Project Details	
Project Code	MRCNMH25Ba Nikolaou
Title	Developing in vitro and in vivo genetic models to study aberrant neuronal network activity in dementia
Research Theme	Neuroscience & Mental Health
Summary	Alzheimer's disease (AD) is the leading cause of dementia characterized by memory loss and cognitive decline. Whilst cognitive decline in dementia is a progressive process affecting various aspects of mental functioning, an understanding of the early changes in the brain could provide the means for early detection, effective treatment, and the necessary support to individuals and their families. This project will utilise experimental approaches in human induced pluripotent stem cells (hiPSCs) and zebrafish to identify and characterise the early neuronal network dysfunctions caused by AD causative gene mutations, which could lead to large-scale small molecule screens to identify novel therapeutics.
Description	**Background and importance:** One of the main symptoms of dementia is cognitive decline, which results in a progressive deterioration of cognitive functions such as memory, thinking, reasoning, problem-solving, communication, and the ability to perform everyday activities. Cognitive decline in dementia is driven by aberrant synaptic signalling and neuronal network dysfunction. These factors lead to a breakdown of communication between brain regions and contribute to the cognitive symptoms observed in dementia. For instance, mutations in genes encoding synaptic proteins manifest as increases or decreases in network excitability depending on the underlying molecular causes and neurochemical phenotypes of the neurons affected. While there is no cure for most types of dementia, a modest improvement in slowing down the progression of cognitive decline can have a massive positive impact on the life of people with dementia. **Overall aims:** Our goal is to develop zebrafish and human cell genetic models to determine how aberrant neural networks are manifested as a result of mutations in genes implicated in Alzheimer's disease (AD), the main leading cause of dementia. Zebrafish will be used to produce genetically altered animals carrying mutations in putative candidate AD risk genes identified from Genome-Wide Association Studies (GWAS). Candidate selection will focus on synaptic proteins that are strongly implicated in dementia. Genetically encoded reporters will be used to monitor brain-wide neuronal network activity in zebrafish and cross-validated in human neurons using microelectrode arrays. Behavioural experiments will be performed to assess how network dysfunction results in abnormal animal behaviour. Collectively the project will utilise highly tractable models to assess the functional impact of genetic risk factors on neuronal network activity providing a novel platform for testing next generation peptide-based therapeutics to stabilise neuronal network function in affected circuits in the future. **Experimental design:** Objective 1: GWAS have played a significant role in advancing our understanding of AD. These studies have provided valuable insights into the genetic factors contributing to AD risk, as well as potential biological mechanisms underlying the condition, including synaptic dysfunction.

	We will compare existing GWAS datasets to Protein-Wide Association Studies (PWAS) from human brain proteomes to identify mutations in genes encoding synaptic proteins that lead to a change in protein abundance in AD patients (e.g. DOC2A). We will then perform validation studies using AD patient tissue to confirm changes in protein abundance. Objective 2: Zebrafish is a genetically amenable vertebrate model that shares high degree of anatomical and physiological similarities to humans. For example, they possess similar major biological and developmental processes and structures with comparative functionality. Moreover, their genome is well characterised, and its sequencing is complete, showing more than 70% of human genes to have at least one zebrafish orthologue and 84% of genes known to be associated with human disease have a zebrafish counterpart. Alongside practical qualities such as their small size, external fertilisation, rapid development, optical clarity, and short generation time, they enable in vivo monitoring of embryos and larvae. We will use zebrafish to produce genetically altered animals to model candidate risk mutant variants. Genetically encoded reporters (e.g., calcium indicators), and light-sheet microscopy will be used to record neuronal activity in the entire larval brain and generate network activity maps to compare with control neural networks. Spatiotemporal patterns of activity will be modelled to inform the dynamics of any changes. Network dysfunction can manifest as cognitive deficits, motor impairments, or behavioural changes, therefore, in addition to brain-wide calcium imaging, we will test the swimming activity of larvae (speed and total distance covered) and behavioural responses to cues e.g., visual, auditory, or tactile. An automated tracking system and video recording will be used to collect data more objectively for subsequent analysis. Objective 3: Genetically altered zebrafish lines demonstrating clear phenotypes will be validated for effects on neural network function in human iPSC-derived neurons carrying the same AD gene mutation using microelectrode arrays.
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