developmental trajectories for understanding neurotypical and pathological cortical physiology.

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SCHIZOPHRENIA IS CHARACTERIZED BY AGE- AND SEX-SPECIFIC EFFECTS ON EPIGENETIC AGING

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Background: Schizophrenia (SCZ) is a severe mental illness that is associated with an increased prevalence of age-related disability and morbidity compared to the general population. An accelerated aging process has therefore been hypothesized as a component of the SCZ disease trajectory. Clear evidence of altered aging on a molecular level, however, has not yet been demonstrated. Recent advances have been made to study molecular features of aging and mortality through DNA methylation (DNAm) profiling and the development of different epigenetic clocks.
Methods: We used three DNAm clocks (i.e. Hannum, Horvath, Levine) each capturing different features associated with aging, in a multi-cohort SCZ case-control sample consisting of ∼1,100 cases and ∼1,200 controls. Using a multiple regression and meta-analysis framework, we estimated differential aging between cases and controls using Δage, the difference between DNAm age and chronological age, as a response variable. Analysis were performed across the full sample and stratified by age groups and sex while adjusting for technical covariates. SCZ polygenic risk scores (PRS), age at onset, duration of illness, DNAm smoking scores and blood cell type proportions were used to gain further insights into differential aging patterns.
Results: We observe that blood-based DNAm aging is significantly altered in SCZ and can be decomposed to age- and sex-specific effects that are different between clocks. Most notably, the predicted phenotypic age (Levine clock) in female SCZ patients, starting at age 36 and beyond, is 3.21 years older compared to matching control subjects (CI: 1.92-4.50, P=1.3e-06). This increased phenotypic age is most apparent for female patients with high SCZ polygenic risk scores. A 1-year increase in phenotypic age is associated with a 9% increased risk of all-cause mortality. With an observed accelerated phenotypic age of 7.83 years (CI: 4.62-11.04, P=8.2E-06), our finding suggests that this group of female patients carrying high SCZ genetic risk is at greater mortality risk. Further significant results include an age deceleration during early adulthood as measured by the Horvath clock, a multi-tissue clock that measures intrinsic cellular aging and associates with biological mechanisms associated with human development.
Discussion: In summary, we performed one of the largest aging and epigenetic studies in SCZ to date using multiple epigenetic clocks based on whole blood DNAm data. Our findings provide new biological insights into the aging landscape of SCZ with age- and sex-specific effects and strengthen the need for future large-scale epidemiological studies of DNAm aging in SCZ, and other psychiatric disorders. Our results suggest that specific and identifiable patient groups are at increased mortality risk as measured by the Levine clock, warranting further investigations into the potential of DNAm clocks as clinical biomarkers that may help with disease management and prevention.

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Oral Session: Mood Disorders
1:30 p.m. - 3:00 p.m.

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EXAMINING THE SHARED GENETICS BETWEEN EDUCATIONAL ATTAINMENT AND DEPRESSION: RESULTS FROM THE AUSTRALIAN GENETICS OF DEPRESSION STUDY

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Background: Educational attainment (EA) is a strong proxy trait for cognitive ability. Individual differences in EA have been shown to correlate with cognitive test performance and a wide variety of social, health and economic outcomes. Educational attainment (EA) has also been associated with risk of depression. However, the direction of this association remains unclear, as are the genetic and environmental effects underlying this association. Furthermore, the causality between EA and depression is yet to be assessed.
Methods: We have collected data from $>$ 15 000 individuals suffering from depression in the Australian Genetics of Depression (AGDS) study. Additional information on antidepressant response, comorbidities and genotype data was collected. Here, we quantified the liability to EA in the participants of AGDS by calculating polygenic risk scores (PRS) using data from the most recent EA meta-analysis. The predictive ability of EA PRS for various depression-related (diagnosis, number of episodes, age of onset) and treatment response phenotypes was assessed. Additionally, the effect of various environmental factors, such as socio-economic status and traumatic life events, on these associations were assessed. Finally, Mendelian Randomization was used to assess whether a causal relationship between EA and depression exists.

Results: EA PRS significantly predicted depression status (determined by both self-report and DSM criteria), number of depressive episodes, number of depressive symptoms and response to antidepressants (maximum variance explained ~0.5%, P <0.001 after Bonferroni correction for multiple testing). EA PRS was positively associated with depression diagnosis, but negatively associated with the number of depressive episodes, number of depressive symptoms and age of onset for depression. EA PRS also predicted a unique profile of overall antidepressant side-effects including headaches, suicidality, nausea but not weight loss/gain, anxiousness or dizziness. Interestingly, Mendelian Randomization showed significant evidence for a bidirectional causative effect.
Discussion: This study implicates shared genetic factors in the association between EA and depression and treatment response phenotypes. Our results suggest that individuals with high educational attainment have a higher risk of developing depression. However, these individuals are less likely to experience severe depression and are more likely to respond to treatment. These results are consistent with previous findings that associated lower cognitive ability with severe depression and other externalising disorders. The association between EA PRS and some specific side-effects might be explained by the shared aetiology identified between EA and depression. However, the specific mechanisms through which EA PRS is linked to response remains enigmatic. Understanding these mechanisms underpinning the association between EA and depression is crucial for its implication in prevention and treatment strategies for depression. This study represents a first step towards elucidating the causal role of EA (and potentially IQ) on depression.

Disclosure: Nothing to disclose.

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NOVEL GENOME-WIDE ASSOCIATIONS FOR ANHEDONIA, GENETIC CORRELATION WITH PSYCHIATRIC DISORDERS, AND POLYGENIC ASSOCIATION WITH BRAIN STRUCTURE

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Background: Anhedonia is a core feature of several psychiatric disorders, but its biological underpinnings are poorly understood.
Methods: We performed a genome-wide association study of anhedonia in 375,275 UK Biobank participants and assessed for genetic correlation between anhedonia and neuropsychiatric conditions (major depressive disorder, schizophrenia, bipolar disorder, obsessive compulsive disorder and Parkinson's Disease). We then used a polygenic risk score approach to test for association between genetic loading for anhedonia and both brain structure and brain function. This included: magnetic resonance imaging (MRI) assessments of total grey matter volume, white matter volume, cerebrospinal fluid volume, and 15 cortical/subcortical regions of interest; diffusion tensor imaging (DTI) measures of white matter tract integrity; and functional MRI activity during an emotion processing task.
Results: We identified 11 novel loci associated at genome-wide significance with anhedonia, with a SNP heritability estimate (h2SNP) of 5.6%. Strong positive genetic correlations were found between anhedonia and major depressive disorder, schizophrenia and bipolar disorder; but not with obsessive compulsive disorder or Parkinson's Disease. Polygenic risk for anhedonia was associated with poorer brain white matter integrity, smaller total grey matter volume, and smaller volumes of brain regions linked to reward and pleasure processing, including nucleus accumbens, caudate and medial frontal cortex.
Discussion: The identification of novel anhedonia-associated loci substantially expands our current understanding of the biological basis of anhedonia and genetic correlations with several psychiatric disorders confirm the utility of this trait as a transdiagnostic marker of vulnerability to mental illness. We also provide the first evidence that genetic risk for anhedonia influences brain structure, particularly in regions associated with reward and pleasure processing.

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INVESTIGATING RARE PATHOGENIC/LIKELY PATHOGENIC EXONIC VARIATION IN 3,987 BIPOLAR PATIENTS

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Background: Bipolar disorder (BD) is a common, severe mood disorder that affects more than 1% of the worldwide population. Despite high heritability, the genetic architecture of BD remains elusive. While large genome-wide association studies (GWAS) identified dozens of BD loci, the role of rare variants of BD has not been studied on a large scale. This study aims to investigate whether rare, protein-altering single nucleotide variants (SNVs) contribute to the