Abstract:

This project aims to improve the analysis of time-resolved metabolic data in human subjects, especially rhythms associated with severe mental illnesses (SMI), using machine learning and deep learning approaches. Severe mental illnesses present a variety of metabolic associations and there are clear impacts on circadian rhythms to some SMIs, especially bipolar disorder. As part of the MRC-funded Hub for Metabolic Psychiatry, we will obtain highly time-resolved metabolomics data from our parter Dynamic Therapeutics's U-RHYTHM device, which has the potential to allow us to extract mechanistic relationships between SMI and metabolic rhythms. The approach will focus on regression models, time-series autoencoders and other techniques for dimensionality reduction and representation learning. Applications include new biomarkers for diagnosis, disease staging and treatment efficacy, as well as the potential for a molecular understanding of SMIs.

Introduction:

Analysis of the metabolic impact and causes of psychiatric disorders can lead to novel treatment approaches for SMI. People with SMI have high rates of obesity, type 2 diabetes (T2D) and increased risk of cardiovascular disease [1, 2]. Additionally, there are shared mechanisms between metabolic dysfunction (insulin resistance, obesity and T2D) and psychopathology (psychosis, mania and severe depression) [3, 4]. Recent studies (including one involving our group) provided evidence that the ketogenic diet [5], and the insulin-sensitising drug metformin [6] could lead to improvements in both mental health and metabolic status of people with SMI. Additionally, there are clear circadian components to SMI, with disruption of sleep/wake patterns well studied in bipolar disorder [7] and episodes of psychosis triggered by significant time zone changes [8].

The hypothesis, therefore, is that not only are some of the fundamental mechanisms of SMI metabolic in nature, but that these are rhythmic over a circadian pattern that could be detected using novel technologies such as Dynamic Therapeutics' U-RHYTHM device and the use of AI techniques to extract meaning from noisy biological patterns.

Research challenge:

Our overall goal is to develop a framework for the analysis of high-resolution metabolomics data from patients with SMI. More specifically we will:

1) Model time-series data from patients and healthy volunteers using regression models, signal processing and tools from unsupervised and representation learning.
2) Extract rhythmic features and features associated with events such as meals or exercise, as well as those in patients with disordered metabolism.
3) Correlate the detected features to build a metabolic model of SMI and its relationship to circadian rhythms.

Data & Methodology:

The project will rely on the use of well adopted packages for machine learning such as scikit-learn, pytorch and tensorflow. Data will be obtained via metabolomics from a combination of healthy volunteers and patients, whose consent has already been obtained as part of the MRC Hub for Metabolic Psychiatry.

In **Objective 1**, we will collect data from patient samples using standard metabolomics methodologies [9] – a typical dataset will consist of 72 samples (one every 20 minutes over 24 hours) and produce roughly 2000 metabolites per datapoint with varying levels of identification quality and quantitative accuracy. Optimisation of mass spectrometry and sample preparation parameters will be required to obtain high quality data. Additionally, data must be processed and sifted for noise, reproducibility and metabolite degradation arising from storage in the U-RHYTHM device over the collection period.

In **Objective 2**, once processed into a numerical dataset, high dimensional data will be encoded using machine learning processes to extract rhythmicity parameters. We will generate 1) a list of rhythmically modulated metabolites with confidence values pertaining to the quality of periodicity and identification will be obtained, and 2) a list of metabolites positively and negatively associated with SMI with confidence values.

In **Objective 3**, advanced pathway analysis tools will be used, as well as incorporating our recent work on metabolic anisotropy [10], to develop a mechanistic understanding of the biochemical pathways underpinning periodicity in human metabolism, biochemical mechanisms associated with SMI, and the linkage between them. These will be explored for potential as diagnostics and treatment targets.

RRI/Ethical considerations:

SMI patients and patient groups have been involved in all aspects of the design for the Hub, and we will ensure that they are involved in dissemination of findings. The Hub is accessible to a diverse participant group, avoiding discrimination based on socioeconomic status, race, or gender. It will ensured that participants in the study fully understand the aims, including potential risks, benefits and their right to withdraw.

We will adhere to relevant ethical guidelines and regulatory requirements of our sponsor (Edinburgh Academic and Clinical Office for Research and Development - ACCORD). Research ethics committee and sponsorship approvals have been obtained and follow established governance processes operated by the registered Edinburgh Clinical Trials Unit. We will protect participant data and ensure confidentiality, using anonymized data where possible and keeping to a minimum those with access to enhance privacy.

Expected outcome & Impact:

The project will deliver a suite of data, models and software for the analysis of metabolism in SMI. Our approach will leverage, for the first time, a unique ability to perform highly time-resolved sampling of patients with the breadth of biochemical detection provided by metabolomics. This project will not only contribute to the aims of the Edinburgh University led 4.3 M GBP Hub for Metabolic Psychiatry, but will potentially provide avenues to new treatments, diagnostics and staging for SMI.

References:

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