Project Details	
Project Code	MRC21NMHEx Witton
Title	Does the remodelling of inhibitory interneurons contribute to brain circuit malfunction in preclinical Alzheimer's disease?
Research Theme	Neuroscience & Mental Health
Summary	Alzheimer's disease (AD) is characterised by the malfunction of neural circuits. Recent evidence suggests that this is initiated by an imbalance between excitatory and inhibitory neuronal activity. This project combines cutting-edge mouse genetics, brain imaging and computational modelling to decipher how changes in inhibitory interneurons cause neural circuits to malfunction early in AD, providing an opportunity for early intervention.
Description	Rationale: Alzheimer's disease (AD) is a devastating neurodegenerative disease affecting 50 million people worldwide. The main symptoms of AD are learning and memory loss, which is caused by the malfunction of neural circuits in the brain. However, evidence suggests that neural circuits become hyperactive even before the onset of clinical symptoms, and that this is caused by the build-up of the protein amyloid-β (Aβ). An important open question is therefore how Aβ causes neural circuits to become hyperactive. Addressing this question presents a significant opportunity for AD treatment, since therapies that prevent this early circuit dysfunction could potentially stop people from developing AD. The function of neural circuits requires a precisely coordinated balance between excitatory and inhibitory activity. Evidence from human and mouse studies, including work by our lab (Witton et al. J. Physiol. 2016), suggests that this excitatory-inhibitory balance breaks down early in AD, and that a cause of this is disrupted inhibitory signalling. Aβ pathology is known to cause structural changes in excitatory neurons, including the remodelling and loss of synaptic connections, but little is known about how Aβ affects the structural plasticity of inhibitory interneurons. Our hypothesis is that interneurons are vulnerable to structural and synaptic changes caused by Aβ early in AD, and that this leads to the abnormal rewiring of inhibitory connections to facilitate the emergence of hyperactivity in neural circuits. Aims and objectives: The overall aim of this project is to study how Aβ causes inhibitory interneurons and their synaptic connections become disrupted in the early stages of AD, and to understand how these changes contribute to subsequent neural circuit malfunction. Our specific objectives are: (1) To track the structural dynamics of axonal boutons, dendritic spines, and their parent neurites in subtypes of interneurons in tandem with the development of Aβ pathology. (2) To develop a neural network model to test how pathological changes in interneuron anatomy and connectivity alter the function of cortical brain circuits. Project design: Aim 1 will be approached using in vivo brain imaging in a mouse model of AD. Because it is not yet possible to study individual neurons or synapses in people, we will use a novel mouse line (APP-NL-G-F mice) whose amyloid precursor protein (APP; the precursor to Aβ) gene has been humanised and altered to contain mutations that cause AD. We will use a new viral-genetic tool to express a marker of neuronal structure (EGFP) in interneurons in APP-NL-G-F mice, and then track changes in the neurites and synaptic structures of these cells across time using in vivo two-

	photon microscopy. Our analysis will focus on the early, preclinical phase of AD in APP-NL-G-F mice, since it is known that this phase of the disease is when treatments are likely to be most effective. This will be confirmed by measuring the development of Aβ pathology using the fluorescent probe methoxy-X04. Interneurons imaged in vivo will be subsequently identified ex vivo and characterised for subtype using immunohistochemistry. To address Aim 2, we will build a computational neural network model and introduce our experimentally observed changes in interneuron structure and synaptic connectivity into the model to understand how these changes affect the output of local and large-scale cortical networks. Outcomes: The project will use advanced in vivo experimental and computational methods to define how changes in inhibitory interneurons drive brain circuit malfunction in the early stages of AD. Our aim is that these findings will lay necessary theoretical groundwork to develop new interneuron-targeted treatments for AD. The highly interdisciplinary nature of this project means that it offers an exceptional training opportunity in an exciting and rapidly developing field of neuroscience.
Supervisory Team	
Lead Supervisor	
Name	Dr Jonathan Witton
Affiliation	Exeter
College/Faculty	College of Medicine and Health
Department/School	Institute of Biomedical and Clinical Science
Email Address	j.witton@exeter.ac.uk
Co-Supervisor 1	
Name	Dr Cian O'Donnell
Affiliation	Bristol
College/Faculty	Faculty of Engineering
Department/School	Computer Science
Co-Supervisor 2	
Name	Dr Jonathan Brown
Affiliation	Exeter
College/Faculty	College of Medicine and Health
Department/School	Institute of Biomedical and Clinical Science
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	
Co-Supervisor 4	
Name	
Affiliation	
College/Faculty	
Department/School	