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Summary of research

Key words: Depression, MRI, Genetics, Cognition

Progress in understanding the causes of major depressive disorder has been slow. Dividing depression into subtypes, a process called stratification, could ultimately lead to faster progress.

We will stratify or divide individuals with MDD and depressive syndromes into more similar groups of people in UK Biobank.

Our aims are to:

1. Identify and describe specific subtypes of depression
2. Identify the causes underlying different types of depression using GWAS and MRI
3. Test whether resistance to depression (i.e. resilience) to depression can be accurately measured.
4. Identify the mechanisms underlying resilience using genetic and brain imaging data.

This research seeks to use the medical, cognitive, imaging and genetic data from UK Biobank to study the mechanisms of common medical conditions and use them as a platform to better diagnosis. These aims are consistent with UK

Biobank's. Providing this information will help to identify new drug targets for depression. Stratifying depression into more homogenous categories will provide better 'disease' targets for other research studies because there will be less lumping together of individuals with different causes for their illness within the same broad category of depression.

We will test whether these sub-classes of depression and depressive symptom have neurobiological associations in UK Biobank by comparing them with depressed individuals as w whole, as well as controls, using MRI and genetic data.

We will firstly examine the associations of depression with cognition (baseline measures and web-based measures of attention and memory, for example), brain structure, function and connection strength (MRI).

We will examine the association of different depression types with biological intermediates (measurable variables important in the causation of depression) using a technique called polygenic profiling.

We will also compare resilient and non-resilient individuals.

We are interested in the full UK Biobank cohort for most analyses - and the subgroup of UK Biobank with genetic and imaging (brain MRI) data for more detailed analysis.

We appreciate the time scale for the availability of genotyping and imaging data.

Project Extension:

In order to proceed, we now seek to ascertain the overlap between individuals in the UKB and the PGC datasets. There is an established methodology for doing this, that would flag individuals in the UK Biobank dataset for removal. We would then use this data to exclude overlapping individuals and we would also return a flag to UK Biobank indicating an overlapping individual with the PGC's current data freeze (referred to as PGC-MDD2).

The current proposal aims to look at genetic and environmental risk factors for harmful alcohol consumption in the UKB. This will build a clinical and demographic profile of hazardous alcohol consumption and allow us to study individuals who consume alcohol regularly but are resilient to alcohol related harm. Using genetic factors we will seek to understand the causal relationship between alcohol consumption and risk factors for hazardous drinking. Furthermore, using MRI neuroimaging data and genetic data we will investigate the biological pathways which underpin harmful drinking. This is a similar strategy to that being employed in proposal #4844 which aims to stratify depression and study resilience. This project will overlap with #4844 as mood disorders will be studied in relation to alcohol consumption as a potential risk factor for harmful drinking.

Project extension:

Progress in understanding the causes of major depressive disorder has been slow. Dividing depression into subtypes, a process called stratification, could ultimately lead to faster progress.

We will stratify or divide individuals with MDD and depressive syndromes into more similar groups of people in UK Biobank.

Our aims are to:

1. Identify and describe specific subtypes of depression and other neuropsychiatric traits
2. Identify the causes underlying different types of depression and neuropsychiatric disorders using GWAS, MRI and other available biomarker data
3. Test whether resistance to depression (i.e. resilience) and other neuropsychiatric disorders can be accurately measured.
4. Identify the mechanisms underlying resilience using genetic and brain imaging data.

5. Identify the causes, ameliorating factors and consequences of brain age and how these relate to depression and neurologicalpsychiatric disorders and diseases