A Genome-Wide Association Study of the Longitudinal Course of Executive Functions

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Introduction

Executive functions, i.e. cognition involving control and coordination of mental processes, are impaired in severe mental disorders. Here, we present new findings of our ongoing research on the molecular genetic basis of the longitudinal course of executive functions. We use data of the PsyCourse study (Budde et al., 2018), a longitudinal multi-center study of the affective-to-psychotic continuum, including healthy controls, and research the time course of two core aspects of executive functions: set-shifting and updating (Myiake et al., 2000). Specifically, we use linear mixed model (LMM) analyses to study the interactions of SNP and time on a genome-wide level.

Methods

Phenotypes

Data were collected at four measurement points across a period of 1.5 years. The Trail-Making-Test Part B (TMT-B, time, Figure 1, upper panel) and the Verbal Digit Span Backwards (VDS, digit span, Figure 1, lower panel), a subtest from the Wechsler Intelligence Test for Adults, were used to measure set-shifting and updating capabilities, respectively. Individual time courses (selected at random) of performance on the TMT-B (upper panel) and the VDS (lower panel) are shown in Figure 2. We included all genotyped patients and healthy control individuals that completed at least one measurement point. In total, these were n= 1338 individuals. Of these, n=550 were DSM-IV affective (predominantly bipolar) patients (296.0x/296.4x/296.5x/296.6x/296.8x/296.3x, mean age at baseline 45 years, 49.8% female), and n=530 DSM-VI psychotic patients (295.10/295.20/295.30/295.60/295.90/295.40/298., mean age at baseline 41 years, 39.6% female), and 258 healthy controls (mean age at baseline 37 years, 58.1% female). We performed LMM analyses to study VDS or log(TMT-B) as outcomes. Subject-specific time courses were modeled, allowing for random intercepts and slopes. We also included SNP, time, interaction of SNP and time, age, sex, diagnostic group and the top five ancestry principal components as fixed effects and recruiting center as additional random effect in each LMM.

Genotypes

Individuals were genotyped with the Illumina PsychArray, and common variants (MAF≥0.01) were imputed using the 1000 Genomes Phase 3 reference panel.

Results

For the phenotype TMT-B, nine SNPs reached genome-wide significance (5 x 10^{-8}), located within the same LD block (r^2>0.85) on chromosome 5 (Figure 3, lower panel). These SNPs are located in or near the following genes (Figure 3, upper panel): Ring Finger Protein 180 (RNF180), Regulator of G Protein Signaling 7 Binding Protein (RGS7BP), and the 5-Hydroxytryptamine Receptor 1A (HTR1A). No significant SNP was found for the VDS phenotype (Figure 4).

Discussion

No molecular genetic factors were associated with the interaction effect of SNP and time of the updating component (VDS) of executive functions. The interaction effect of SNP and time of the set-shifting component (TMT-B) was associated with genes that had previously been identified in genetic studies of intelligence (RNF180, Davies et al., 2018), and educational attainment (RGS7BP, Lee et al., 2018). Also, the HTR1A is an important regulator of the serotonin system of the brain. We are currently working on a replication of our results in an independent sample.

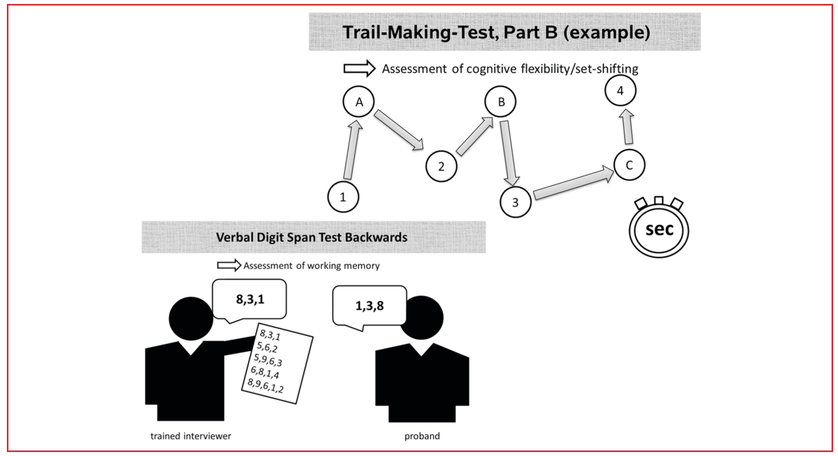

Figure 1. Schematic description of the assessment of TMT-B and VDS.

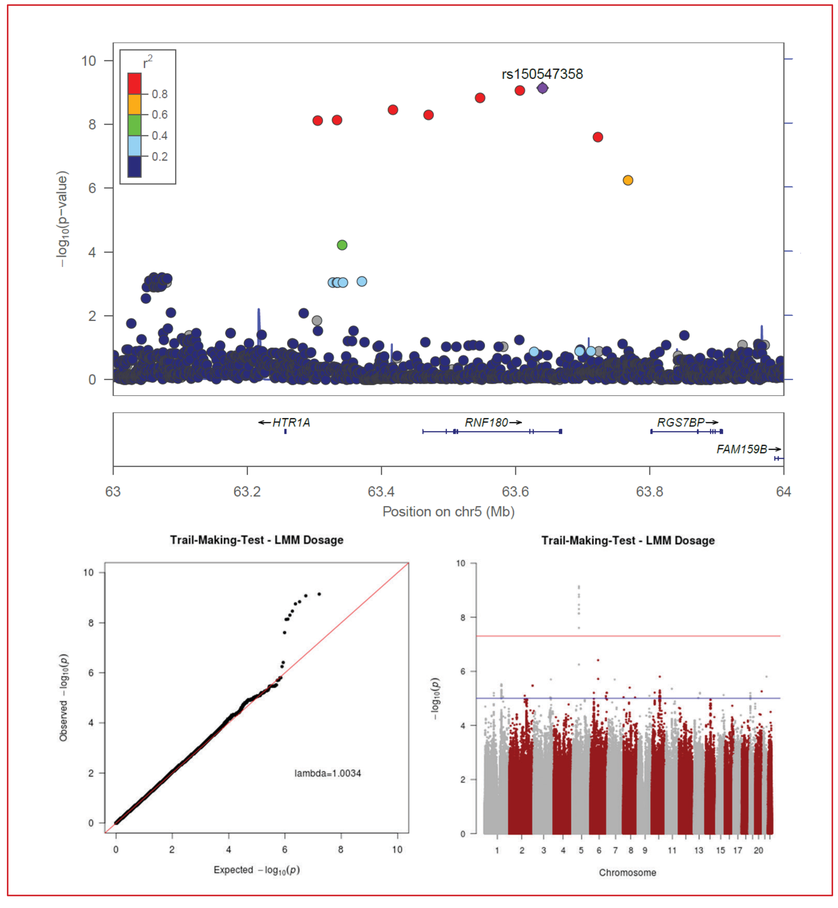

Figure 3. GWAS of the interaction effect of SNP and time of the TMT-B phenotype. Upper panel: Regional association plot of chromosome 5. Lower panel: Q-Q and Manhattan plots.

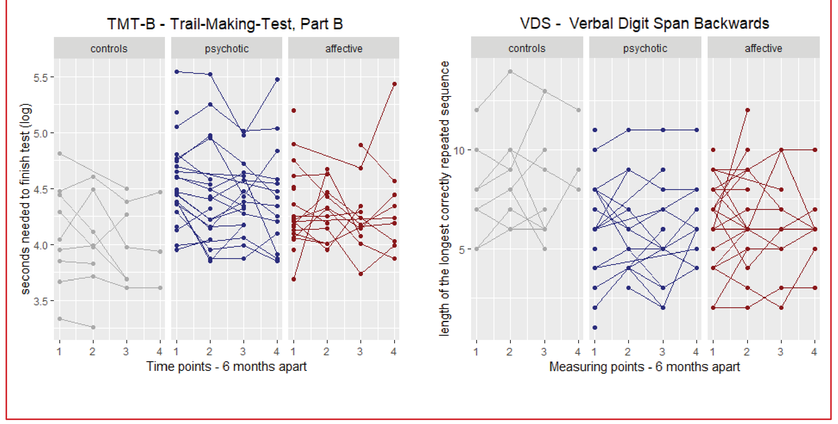

Figure 2. Individual time courses (selected at random) of the TMT-B (left) and the VDS (right).

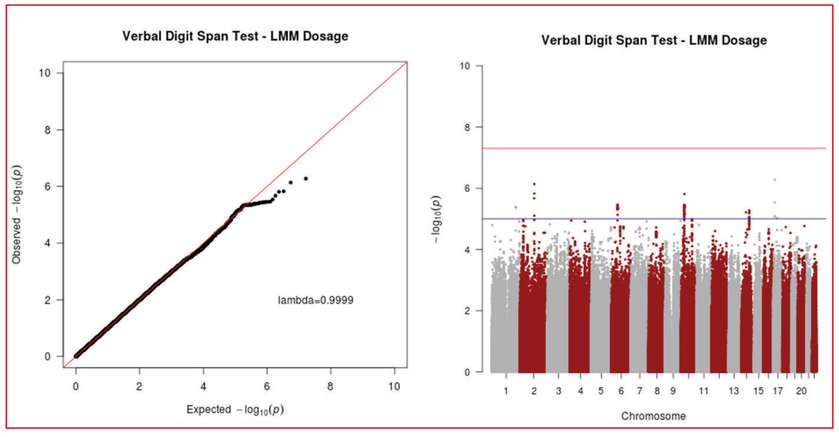

Figure 4. GWAS of the interaction effect of SNP and time of the VDS phenotype. Q-Q and Manhattan plots.

References

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