‘Genetics of Attention and Executive Functioning’, by Tinca Polderman

The thesis ‘Genetics of Attention and Executive Functioning’ examined the genetic architecture of attention problems, attention, executive functioning, and intelligence (IQ). In addition, the (longitudinal) genetic relation among attention problems, executive functioning and IQ were investigated. Data were collected twice in a sample of twin children registered at the Netherlands Twin Registry (NTR): when they were 5 years old, and seven years later, when they were 12 years old. In this last chapter the results as presented in this thesis and other publications that have resulted from this project will be summarized and discussed.

First the genetic architecture of attention problems as assessed by different instruments and by different raters at ages 5 and 12 years is summarized. Next, an overview of the genetic studies on executive functioning and IQ, and their relation to attention problems is presented. Finally, the results of this thesis are discussed and put into the perspective of future directions for research into attention and attention problems.

Attention Problems

Attention problems in 5 and 12-year-old children were assessed by asking parents, teachers and children themselves to rate their behaviors. Genetic analyses of teacher ratings in young children are scarce. Chapter 3 presents a study on the sources of variation in the Teacher’s Report Form (TRF, Achenbach, 1991a) problem scales in 5-year-old children. In the genetic modeling we accounted for differences in ratings between twin pairs rated by the same teacher and twin pairs rated by different teachers. Means and variances of all problem scales, including the attention problem (AP) scale, were lower and twin correlations were higher, for children who were rated

by the same teacher, compared to children who were rated by different teachers. The heritability estimates of the 8 problem scales of the TRF (Anxiety, Social problems, Withdrawn, Aggression, Rule breaking, Somatic complaints, Thought problems, and Attention problems) ranged between 30 and 63%.

Chapter 2 presents longitudinal genetic analyses (age 5 and 12) on the AP scale as rated by parents and teachers. Parental ratings on attention problems at age 5 were collected with a short form of the Devereux Child Behavior Rating Scale (DCB, Spivack and Spotts, 1966, Van Beijsterveldt et al 2004). At age 12 parental ratings were of AP were obtained with the Child Behavior Checklist (CBCL, Achenbach, 1991b). For teacher and parental ratings a longitudinal genetic analysis on the AP scales was performed. For teacher ratings the pattern of twin correlations indicated influences of additive genetic factors at age 5 and at age 12. For parental ratings at both ages DZ correlations were lower than half the MZ correlations, pointing to additive and non-additive genetic factors influencing variation in AP. The heritability estimates for attention problems at age 5 and 12 as rated by their parents were 59% and 67%, and as rated by the teachers 81% and 71% respectively.

Other behavior questionnaires assessing attention problems that were collected at age 5 were the Conner's Rating Scale (Conners, 2001) as rated by teachers, and the Aandachttekort Stoornis met Hyperactiviteit (ASH, Gunning, 1992) as rated by parents and teachers. At age 12 the Youth Self Report (YSR, Achenbach, 1991c) was collected. There are no publications of these measures as assessed in the current sample but Table 1 provides an overview of twin correlations of AP measures on all behavior questionnaires assessed at age 5 and 12 in the current sample. When available, twin correlations for these questionnaire data that were published in larger NTR samples are also included.

At age 12 also data on the Strengths and Weakness of ADHD symptoms and Normal behavior Scale (SWAN, Swanson et al., 2006) were collected.These data were also available in an additional NTR sample that was selected for attention problems (Derks et al 2006a). The SWAN measures Hyperactivity/Impulsivity (HI) and Attention Deficit (AD) with item scores on a 7 point scale, ranging from ‘average behavior’ to the extremes ‘far below average’ and ‘far above average’. So in contrast to most regular checklists the SWAN scores cover the strengths as well as the weaknesses of a child, ranging from severe hyperactivity to normal activity and from serious attention deficits to a high level of attention. The results of this study, presented in chapter 4, showed that scores on the SWAN rating scales show a normal distribution. Variation on the SWAN/HI and SWAN/AD scale was explained by additive genetic influences (90% and 82% respectively) and unique environmental influences.

Table 1

Monozygotic (MZ) and dizygotic (DZ) twin correlations for attention problems as assessed with behavior questionnaires at age 5 and at age 12 in the current sample and in larger samples of the NTR.

Age 5	**N twin pairs**	**MZ**	**DZ**
DCB M[1]	228	0.60	0.04
DCB M Van Beijsterveldt et al (2004)	7679	0.62	0.05
ASH M	234	0.77	0.15
TRF T[1]	209	0.80	0.48
ASH T	209	0.73	0.33
Conners (old version) T	209	0.72	0.39
Age 12			
CBCL M	198	0.68	0.08
CBCL M Rietveld et al (2003)	1516	0.72	0.26
CBCL M Derks et al (in revision)	2850	0.75	0.34
Conners M	181	0.79	0.10
Conners M Derks et al (in revision)	2443	0.84	0.38
SWAN/Hyperactivity M	561[2]	0.91	0.43
SWAN/Attention Deficit M	561[2]	0.85	0.38
TRF T	94	0.72	0.25
Conners T	90	0.63	0.24
YSR C[1]	172	0.51	0.33

Note[1]: M = mothers, T = teachers, C = children

Note[2]: original sample extended with SWAN data of additional 12-year old NTR sample

Attention (problems) and the SNAP-25 gene

An association study was performed between SNPs on the SNAP-25 gene and SWAN/HI and SWAN/AD scores. Previous studies have reported significant associations between the SNAP-25 gene and attention problems (Barr et al 2000; Brophy et al 2002; Mill et al 2002; Kustanovich et al 2003; Feng et al 2005; Mill et al 2004). The SNAP-25 gene is differentially expressed throughout the brain and is during development involved in synaptic plasticity, dendrite formation and axonal growth. In addition the gene has a regulatory role in the dopamine system (Osen-Sand et al 1993; Grosse et al 1999). The results as presented in chapter 5 showed that of 8 tagging SNPs, covering the SNAP-25 gene, one SNPs was significantly associated with scores on the SWAN/AD, and two SNPs showed a trend for association. The significant SNP has also been found to be associated with IQ in this sample (Gosso et al, 2006).

Executive functions

The genetic background of three different aspects of executive functioning was investigated, namely of working memory, selective- and sustained attention. Working memory and attention are mainly anchored in the frontal brain regions (Fuster, 1997, Smith and Jonides, 1999, Carpenter et al 2000, Hampson et al 2006), and these areas are partially overlapping with neural systems that seem to be affected in neuropsychiatric disorders like ADHD (Castellanos and Tannock, 2002; Casey & Durston, 2006; Durston et al., 2006). Previous studies had reported impairment of these functions in children with attention problems (Swaab-Barneveld et al 2000, Swanson 2003; Joseph 1999, Carter et al 1998, Pennington & Ozonoff, 1996;

Tannock, 1998; Barkley, 1997; Manly et al 2001). A sub sample of the current sample was compared with children diagnosed with ADHD on inhibition tasks (Slaats-Willemse et al 2003) and selective- and sustained attention tasks (Stins et al 2005). The affected ADHD group performed significantly worse on reaction time and accuracy than the normal twin controls.

In chapter 6 the genetic background of working memory was analysed. A distinction was made between working memory speed and capacity and the phenotypic and genotypic relationship between these working memory components was investigated. The phenotypic correlation between working memory speed and capacity was -0.30, demonstrating that both components involve partly similar working memory processes. The genetic correlation was -0.54 which indicates that working memory speed and capacity are partly mediated by the same set of genes. As on a phenotypic level intelligence and WM performance are strongly related (Kyllonen and Christal 1990, Colom et al 2004) it was tested whether the genetic correlation of -0.54 was not explained by intelligence (*g*), instead of a genetic relation between WMS and WMC per se. Adding general IQ to the genetic models revealed that that both *g* and working memory itself are responsible for the shared genes between working memory speed and capacity.

In chapter 7 working memory, selective- and sustained attention were analysed in a longitudinal genetic design. These results showed that in young children (age 5) the relative contribution of genes on variation in these executive functions ranged between 28 and 59%, and in older children (age 12) between 42 and 73%. It was also shown that the stability over time of working memory, selective- and sustained attention was due to genetic factors only. At age 12, the genetic influences on variation in executive functioning could be distinguished into stable

genetic effects, which were transmitted over time, and new genetic influences which emerged at age 12. The longitudinal genetic correlations of executive functioning were between 26 and 59%. Table 2 presents an overview of twin correlations of IQ and the executive functions as investigated in this thesis.

Attention problems, executive functions and intelligence

Chapter 2 of this thesis describes genetic influences on variation in IQ during childhood. In young children (age 5) common environmental and genetic factors play an equally important role explaining 37% and 31% of the total variance respectively. At age 12 years the influence of common environment has disappeared and the heritability is estimated as 81%. Also the longitudinal genetic relation between these traits was investigated. The longitudinal phenotypic correlation between IQ at age 5 and IQ at age 12 was 0.51, and the longitudinal genetic correlation was 0.81.

It was examined to what extent IQ performance, executive functions, and attention problems at age 5 predicted IQ performance at age 12. Executive functioning at age 5 was only weakly correlated with IQ scores at age 12 (r = 0.10 - 0.16). The genetic correlations fell in the same range except for selective attention of which the longitudinal genetic correlation with IQ was higher, namely 0.31. Thus, the phenotypic correlation is partly explained by common genes.

Notable was the significant phenotypic correlation between attention problems at age 5, as rated by mothers and teachers, and IQ performance at age 12 (r = -0.28 and -0.36 respectively). This means that attention problems in preschool children are predictors for IQ scores later in childhood. The longitudinal phenotypic correlation was partly explained by a common genetic factor; the genetic correlations were -0.42 and -0.39 respectively. In other words, there is a

common set of genes that influences attention problems at age 5 *and* IQ performance at age 12.

At age 5, executive functions among each other showed very high genetic correlations (r = 0.80, 0.82 and 0.90), and with IQ the genetic correlations were between 0.36 and 0.70. The genetic correlation between executive functioning and attention problems as rated by the teacher ranged between -0.31 and -0.38 (both at age 5). The genetic correlation between executive functioning and maternal ratings of attention problems at this age was low (-0.17 - 0.08).

Age 5	**N twin pairs**	**MZ**	**DZ**
IQ	237	0.68	0.54
Working Memory	235	0.55	0.35
Selective attention	233	0.50	0.35
Sustained attention	237	0.60	0.28
Age 12			
IQ	176	0.81	0.43
Working Memory	171	0.73	0.54
Selective attention	171	0.60	0.48
Sustained attention	172	0.61	0.49

Table 2: Overview of twin correlations of IQ, working memory, selective attention, and sustained attention at age 5 and at age 12