A genetic perspective into impulsive and compulsive behaviours

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Summary

The work presented in this dissertation is largely focused on uncovering and quantifying the genetic factors contributing to the development of disorders within the obsessive-compulsive spectrum. The two main approaches used to analyze data on obsessive-compulsive (OC) symptoms, tics and hoarding were genetic association analysis and twin studies, which intersect within genetic epidemiology. The findings are summarized below.

Chapter 1 provides an overview on the genetics of tic disorders, obsessive-compulsive disorder (OCD), and hoarding disorder (HD).

Chapter 2 describes a genetic epidemiological twin study on OC symptoms, indicating that OC symptoms are highly stable across time (a 6 year time period), in a population of around 5,500 adult twins (age range between 17-90 years). This study modelled the longitudinal phenotypic variance of OC symptoms as a function of genetic and environmental factors. It showed that individual differences in stability are due to a combination of genetic (heritability: h2=56%) and unique environmental factors, with heritability estimated at 56%. Furthermore, it showed that genetic influences on OC symptoms are stable across time with longitudinal genetic correlations of rG=0.58. The longitudinal unique environmental correlation was rE=0.46. This suggests that measurement error alone may not be enough to explain time-point specific variance. It also highlights the role that individual experiences, in childhood and adolescence, may have on OCD far into adulthood. The broad-sense heritability consisted of additive genetic variance, and the bivariate (two time points) model also captured non-additive (dominant) genetic effects contributing to the phenotypic variance. Genetic dominance explained around 22% and additive influence around 36%.

Chapter 3 reports on a heritability analysis using different definitions of tic disorders. A sample of 8,323 mono- and dizygotic adult twins was included, in addition to their 7,164 family members who had been measured on lifetime occurrence and characteristics of tics. This chapter explored the extent to which the contribution from genetic and environmental influences differed across different definitions of tic disorders. The different tic definitions, following the current DSM-5 criteria, represented a range of mild to severe tic symptoms. Heritability was estimated to contribute between 25-37% depending on the phenotype definition. These heritability estimates had overlapping confidence intervals, which suggested a similar genetic liability for the different tic phenotype definitions. Interestingly, the heritability of the most lenient tic definition (including any tic) showed the narrowest

confidence interval (h2=30%; 95% CI= .23-.38), indicating that the core phenomenological characteristics of tics ("sudden, rapid, recurrent, non-rhythmic, stereotyped motor movements or vocalizations") render the highest heritability estimate.

In Chapter 4 we analysed phenotypic data on OC symptoms, hoarding symptoms, and tics, and explored the amount of underlying genetic and environmental influences shared between these three phenotypes, to further explore the common etiology across these three disorders. We had at our disposal population-based data from the NTR for which N=5,293 individuals had phenotypic data available on all three phenotypes. This revealed substantial genetic correlations (between 0.35-0.41), with the highest genetic correlation of 0.41 to be found between OC symptoms-Hoarding symptoms. This specific result is of interest in light of the latest development in DSM-5, in which HD was separated from OCD as a distinct disorder and placed in the category of OC spectrum disorders. Moreover, our findings corroborate the findings by Iervolino (2009; 2011) and Tambs (2009). These results suggest that the symptoms related to OCD and HD share less genetic variance than the shared genetic variance observed between OCD and internalizing disorders such as panic disorder, generalized anxiety, phobias, and PTSD (genetic overlap of 0.55). To conclude, HD can be considered a separate, albeit related, entity to OCD, in line with its current position in DSM-5. Lastly, the results regarding the common factor model that was tested point to shared genetic etiology among the three phenotypes (with genetic correlations between .32-.43). With respect to the total environmental variance, tics had a considerably smaller loading of only 4.4% on the common factor. Based on these results, it can be hypothesized that commonalities in genetic architecture dictate underlying similarities in dysfunction at the structural and functional level in cortico-striato-thalamo-cortical circuitries – the regions so far implicated in these disorders by neuroimaging studies. In view of the lower environmental correlations between tics and both OC symptoms and Hoarding symptoms, it seems that unique environmental experiences that determine the development of tics, are by and large different from the unique environmental factors involved in OC spectrum disorders.

Chapter 5 introduces the use of genome wide array-SNP data in a series of exploratory analysis on the genetics of OC symptoms. It expands the work performed in Chapter 2. Here, 6,931 subjects were included (twins, their siblings, parents and spouses), for whom genetic data were available, i.e. genome wide SNP data, which together with phenotype information were analyzed in genetic association studies (GWAS), with polygenic risk scores,

SNP-based heritability (GCTA), and gene-based testing. For polygenic risk score calculations, GWAS results from a large clinical sample of OCD patients who were of European ancestry (the OCF-GC) were used (Stewart et al., 2013). Polygenic scores summarize genetic effects among a large set of markers that do not individually achieve significance into a single value per subject. These scores significantly predicted OC symptoms in the NTR population-based sample (with 0.2% explained). In the same sample, SNP-based heritability was estimated at 14%. The total variance explained by genetics, i.e. SNP and other heritability, captured using GCTA was of 34%. This means that 14% of the OCS phenotypic variance is attributable to genotyped SNPs, and 20% attributable to genetic variance not captured by the currently used genotyping SNP-arrays. The combined association analysis (GWAS and gene-based test) revealed a significant SNP (rs8100480), located within the MEF2BNB-MEF2B gene ($p=2.56\times10\text{-}8$), and four significant genes (RFXANK, MEF2B, MEF2BNB, MEF2BNB-MEF2B), all located in the chromosomal region (19p13.11).

Chapter 6 reports on a meta-analysis between genome-wide association results on tic disorders performed at the NTR (N=88 cases, using a narrowly defined phenotype; 6,381 controls) and results from a clinically based sample from the Psychiatric Genomics Consortium Tourette's workgroup (PGC-TS) (N=778 cases; 4,414 controls). In line with the results on OCS from Chapter 5, the results showed that polygenic risk scores calculated from the PGC-TS case-control sample significantly predicted tic disorder in the NTR population-based sample. In sum, this chapter showed the added value of combining clinically-based and population-based samples in the context of association analysis. Extending the results on heritability analysis on different tic phenotypes (Chapter 3), screened subjects from the NTR were included in the analysis, consisting of 88 cases diagnosed for the most severe manifestation of a tic disorder ('chronic tic disorder - motor/vocal' or 'Tourette Disorder'), and excluding 173 individuals diagnosed with a milder tic disorder ('transient tic disorder' or 'tic disorder not otherwise-specified'). The GCTA analysis showed that 14.6% of the heritability of the tic phenotype from the NTR is attributable to common SNPs. The top SNP from the meta-analysis, rs7783290, is located on chromosome 7, with a p-value of 1.49x10-7 and a Z-score of -5.25.

In Chapter 7 the first ever-reported meta-analysis on hoarding symptoms is presented. Two population-based samples from the NTR (N=6,521) and TwinsUK (N=5,190) were combined, with genotype data imputed to 21,775,582 and 47,072,643 SNPs, respectively. This study constitutes the

largest sample available to date for hoarding symptoms, and a good solid groundwork for future studies. The two top SNPs from the meta-analysis were rs139052 (p=8.30x10-7) and rs12873866 (1.32x10-6), both with a protective-effect for its major allele. The SNP rs139052 is located in the PNPLA3 gene in 22q13.31, and the SNP rs12873866 is located in 13q33.1, a large intronic region of high LD. Given the observed scenario for other psychiatric traits, future genetic studies in HD will gain further relevance.

Chapter 8 presents a polygenic dissection of OC symptoms, based on data used for the work described in Chapter 5. Building on the recent and ever-growing availability of data from large-scale GWASs, polygenic scores were built for a set of clinically-derived phenotypes chosen for their epidemiological relation to OCS, i.e., Attention Deficit Hyperactivity Disorder (ADHD), Bipolar Disorder (BD), Schizophrenia (SCZ), major depressive disorder (MDD), Autism and Migraine. PRS were also built for clinically-derived OCD samples from the International OCD Foundation Genetic Collaborative (IOCDFGC) and OCD Collaborative Genetics Association Study (OCGAS). A genetic risk score was calculated on these scores and tested for its predictive value for OC symptom. The polygenic scores for OCD (p=3.0x10-4), SCZ (p=1.4x10-6), MDD (p=5.6x10-5) and BP-SCZ combined (p=8.1x10-7) significantly predicted OC symptoms in the population-based sample, accounting for between 0.38-0.79% of its total variance. Following on the increasing value of PRS, these findings show the presence of sub-clinical OC symptoms based on psychiatric genetic risk factors, therefore strengthening the usefulness of using a phenotype derived from clinically significant symptoms. It further extends the work in Chapter 5 in illustrating the polygenicity of OC symptoms and its complex etiology. The growing availability of PRS renders it with a higher predictive value than GWASs, for which epidemiologically-based phenotypes seem to be equally suitable as disorder-based phenotypes.

In Chapter 9 the first Epigenome-wide association study (EWAS) of tics is presented. This study was conducted on 411,169 autosomal methylation sites for 1,678 individuals measured for tic disorders. Of these, all individuals within the NTR with current or retrospectively reported tics ('any probable lifetime tic' as defined in Chapter 3) were included as a case in the analysis for a total of 188 Cases and 1,490 Controls. Gene-ontology analyses for the higher-ranking methylation sites found that the following sites were involved: a methylation site involving anatomical structure morphogenesis (GO:0009653, p=4.6x10-15), one involving developmental process (GO:0032502, p=2.96x10-12), and one involving cellular developmental process (GO:0048869, p=1.96x10-12).