Depression is one of the world's most prevalent illnesses, and according to the World Health Authority it is also the world's most expensive illness in terms of working time lost to disability. Antidepressant drugs have been in use for over half a century, but a high proportion of patients fail to respond to them. This condition is known as treatment-resistant depression (TRD). In a very exciting recent discovery, it was found that many patients who fail to benefit from antidepressant drugs do benefit from electrical stimulation of some very specific brain areas. The patient receives stimulation through an electrode implanted into the brain on a long-term basis ("deep brain stimulation", or DBS). The patient cannot feel the stimulation, which switches off brain activity in its immediate vicinity.

Much of the research that tries to understand how the brain works, and what happens differently when people experience mental disorders, uses procedures known as animal models, in which symptoms similar to aspects of human brain function can be produced and studied in animals (typically rats or mice). Several recent studies have shown that animal models of depression that are known to respond to antidepressant drugs also respond to DBS. In this project, we aim to set up two animal models of TRD, and use them to start to understand how DBS works to improve depression in patients who do not respond to antidepressant drugs.

The study will employ a very widely used animal model of depression, chronic mild stress (CMS), to produce depression-like behaviours in rats. In the CMS model, the animal is bombarded with a variety of mild stressors – things like putting it together with another unknown rat, or leaving the lights on overnight. After a few weeks, the animal starts to show behavioural changes that are very similar to symptoms of depression: in particular, it becomes less responsive to rewards, which is thought to model the main symptom of depression, anhedonia (loss of pleasure). This is usually measured by giving the animals access to a sweet drink and measuring how much they consume. Stressed animals typically drink less of the sweet solution, but if they are then treated daily, for a few weeks, with an antidepressant drug, their behaviour returns to normal: that is, they recover. CMS also makes them more anxious and bad at solving problems (for example, recognizing that something in their environment has changed), and again, these behaviours also recover with antidepressant treatment.

This is the situation in most rats. However, there are some rats that do not respond well to antidepressant treatment. Some non-responsive animals are found among the "normal" population of rats: they continue to show depression-like behaviours even after antidepressant treatment. (An example of the "normal" population are rats of the Wistar strain, which are very widely used in behavioural research.) There are also some rat strains that were bred for other purposes, but have been found incidentally to be generally insensitive to antidepressants. An example is the Wistar-Kyoto (WKY) strain, which was bred many years ago as part of a research project into the control of blood pressure, but turned out to be more emotional than ordinary Wistars, and resistant to antidepressant treatment. We will study both types of antidepressant non-responders.

In preliminary studies we will first confirm that, when tested in our laboratory, (i) DBS has antidepressant effects in Wistar rats, and (ii) antidepressant drugs do not work in WKY rats. In the main studies, we will compare the effects of antidepressant drugs and DBS in the two models of TRD: the minority of stressed Wistar rats and the majority of WKY rats that do not recover when treated with antidepressant drugs. These experiments will involve both behavioural and biochemical measures. We first expect to see that DBS causes a recovery of depressive behaviour in these models of TRD, while antidepressant drugs – by definition – do not. At the end of the experiments the animals will be humanely killed and brains taken for analysis, in which we will be looking for differences that could explain the different actions of DBS (effective) and antidepressant drugs (ineffective). We will examine two brain areas that are known from both laboratory and clinical studies to be important in depression and recovery, the hippocampus and the prefrontal cortex. We are particularly interested in the levels of stress hormones and receptors in those areas, as well as a compound known as BDNF (brain-derived neurotrophic factor) that plays an important role in brain repair, and the receptors for one of the most important signalling molecules in the brain, glutamatic acid. These compounds are all proteins. We will study them by measuring both the levels at which they are found, and the activity of the genes that produce them. We will also search more generally for other genes that respond differently to antidepressant drugs and DBS.

We expect that the study will have a significant impact on the search for pharmacological treatments for TRD, which affects upwards of a hundred million people worldwide. What we now know, from the clinical use of DBS, is that TRD is in principle treatable. However, standard antidepressant drug discovery methods cannot distinguish between novel drugs that might work in TRD and drugs that resemble existing antidepressants, which by definition are ineffective in TRD. Models that specifically address the problem of TRD provide the obvious solution to this problem, but there has been almost no previous research using this approach as a platform to develop treatments for TRD. Assuming that we are able to confirm that DBS is effective in the models that will be used in this project, we will also be able to make a start on investigating the neurochemical mechanisms that distinguish the effect of DBS from the non-effect of antidepressant drugs. This will then serve as a basis for future research that could make important contributions to the treatment of chronic depression.