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S2: Local inhibitory cell circuit: basic principles and disregulation in major mental illnesses

Chair: Etienne Sibille, Canada
Co-Chair: Seung-Hwan Lee, Republic of Korea

Speaker 1: Xiao-Jing Wang, China
Title: Computational modeling of GABA microcircuitry and cognitive deficits in schizophrenia

Abstract
I will first introduce the concept of “cognitive-type” cortical microcircuit exemplified by the prefrontal cortex. Since mental disorders primarily implicate cognitive-type brain systems such as the prefrontal cortex, rather than early sensory systems, progress in this area holds the promise for a new approach to psychiatric diagnosis and treatment.

I will review experimental and computational research on the generation of brain oscillations during awake, behaving conditions, which depend on various subtypes of interneurons and may serve as endophenotypes for detecting abnormality of GABAergic systems associated with Schizophrenia.

However, interneurons are important not only for synchronous rhythms, but also other important functions such as stimulus selectivity of neural populations, winner-take-all competition or normalization. In particular, working memory is a cardinal cognitive function impaired in mental disorders. Interestingly, computational circuit modeling of the prefrontal cortex suggested that working memory deficits in Schizophrenia are manifest not so much in terms of working memory storage but more in the inability to filter out distractors that are behaviorally irrelevant, in a specific way that was confirmed by human study. Furthermore, we proposed that this resistance against distractors in a working memory circuit depends on several subtypes of interneurons and may serve as endophenotypes for detecting abnormality of GABAergic systems associated with Schizophrenia.

We have recorded from identified GABAergic interneurons that control the output of excitatory pyramidal cells, dendrite-targeting interneurons that control the inputs to pyramidal cells, and interneuron-targeting interneurons that preferentially target the dendrite-targeting interneurons. These different interneuron types are modulated by dopamine differentially.

Finally, I will present our unpublished work on how different types of interneurons can instantiate a gating mechanism utilized by the brain to flexibly route information flow to the right place at the right time. This long-standing gating problem has recently gained urgency with the increased attention to studies of large-scale global brain connectivity and dynamics and their impairments in mentally ill subjects. Our work suggests a novel perspective on GABA signaling impairment in mental disorders.

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Speaker 2: Thomas Klausberger, Austria
Title: Contribution of distinct types of GABAergic interneuron to working memory and decision making

Abstract
The distributed temporal activity in neuronal circuits of the prefrontal cortex combines emotional information with episodic and spatial memory to guide behavioural action. Single neurons of often unknown identity have been shown to exhibit specific firing patterns during spatial navigation and decision-making tasks. The cerebral cortex consists of highly diverse neuronal types with distinct synaptic connectivity, molecular expression profile and contribution to network activity. Neurons can be divided into excitatory pyramidal cells, which use glutamate as a neurotransmitter and give both local and long-range axonal projections, and inhibitory interneurons, which are GABAergic and control the activity and timing of pyramidal cells mainly through local axons. These neurons can be further subdivided on the basis of their distinct axo-dendritic arborisations, subcellular post-synaptic targets, and by their differential expression of signalling molecules, including receptors, ion channels, neuropeptides, transcription factors and Ca2+ binding proteins. We aim to determine how distinct types of neuron support the executive functions of the prefrontal cortex.

We have recorded from identified GABAergic interneurons and pyramidal cells in the prefrontal cortex of freely-moving rats using the juxtacellular recording and labelling technique. We investigated their contribution to network oscillations and a delayed cue-matching-to-place task involving working memory and decision making. The neuronal identity was determined with post-hoc histochemical analysis.

We observed two groups of pyramidal neurons, which showed task-related firing patterns: neurons that represented the future goal and neurons that fired preferentially during distinct periods of the task. These firing patterns were modulated by the activity of distinct types of interneuron. For example, we observed that the firing of parvalbumin-expressing basket cells displayed strong modulation according to the task episode. Interestingly,
different parvalbumin-expressing basket cells fired preferentially at different episodes during the task (e.g. stimulus, delay, execution). A difference in the firing of parvalbumin-expressing basket cells according to the decisions was observed only after its execution and during or shortly after reward consumption. Thus, parvalbumin-expressing basket cells support the encoding of temporal sequences and distinct task episodes during working memory and decision making.

We have developed a novel technique that allows the recording of unequivocally identified neurons and show how distinct types of neuron contribute to prefrontal network operations and executive behavior. Our results indicate that GABAergic interneurons release GABA at distinct times to different domains of pyramidal cells contributing to the formation of cell assemblies and representations in the prefrontal cortex.

Speaker 3: John Krystal, USA
Title: Cortical disinhibition, noisy circuits, and schizophrenia: clinical and therapeutic implications.

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Abstract
It is not yet clear how the molecular and cellular alterations identified in post-mortem tissue from individuals diagnosed with schizophrenia translate into the disabling symptoms and cognitive impairments associated with this disorder.

Approach: The purpose of this presentation is to present results from a series of fMRI and EEG studies evaluating healthy individuals, schizophrenia patients, and healthy individuals administered the NMDA-R antagonist, ketamine that have been analyzed and interpreted within the context of parallel studies employing biophysically-informed computational neuroscience models of the behavior of cortical microcircuits and macrocircuits.

Results: Three types of network disinhibition are described: 1) gross disinhibition, “hyperactivity” that is associated with symptoms of psychosis, 2) disinhibition of the spatial dispersion of activation resulting in impairment in sparse coding of information, reduced memory precision, increased cortical signal variance “noise”, and the emergence of “false” memories, and 3) disinhibition of suppressed inputs, resulting in pathological hyperconnectivity. We will show evidence that the progression of schizophrenia is associated with altered signal properties of cortical functional connectivity, potentially creating the opportunity for illness phase-specific pharmacotherapies for this disorder.

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Speaker 4: Etienne Sibille, Canada
Title: SST-positive GABA neurons in depression and antidepressant treatment

Abstract
Background: Somatostatin (SST) deficits are common features in neurological disorders with mood disturbances, but little is known about the contribution or cause of these deficits to mood symptoms.

Methods: Human postmortem molecular and animal genetic/pharmacological studies.

Results: Results from human postmortem brains demonstrate molecular changes affecting SST-positive GABA neurons in depression. The mouse genetic studies suggest that low SST and reduced SST-positive GABA neurons have causal roles in generating illness symptoms and are targets for novel antidepressant modalities. Specifically, we show that mice lacking Sst exhibit elevated behavioral emotionality, high basal plasma corticosterone and reduced gene expression that recapitulate behavioral, neuroendocrine and molecular features of human depression. Using laser-capture microdissection, we show that cortical SST-positive interneurons display greater transcriptome deregulation after chronic stress compared to pyramidal neurons. Protein translation through eukaryotic initiation factor 2 (eIF2) signaling, a pathway implicated in neurodegenerative diseases, was most affected and suppressed in stress-exposed SST neurons. We show that activating eIF2 signaling through eIF2 kinase inhibition mitigated stress-induced behavioral emotionality in mice. Finally, as the function of SST-positive GABA neurons is mediated by post-synaptic GABA-A receptors containing the alpha5 subunit, we show that boosting Alpha5-mediated GABA function (through positive allosteric modulation) has antidepressant activity in chronically stress mice.

Conclusions: The data presented suggest that (1) low SST plays a causal role in mood-related phenotypes, (2) deregulated