Universität Basel

Research Project

Identification of molecular patterns linked to human memory

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Increasing evidence points to the role of the immune system in regulation of memory processes. A recent study conducted by our group notably described a link between peripheral epigenetic markers with cortical thickness measures and memory. The molecular mechanisms underlying immune-memory relationship remain yet elusive.

In this project we proposed to further investigate this link by capitalizing on recent well-powered human genetic studies of a wide range of peripheral immune related traits.

Specifically, we relied on this unprecedented resource and a behavioral-imaging genetic data of a maximum N=1,625 healthy young subjects to (i) investigate the relationships between cortical thickness, episodic memory (EM) and a panel of 200 immune-related traits (ii) identify which subset of molecular markers contribute significantly to these relationships, and (iii) explore their molecular profiles in whole-blood.

In a first phase, we performed exhaustive hypothesis-free association testing between 200 blood measures derived polygenic risk scores (PRS) and brain related traits. This yielded to the identification of a significant correlation ($r = -0.12$, FDR <0.05) between peripheral Acetate derived PRS, and a regional thickness pattern characterized by a circumscribed set of regions including the entorhinal cortices and temporal poles. This first result suggests existence of shared genetic contributions between levels of Acetate in blood and variability in cortical thickness, in regions known to be relevant to EM function. Downstream functional annotation analyses yet didn't allow the identification of specific molecular patterns robustly linking Acetate levels to cortical thickness in our study population.

In a second phase of the project, we capitalized on recently published large-scale GWAS on neuropsychiatric disorders, to further target specific blood related traits amenable to downstream analysis. Specifically, relying on genetic correlation method, we identified significant negative relationship between both schizophrenia (SCZ) and major depression (MDD), and Citrate levels (SCZ: $r = -021$, $p = 7e\text{-}4$; MDD: $r = -0.21$, $p= 2.5e\text{-}3$). Both disorders being characterized by deficits in EM performance, Citrate levels derived PRS was tested for association with EM performance in our study sample. This yielded a significant positive correlation ($r = 0.06$, $p = 0.02$), replicated in a second independent sample comprising N=1,851 healthy young adults ($r = 0.05$, $p = 0.02$). Downstream functional annotation of traits associated markers, led to the identification of *GRAMD1A* – a gene encoding for GRAM domain containing 1A protein involved in cholesterol homeostasis - showing simultaneously significant association with Citrate levels and EM performance. In addition, we identified a total of 15 individual CpG sites at which estimated DNAm in whole-blood showed significant correlation with Citrate levels. This result suggests that genetic markers might partially exert their effect on Citrate levels through whole-blood DNAm, although none of these sites showed robust association with EM performance in our study sample.ă

In sum, Citrate levels, which are genetically linked to schizophrenia and major depressive disorder, showed a significant genetic correlation with EM performance in our study population comprising heathy young adults. Functional annotation of genetic markers further pointed to *GRAMD1A* as linked to both EM performance and citrate levels. It remains though unclear whether the identified genetic contributions do overlap with genetic contributions linking Citrate to MDD or SCZ, or represent independent genetic factors. Hence, these results warrant independent replication before considering downstream functional validation.

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