Title. Genetic and Polygenic Risk Analysis of Antidepressant Response and Cognitive Domains in Late-Life Depression

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Background. Late-life depression (LLD) is often accompanied by cognitive decline, which is associated with poor response to antidepressant treatment. Here, we aimed to investigate the genetic profile of cognitive function and its association with antidepressant response in individuals with LLD.

Methods. In the Incomplete Response in Late-Life Depression: Getting to Remission (IRL-GRey), 307 older adults (60 ≤ age ≤ 93) with a major depressive disorder were treated with venlafaxine for 12 weeks. We performed a GWAS of five cognitive domains (i.e., Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory) assessed with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). We performed functional annotations by mapping SNPs to genes and pathways using Functional Mapping and Annotation (FUMA) for GWAS. We then constructed polygenic risk scores (PRSs) of antidepressant non-remission and symptom improvement from GWAS summary statistics of the PGC using the clumping and thresholding method (with PRSice v2). Lastly, we assessed the associations between PRSs with the cognitive domains in our sample co-varying for age, sex, and the first two genomic principal components to adjust for population stratification. Bonferroni correction for multiple testing and 10000 permutation tests were also applied to mitigate overfitting.

Results. Out of the five cognitive domains, we identified significant SNPs for the attention domain (lead SNP rs67854110, beta = -9.91, CI = [-13.12, -6.70], P = 4.4e-09). Top suggestive genes (extracted from SNPs with P < 0.05e-06) associated with language showed differential expression in the brain (P_{bon} = 0.001), particularly in the hypothalamus, cortex, and nucleus accumbens. Moreover, the language gene set analysis showed a significant enrichment with the GWAS Catalog set *response to cognitive-behavioural therapy in depression* (P = 9.24e-11). Likewise, the top SNP associated with the delayed memory (rs13087568, beta = -8.24, CI = [-11.36, -5.11], P = 4.5e-07) was previously reported to affect depressive symptoms by other studies.

PRS for non-remission negatively correlated with attention ($P_{Threshold}$ = 0.0001, N_{SNPS} = 39, OR = 0.105 [0.016, 0.686], P = 0.019), immediate memory ($P_{Threshold}$ = 0.001 , N_{SNPS} = 320, OR = 0.074 [0.011, 0.490], P = 0.0072), and delayed memory ($P_{Threshold}$ = 0.01, N_{SNPS} = 2449, OR = 0.107 [0.021, 0.540], P = 0.0074). PRS for symptom improvement showed a positive correlation with delayed memory ($P_{Threshold}$ = 0.001, N_{SNPS} = 385, OR = 5.329 [1.056, 26.885], P = 0.044). However, none of the PRS associations survived the Bonferroni threshold (0.005) before or after a 10,000 permutation test.

Discussion. Our exploratory findings suggest a potential genetic correlation between cognitive domains and antidepressant response in late life and confirm previously reported associations. Our findings might contribute to better understand the contribution of genetics in detecting cognitive decline in older adults receiving treatment for depression, and hence, allow early identification interventions to prevent dementia.