PCL/17/01 - Circuit-level pathophysiology and amelioration of NMDAR-channelopathies in two new rat models

The N-methyl-D-aspartate receptor (NMDAR) is an important protein in the brain that helps to transmit chemical signals between brain cells. Some people with brain disorders like intellectual disability, autism and epilepsy, have mutations in their genetic code for these receptors. Some of these mutations have been shown to alter the function of NMDARs, and the brain cells they are found in. It is therefore probable that these mutations are at least part of the cause of the disorders with which they are associated.

However, it isn't known exactly how the changes in receptor and cell functioning might lead to a change in brain function. NMDARs help brain cells fire together, so it is likely that changes in NMDAR function would alter this. The aim of this proposal is thus to assess whether NMDAR mutations lead to changes in how groups of brain cells coordinate their activity.

This will be done using animal models where two types of mutations have been purposefully introduced into rats' genetic code. One is a mutation which alters the receptor's normal properties. One is a mutation which prevents one of the receptor genes being expressed. Regions of brain from rats carrying these mutations will be examined for coordinated brain cell activity by making recordings simultaneously from a large grid of electrodes. If further funding becomes available, electroencephalograms can be made, combined with video monitoring. If abnormalities are found using either of these techniques, there are some chemicals available which can be used to try to reverse the changes.

In summary, I aim to use innovative electrophysiological techniques to make the first assessment of brain function at the circuit level in two new rat models of epilepsy and intellectual disability, with the aim of improving understanding and future treatments for these and related disorders.