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A cross-sectional study investigating the role of genetic and sleep influences on internalising symptoms in autistic patients

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Key Terms

- **Polygenic Risk Score (PRS)** is calculated by summing up many common genetic variants that confer a risk of getting a particular disease, giving an estimate of the cumulative genetic risk. [1]
- **Internalising Symptoms** are more inwardly experienced symptoms that are associated with anxiety and depression. [2]

Introduction

- Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder affecting 1 in 54 children in the US, impacting their social interactions, communication, cognition, and behaviours. [3]
- ASD individuals are four times more likely to experience unipolar depression in their lifetime, compared to a typically developing child. [4]
- PRS for adult major depression, neuroticism, BMI & insomnia are positively associated with childhood psychopathology. [5]
- Genetic risk for depression may manifest as behaviour difficulties, particularly internalising and externalising symptoms in childhood.
- ~80% of ASD individuals experienced sleep difficulties, e.g. initial insomnia and multiple night wakings. [6]
- Sleep problems are known risk factors for mood disorders and, occur before and during episodes of mood disorders. [7]
- Poorer sleep in individuals with ASD leads to more reported behavioural problems. [8]

Study Hypothesis:
Genetic risk for depression is predictive of internalising and externalising symptoms in autistic children and is modified by sleep.

Aim:
To investigate if the polygenic risk for depression increases internalising and externalising symptoms with autism individuals and is modified by sleep in a large cohort of autistic children (Simons Simplex Collection).

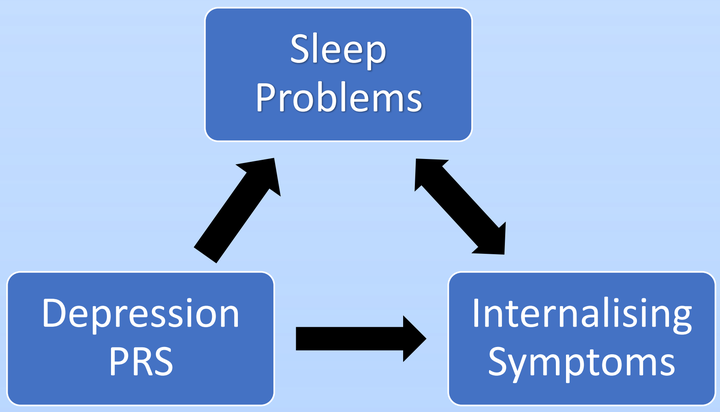

Figure 1 : Research Model suggesting the relationship between our 3 main variables.

Methods

The study is based on a secondary data analysis using the Simons Simplex Collection (SSC). The SSC is a large collection of autistic individuals and their families (n=2600) with associated genetic and phenotypic data (www.sfari.org)

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Phenotype measures of interest:

1) the Simons Simplex Collection Sleep Interview (SSCSI), a parental-reported questionnaire describing the children's night-time, daytime, and sleep duration problems. [9]. A composite variable for sleep difficulties based on the responses on the SSCSI will be generated.
2) Internalising and Externalising scores in the Childhood Behaviour Checklist (CBCL) 6 -18 years old, a standardised caregiver report questionnaire used to identify emotional and behavioural problems in children and adolescences.

Statistical analysis:
Multiple linear regression models will be created to test the relationship between genetic risk, sleep and internalising/ externalising problems. Predictor variables: PRS for depression, neuroticism and insomnia and the composite SSCSI sleep score.
Outcome variables: CBCL internalising and externalising symptoms.
Covariates: Age, Gender, IQ, and ASD severity.

As there is a significant overlap in a number of neuropsychiatric PRS, we will also test the relationship between the PRS for schizophrenia and cross-disorder PRS, with internalising and externalising symptoms.
A model with PRS for height will be the control.

Results - Descriptive data analysis

Sleep and CBCL 6-18 variables were available for 2102 individuals, after omitting significant outliers.
Initial exploratory analysis (Figure 3) showed that a large proportion of children on the autism spectrum reported elevated levels of internalising problems. Our T score analysis revealed that 52 % of the ASD children have an internalising problems T score greater than 60. Figure 2 shows the total nighttime problems reported ever and current.

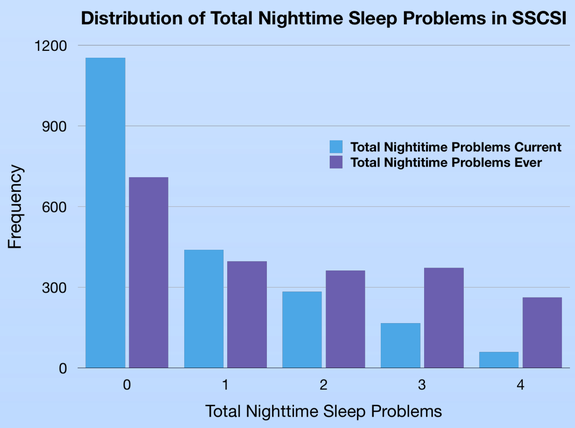

Figure 2: A bar plot summarising the distribution of Total Nighttime Sleep Problems of ASD children aged 6 to 18 years old recorded in SSCSI.

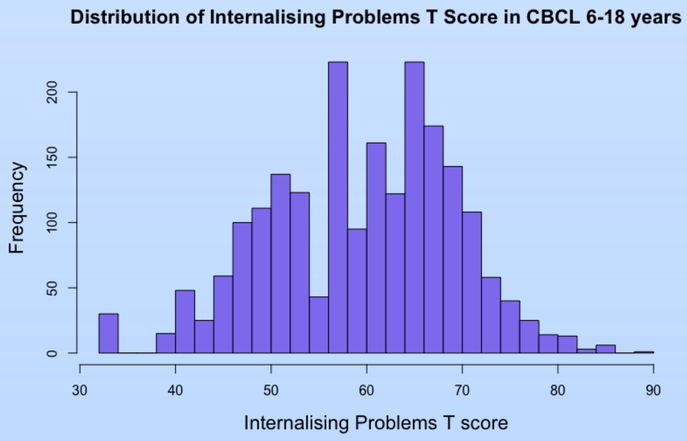

Figure 3: A histogram summarising the distribution of internalising problems T score of ASD children recorded with the CBCL 6 to 18 years old in the SSC dataset.

Future Directions

First, we will assess the relationships between the predictor variables using correlation and remove highly correlated variables from the analysis. Dr. Richard Anney, a Senior Lecturer in Bioinformatics at Cardiff University, will generate PRS for depression, schizophrenia, cross-disorder, and height for inclusion in our multivariate analysis.

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