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The Synaptome Architecture of the Brain: Lifespan, disease, evolution and behavior

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SPEAKER

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BIO

Seth Grant is Professor of Molecular Neuroscience at the Centre for Clinical Brain Sciences, Edinburgh University, is affiliated with Simons Initiative for the Developing Brain and UK Dementia Research Institute, and a Fellow of the Royal Society of Edinburgh. He established and leads the interdisciplinary Genes to Cognition Programme. His research has made landmark contributions to our understanding of the neuroscience underlying learning, memory and behavior, revealing how synapse dysfunction contributes to a wide range of developmental, neurodegenerative and psychiatric brain disorders. These studies in humans and in genetic models of disease have encompassed all scales of analysis, from molecular proteomics and transcriptomics to whole-brain networks and whole-animal behavior. This seminal work on the genetics of cognition, synapse proteomics and synaptopathies has been recognised in prestigious national and international awards, most recently the 2019 IBANGS Distinguished Investigator Award and 2020 FENS EJN Award. His current research efforts in the field of synaptomics focus on the remarkable molecular diversity of synapses in the mouse and human brain, and are providing important new insights into the mechanisms of memory and learning during the lifecourse and in neurological disorders.

RESEARCH

The overall aim of my research is to understand how the organisation of the synapse, with particular reference to the postsynaptic proteome (PSP) of excitatory synapses in the brain, informs the fundamental mechanisms of learning, memory and behaviour and how these mechanisms go awry in neurological dysfunction. The PSP indeed bears a remarkable burden of disease, with components being disrupted in disorders (synaptopathies) including schizophrenia, depression, autism and intellectual disability.

Our work has been fundamental in revealing and then characterising the unprecedented complexity (>1000 highly conserved proteins) of the PSP in terms of the subsynaptic architecture of postsynaptic proteins such as PSD95 and how these proteins assemble into complexes and supercomplexes in different neurons and regions of the brain. Characterising the PSPs in multiple species, including human and mouse, has revealed differences in key sets of functionally important proteins, correlates with brain imaging and connectome data, and a differential distribution of disease-relevant proteins and pathways. Such studies have also provided important insight into synapse evolution, establishing that vertebrate behavioural complexity is a product of the evolutionary expansion in synapse proteomes that occurred ~500 million years ago.

My lab has identified many mutations causing cognitive impairments in mice before they were found to cause human disorders. Our proteomic studies revealed that >130 brain diseases are caused by mutations affecting postsynaptic proteins. We uncovered mechanisms that explain the polygenic basis and age of onset of schizophrenia, with postsynaptic proteins, including PSD95 supercomplexes, carrying much of the polygenic burden. We discovered the "Genetic Lifespan Calendar", a genomic programme controlling when genes are regulated. We showed that this could explain how schizophrenia susceptibility genes are timed to exert their effects in young adults.

The Genes to Cognition programme is the largest genetic study so far undertaken into the synaptic molecular mechanisms underlying behaviour and physiology. We made important conceptual advances that inform how the repertoire of both innate and learned behaviours is built from unique combinations of postsynaptic proteins that either amplify or attenuate the behavioural response. This constitutes a key advance in understanding how the brain decodes information inherent in patterns of nerve impulses, and provides insight into why the PSP has evolved to be so complex, and consequently why the phenotypes of synaptopathies are so diverse.

Our most recent work has opened a new phase, and scale, in understanding synapses with the first synaptome maps of the brain. We have developed next-generation methods (SYNMAP) that enable single-synapse resolution molecular mapping across the whole mouse brain and extensive regions of the human brain, revealing the molecular and morphological features of a billion synapses. This has already uncovered unprecedented spatiotemporal synapse diversity organised into an architecture that correlates with the structural and functional connectomes, and shown how mutations that cause cognitive disorders reorganise these synaptome maps; for example, by detecting vulnerable synapse subtypes and synapse loss in Alzheimer's disease. This innovative synaptome mapping technology has huge potential to help characterise how the brain changes during normal development, including in specific cell types, and with degeneration, facilitating novel pathways to diagnosis and therapy.

OBJECTIVES

1. Recognise the molecular logic that explains how the diversity of synapses arises from the hierarchical assembly of protein expression and supramolecular assembly.

2. Understand the concept of synaptome architecture and how it changes across the lifespan.

3. Understand how synaptome architecture can be used to store innate and learned behavioural programs and how genetic diseases results in behavioral phenotypes.

For more information:

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