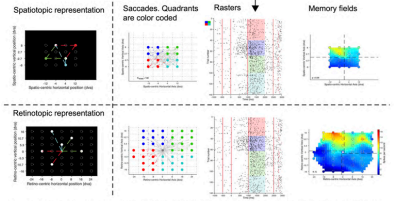
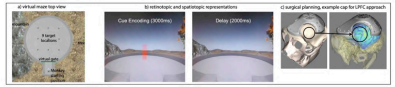


Fig. 2 IRG1. Example neuron with spatiotopic coding determined using an ANOVA test with the corresponding correction for multiple comparisons.

The Virtual reality task: The animal uses a joystick to navigate through a virtual environment. The animal stands in front of a virtual circular arena. 1 target out of 9 is presented for 3 seconds (red fog), then the target dissapeared and there is a delay period of 2 seconds. After the delay the animal is allowed to navigate towards the remembered target location to obtain a reward (**Fig. 3 IRG1** below).



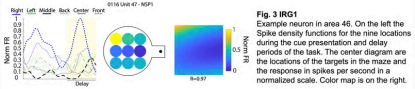
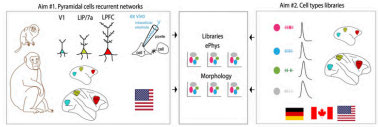


Fig. 3 IRG1
Example neuron in area 46. On the left the Spike density functions for the nine locations during the cue presentation and delay periods of the task. The center diagram are the locations of the targets in the maze and the response in spikes per second in a normalized scale. Color map is on the right.

IRG2: Circuits, ePhys and cell types

Guillermo Gonzalez-Burgos Jochen Staiger Wataru Inoue
David Lewis Andreas Neef

IRG2: In vitro physiology, and circuitry (Lewis, Gonzalez-Burgos: USA; Inoue: Canada; Neef, Staiger: Germany). This group will perform in vitro recordings from slices to study the physiological properties of neurons within microcircuits in LPFC, LIP/7a, V1 of macaques and marmosets. They will also extrapolate stimulation protocols derived from IRG1 experiments to produce a more naturalistic stimulation of neurons. These data will be linked to the transcriptomic profiles obtained in the experiments in IRG3. The collected data will provide essential information for biophysical and network models of microcircuits proposed by IRG4.



Example results:

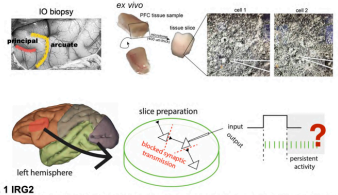


Fig. 1 IRG2
Sketch of protocol for extracting brain tissue and conducting patch clamp of single neurons:

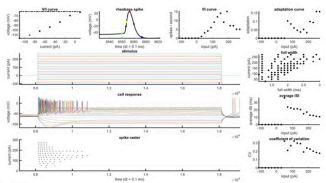


Figure 2 IRG2
Single cell example in macaque area 46. Different panels illustrate different measurements. The onse second square pulse protocol is illustrated by the color lines. Recording traces below and the conversion to spike rasters in the las row.

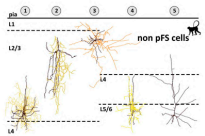
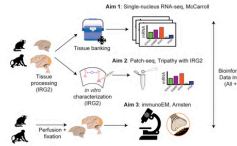


Fig 3 IRG2
Example digital reconstructions of different neurons in different layers of macaque monkeys lateral prefrontal cortex area 46. The black traces are the dendritic trees and the light traces the axons. The reconstructions were conducted using Neurolucida software.

IRG3: Transcriptomics and molecules

Amy Arnsten
Steve McCarroll
Fenna Kriegen
Jochen Staiger
Shreejoy Tripathy

IRG3: Molecular characterization (Arnsten, McCarroll, Tripathy: USA). IRG3 will perform immunoEM (Arnsten) and single-cell-resolution analyses of RNA expression (McCarroll, Tripathy) in macaque, marmoset and human cortex, comparing LPFC, LIP/7a and V1. The Arnsten lab is one of the few performing immunoEM of primate cortex. The McCarroll lab invented highly parallel single-cell RNA-seq (Drop-seq) and has demonstrated the power of this approach in yielding early insights about the evolution of interneuron repertoires in primates. This IRG will also analyze the single cell transcriptomes of neurons from IRG2 using patch-seq techniques (bioinformatic approach by Tripathy).



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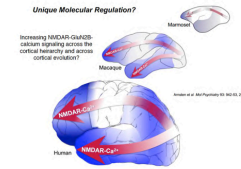
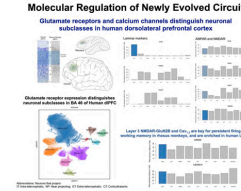
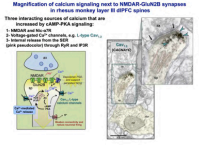
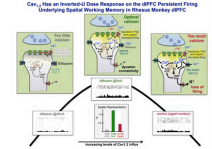




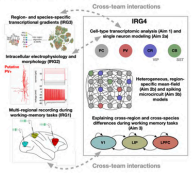




IRG4: Informatics and Computational models

Xiao Jing Wang Fred Wolf Lyle Muller
John Murray Shreejoy Tripathy

IRG4: Modeling (Wang: USA, Wolf: Germany; Muller: Canada). IRG4 will first depart from existing models of working memory circuits to provide a framework for the experiments proposed in the other IRGs. Second, it will generate acentralized database from in vivo and in vitro experiments, integrating data across IRGs that will serve to model neuronal and circuit dynamics at different scales. IRG4 will generateas multilevel picture of the cortical circuits involved in working memory representations and their functional dynamics across species.



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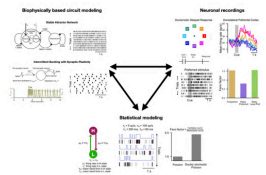
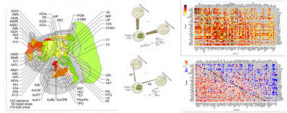


Theodoni et al. *bioRxiv* 2020 The www.marmosebrain.org website provides access to the results of all the retrograde injections and to the underlying histological data.



Our analysis reveals many features of the cortical architecture that have been preserved throughout millions of years, such as the highly heterogeneous log-normally distributed connectivity weights, the broadly distributed in- and out- degree, the three motif and clique distribution, the normally distributed wiring distances, and the decay of the probability of connections as a function of the similarity distance. In addition, there are cortico-cortical connectivity properties that scale with the brain size, such as the smaller the brain the longer the projections and fewer the weak connections, or they are species-dependent such as the density of the connectivity matrix.