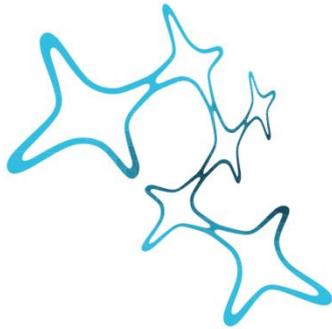


**AN IMAGING (BEHAVIOUR-) GENETICS
PERSPECTIVE ON SCHIZOTYPY AND
ANTISACCADES**



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LMU Munich

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Christine-Johanna Macare

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First Supervisor/Reviewer: Prof. Dr. Ulrich Ettinger

Second Supervisor/Reviewer: Prof. Dr. Dan Rujescu

Third Reviewer: Prof. Dr. Peter Falkai

Examination committee:

Prof. Dr. Ulrich Ettinger

Prof. Dr. Stefan Glasauer

Prof. Dr. Herman Müller

Prof. Dr. Stefan Duschek

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List of Abbreviations

A/a ²	Additive genetic influences
AC	Anterior commissure
ACC	Anterior cingulate cortex
ACE	Model composed of additive genetic, common and unique environmental influences
AC-PC	Anterior commissure - posterior commissure
ADE	Model composed of additive genetic, dominance-related and unique environmental influences
ADHD	Attention-Deficit/Hyperactivity Disorder
AE	Model composed of additive genetic and unique environmental influences
AIC	Akaike's Information Criterion
AS	Antisaccade
BA	Brodmann Area
BOLD	Blood oxygen level-dependent
C/c ²	Common environmental influences
CA	Constricted affect
CBF	Cerebral blood flow
CI	Confidence interval
CNS	Central nervous system
COGS	Consortium of the Genetics of Schizophrenia
CSF	Cerebro spinal fluid
D/d ²	Dominance-related influences
dACC	Dorsal anterior cingulate cortex
Df	Degrees of freedom
DLPFC	Dorso-lateral prefrontal cortex
dmPFC	Dorso-medial prefrontal cortex
DNA	Deoxyribonucleic acid
dPMC	Dorsal pre-motor cortex
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DZ	Dizygotic

DZFF	Female dizygotic
DZMM	Male dizygotic
DZos	Opposite-sex dizygotic
DZss	Same-sex dizygotic
E/e ²	Unique environmental influences
EB	Eccentric behaviour
EEA	Equal environment assumption
EPI	Echo planar imaging
FEF	Frontal eye fields
fMRI	Functional magnetic resonance imaging
FOV	Field of view
FWE	Family wide error
FWHM	Full width half-maximum
GLM	General linear model
GWAS	Genome-wide association study
GxE	Gene-Environment (interaction)
h ²	Heritability
Hb	Haemoglobin
HF	High frequency
HRF	Haemodynamic response function
Hyp	Hypomania
Hz	Hertz
ICC	Intra class correlation coefficient
Imp	Impulsivity
IPS	Intraparietal sulcus
IQ	Intelligence quotient
IR	Ideas of reference
M.I.N.I.	Mini-International Neuropsychiatric Interview
Mag	Magical ideation
MarsBaR	Marseille Boîte à Région d'Intérêt

MATLAB	MATrix LABoratory
MHz	MegaHertz
MNI	Montreal Neurological Institute
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MT	Magical thinking
MWT-B	Mehrfachwahl-Wortschatz-Intelligenztest, Form B
MZ	Monozygotic
MZFF	Female monozygotic
MZMM	Male monozygotic
NCF	No close friends
O-LIFE	Oxford-Liverpool Inventory of Feelings and Experiences
OR	Odds ratio
OS	Odd speech
Pan	Physical anhedonia
PASW	Predictive Analysis SoftWare
PC	Posterior commissure
PCA	Principial Component Analysis
PCC	Posterior cingulate cortex
PDI	Peters et al. Delusions Inventory
PEF	Parietal eye fields
Per	Perceptual aberrations
PFC	Prefrontal cortex
PPS	Psychosis-Proneness Scales
PS	Prosaccade
RF	Radio Frequency
RISC	Rust Inventory of Schizotypal Cognitions
ROI	Region of interest
S	Suspiciousness
SA	Social anxiety

San	Social anhedonia
SC	Superior colliculi
SEF	Supplementary eye fields
SEM	Structural Equation Modelling
SMA	Supplementary motor area
SNP	Single nucleoid polymorphisms
SPD	Schizotypal Personality Disorder
SPM	Statistical Parametric Mapping
SPQ	Schizotypal Personality Questionnaire
SPSS	Statistical Package for the Social Sciences
STA	Schizotypy Traits Questionnaire, Part A
STR	Short tandem repeat
T	Tesla
TE	Echo time
TR	Repetition time
UPE	Unusual perceptual experiences
VCA	Vertical line of anterior commissure
VLPFC	Ventro-lateral prefrontal cortex
WCST	Wisconsin Card Sorting Test

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Abstracts

Study One: Substantial genetic overlap between Schizotypy and Neuroticism: A Twin Study

Schizotypy can be seen as a cluster of personality traits, phenomenologically similar to, yet expressed in an attenuated form compared to the full-blown features of schizophrenia spectrum disorders. By placing schizotypy on the spectrum of schizophrenia spectrum disorders, the former might be used to reveal the aetiology of schizophrenia spectrum disorders. Similar to schizophrenia spectrum disorders, schizotypy correlates phenotypically with personality traits, most notably neuroticism. The aim of the first study was to decompose this phenotypic correlation between schizotypy and neuroticism and quantify its genetic and environmental components. Using a sample of 3,349 (1,449 monozygotic (MZ), 1,105 dizygotic (DZ) same-sex (DZ_{ss}) and 795 DZ opposite-sex (DZ_{os})) twins, we showed that positive schizotypy, specifically, the perceptual and ideational components of schizotypy, correlated on a phenotypical level with neuroticism (Pearson's $r=.37$). Despite the differentiation of positive schizotypy and neuroticism on phenotypical levels, both traits showed a substantial amount of overlap on genetic levels (51% of genetic influences were shared, 95% confidence interval (CI) from 38 to 64%). Even more interesting was that in genetic terms neuroticism was able to explain positive features of schizotypy completely. A Cholesky decomposition including anhedonia, hypomania and impulsivity features of schizotypy fully accounted for the heritable variance in perceptual and ideational components of schizotypy, meaning that the genetic underpinnings of positive features of schizotypy could be explained away by genetic influences on neuroticism and other features of schizotypy (e.g. anhedonia, hypomania and impulsivity). Therefore, positive schizotypy could be considered as an artefact in genetic terms. The findings of the first study help in facilitating and guiding the search for molecular genetic variants of schizotypy and could be extrapolated to the schizophrenia spectrum.

Study Two: The Schizotypal Brain - An fMRI Antisaccade Task Study

Study two aimed at enriching the detailed investigation of psychometric schizotypy (see Study one) by revealing the neural correlates of psychometric schizotypy. Here, we tried to probe the neural correlates of schizotypy by using a measure that shows associations with schizotypy levels, i.e. performance on the antisaccade task. As shown in Study one, positive features of schizotypy are only present at psychometric levels and can be reduced to genetic variation that impacts on neuroticism and other schizotypy features. In Study two, we therefore focussed specifically on negative and disorganisation-related features of schizotypy and investigated their underlying neural correlates. One hundred forty-two healthy participants underwent functional magnetic resonance imaging (fMRI) during the antisaccade task and assessment of psychometric schizotypy. We did not replicate the association between positive schizotypy and antisaccade error rate at the phenotypic level. We did however replicate the brain network underlying antisaccade task performance. Deactivations in occipital areas were linked to schizotypy features, specifically negative schizotypy. Brain activation patterns in schizotypy were broadly consistent with those demonstrated previously across the schizophrenia spectrum. Findings might be interpreted as supporting the neural overlap between schizotypy and the schizophrenia spectrum and help in gaining a better understanding of the neuropathology underlying schizophrenia spectrum disorders.

Study Three: Preliminary Findings of Heritability of the Neural Correlates of Antisaccade Performance

Performance on the antisaccade task is impaired across the schizophrenia spectrum and in schizotypy, has been explicitly stated as one of the most useful endophenotypes across the schizophrenia spectrum (Greenwood, Light, Swerdlow, Radant, & Braff, 2012) and is therefore supposed to be a useful tool for revealing the neural correlates underlying these phenotypes. In a third study, we put this assumption to the test by investigating the amount of genetic influences on the neural correlates of antisaccade task performance. Using a twin fMRI design, we successfully replicated the commonly observed brain activations for the antisaccade task including activations in a fronto-parieto-occipital subcortical network. In a sample of one hundred thirty-two healthy same-sex reared-together twins (90 MZ; 32 male and 42 DZ; 24 male), who first performed the antisaccade task in the laboratory, we found evidence for significant genetic influences as estimated by heritability estimates of 47% (95% CI 22 to 65%) to antisaccade task performance. Of these participants, 96 twins (60 MZ, 28 male; 36 DZ, 22 male) underwent fMRI whilst performing the antisaccade task. We found tentative evidence for significant heritability of the blood oxygen level-dependent (BOLD) response in the left thalamus (50%, 95% CI: 18 to 72%) as shown in the contrast comparing the BOLD response during antisaccades with the BOLD response during prosaccades, an oculomotor control task. Due to the small sample of twins further replication in larger samples is warranted to firmly establish the amount of genetic influences on the neural correlates underlying antisaccade task performance.

1. General Introduction

The current chapter focusses on introducing the main topics and methodological approaches covered in the empirical studies (i.e. chapters two, three and four):

- the importance of heritability for endophenotypes and how heritability is assessed,
- imaging genetics and its place in the broader context of endophenotypes,
- the definition of the construct of schizotypy and its assessment,
- the neural correlates of schizotypy,
- the antisaccade task and its relevance to the schizophrenia spectrum and
- functional magnetic resonance imaging as a means of assessing brain activity.

To facilitate the understanding of heritability and the imaging genetics approach, the concept of endophenotypes needs to be explained.

1.1. Endophenotypes

“Despite continuous misunderstandings and controversies over its use and application, heritability remains key to the response to selection in evolutionary biology and agriculture, and to the prediction of disease risk in medicine. Recent reports of substantial heritability for gene expression and new estimation methods using marker data highlight the relevance of heritability in the genomics era.” (Visscher, Hill, & Wray, 2008, p. 255).

The concept of endophenotypes in the field of psychiatry was introduced three decades ago by Gottesman and Shields (Gottesman & Gould, 2003; Gottesman & Shields, 1973). The concept

has been initially labelled as such by John and Lewis (1966, see Flint & Munafò, 2007). Endophenotypes (the Greek word “endon” meaning “within”) were used to bridge the gap between genotypes and phenotypes and thereby facilitate the search for associations between genotypic and phenotypic variation. The term “gene” originated from the Danish botanist Wilhelm Johanssen (Johanssen, 1909); “genotype” thereby referring to the genetic constitution or the combination of a particular form of the gene, i.e. an allele, at a particular locus for an individual (Plomin, DeFries, McClearn, & McGuffin, 2008). Phenotypes can be defined as observable characteristics of an organism influenced by both, genetic and environmental, influences whereas endophenotypes are defined as “measurable components unseen by the unaided eye along the pathway between disease and distal genotype” (Gottesman & Gould, 2003, p. 636). An endophenotype can be of neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological nature. In order to determine the validity of an endophenotype, the latter must satisfy certain criteria (Gershon & Goldin, 1986; Gottesman & Gould, 2003; Gottesman & Shields, 1973):

- be associated with the disorder in the population,
- be heritable,
- be trait- as opposed to a state-dependent manifestation of the disorder,
- among affected relatives, who show the endophenotype, the prevalence of the disorder must be higher than among relatives who do not show the endophenotype, that is co-segregate within families, and
- among non-affected relatives the endophenotype must be found at a higher rate than in the general population.

1.1.1. The Endophenotype Concept in Psychiatry

The endophenotype concept held the promise to be particularly useful for psychiatric disorders. Using diagnostic entities as schizophrenia as phenotypes is however problematic due to their heterogeneous nature as well as the large number of potential etiological factors underlying these psychiatric disorders (Cannon & Keller, 2006) which altogether complicates the identification of causal factors. In an attempt to shift the focus from observable characteristics or symptoms of mental disorders to more proximal, refined and biologically valid characteristics, which are imperceptible to the naked eye, greater advances in the quest for the genetic basis of psychiatric disorders were expected (Gottesman & Gould, 2003). “Intermediate phenotypes”, as endophenotypes were also called (see Cannon & Keller, 2006, p.272, however also note that this terminology has not unanimously been agreed upon, see Flint, Timpson, & Munafò, 2014), were thought to be less complex in nature and serve as ideal pillars in bridging the gap from the genetic to the phenotypic side. Candidate endophenotypes for schizophrenia are illustrated in Figure 1 and include deficits in oculomotor function, which will be the focus in the current work.

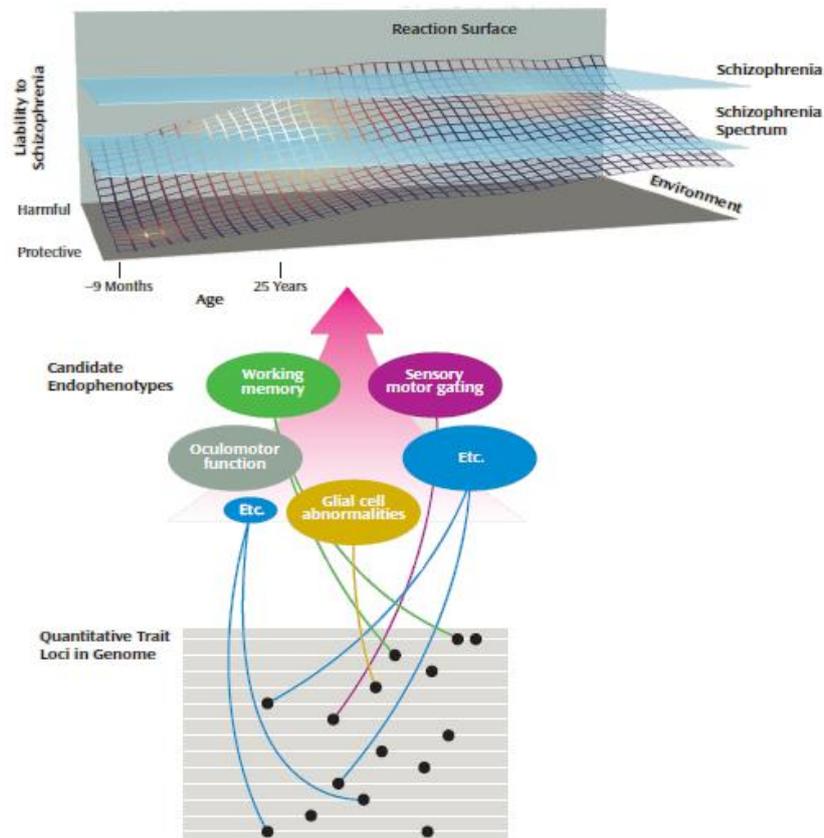


Figure 1 - The Endophenotype Concept, illustrated for schizophrenia.

Adapted from Gottesman and Gould (2003).

1.1.2. Imaging Genetics and the Endophenotype Concept

The search for finding associations between genotypic variation and psychiatric disorders eventually led to extending the nature of the phenotype to include imaging measures, the latter extension gave birth to the concept of imaging genetics. The endophenotype in this case originates from the “neurome” (see Figure 2), and can cover any neuroimaging phenotype such as brain structure, chemistry or functioning and is supposed “to be of greatest use in psychiatric genetics” (Cannon & Keller, 2006, p. 276). Support for this approach rests on the finding that 70% of the genes are expressed in the brain (Hariri & Weinberger, 2003) and are therefore likely to show direct influences at the level of the brain. The potential of using these brain

imaging phenotypes thereby lies in identifying pathways from gene action to increased risk for psychiatric disorders (Meyer-Lindenberg, 2010). This pathway (see Figure 2) starts with variation at the genetic level that is linked to behavioural variation via alterations in brain structure, chemistry or functioning. To reveal these pathways, it is however important to establish whether alterations in brain structure, chemistry or functioning are heritable at all. We put that assumption to the test in the current work.

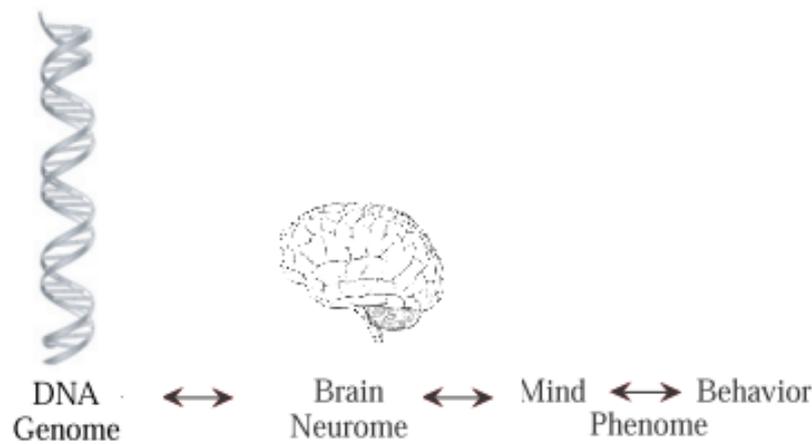


Figure 2 - From genome to phenome.

Adapted from Plomin et al. (2008, p. 285).

1.1.3. Heritability

The field of quantitative genetics evolved around the assessment of heritability. The latter dates back to Sir Francis Galton (1876) and rests on the assumption that if genetic influences are affecting variation on a quantitative trait, then phenotypic resemblance should increase with closer relatedness (Plomin, et al., 2008). Relatedness between individuals thus serves as a mean of identifying inter-individual variation. Quantitative genetics investigates the extent to which inter-individual differences are due to nature or nurture, that is, due to genetic or environmental

influences, yet does not specify the type of influence. Common disorders are seen as quantitative traits in the field of quantitative genetics (Plomin, Haworth, & Davis, 2009).

The amount of genetic influences is quantified by heritability estimates (h^2). Heritability can be defined as the proportion of the phenotypic variation ascribed to genetic differences (Plomin, Owen, & McGuffin, 1994; Tenesa & Haley, 2013). Indicating that a trait is “50% heritable” means thus that 50% of the variation among individuals is due to genetic influences.

Univariate heritability usually refers to the amount of additive genetic influences on one phenotypic trait. Bivariate or multivariate heritability extends this to the amount of shared genetic influences between two or more traits. Multivariate heritability facilitates finding pleiotropic genes that operate in phenomologically distinct disorders (Cannon & Keller, 2006). One way of assessing heritability is to use an experiment given by nature, the classical twin design.

1.1.4. The Classical Twin Design

The classical twin design is often called a natural experiment (e.g. Boomsma, Busjahn, & Peltonen, 2002). Two types of reared-together twins are studied in this design: monozygotic (MZ) or identical, who share 100%, and dizygotic (DZ), non-identical or fraternal twins, who share on average 50% of their segregating genes (the amount of genetic material that DZ twins receive from one parent fluctuates around 42-58% with a mean of 50%, it is therefore that DZ twins are said to share 50% of their genes, Visscher et al., 2007).

Similarity within twin pairs, that is between MZ twins and their co-twins and between DZ twins and their co-twins, is compared and the difference in the degree of similarity between MZ and DZ twins computed. Similarity is thereby expressed by a correlation coefficient and

can be interpreted as the “percentage of the total variation in a trait which is caused by factors shared by members of a pair” (Neale & Maes, 2002, p. 12). These twin correlations, r_{MZ} representing correlation between MZ twins and r_{DZ} representing correlations between DZ twins, can have arisen due to similarity in nature or nurture, that is due to similar genetic or similar environmental influences.

The classical twin design separates similarity between twins into the following components: (additive) genetic (abbreviated A), dominance-related (abbreviated D) or common environmental (abbreviated C) and unique environmental (the latter which includes measurement error, abbreviated E) components. The amount of genetic influences is estimated by h^2 . Heritability can be further differentiated into broad-sense heritability, referring to additive and non-additive sources of genetic influences, and narrow-sense heritability, referring to additive genetic influences. Additive genetic influences represent the sum of all effects from all alleles at all loci that affect a phenotype, explain the biggest part of genetic variations (Rijsdijk & Sham, 2002) and are the ones that we are estimating in the twin studies here. Genes however can act and interact in a variety of ways before their effects on the phenotype take effect; these influences are referred to as non-additive. There are two types of non-additive effects, those due to dominance (that is interaction between alleles at the same locus) and those due to epistasis (i.e. interaction between alleles at different loci). The classical twin design also specifies environmental influences. Sources of environmental influences can be separated into common and unique environmental influences. Common environmental influences are those influences that are shared between twins of a pair and include factors that make them more similar (e.g. child rearing methods or socio-economic status). Unique environmental influences refer to all influences that create differences between twins (e.g. unique childhood friends, accidents or different parental treatment, Plomin & Daniels, 1987). Clear unique environmental factors have proven to be difficult to define (Plomin, 2011).

1.1.4.1. Assumptions of Classical Twin Studies

Classical twin studies rely on a couple of assumptions in order to make valid inferences about the estimates representing genetic and environmental influences. These include the following:

- Equal Environment Assumption (EEA)
- Gene-Environment (GxE) interactions are of negligible influence for the trait under study
- “Biological typicality of twins” (Martin, Boomsma, & Machin, 1997, p. 390)
- Random mating (Rijsdijk & Sham, 2002)

1.1.4.1.1. Equal Environment Assumption

In classical twin studies, shared environmental influences are supposed to contribute to the correlation of both MZ and DZ twins as long as they are reared together. The equal environment assumption (EEA) refers to the hypothesis that MZ and DZ twins are equally correlated in their exposure to environmental events that are important for the phenotype under study. MZ and DZ co-twins share intrauterine environments to equivalent degrees, yet MZ more so than DZ twins. MZ twins for instance might be more likely to have common friends or be treated similarly due to their physical similarity (Cannon & Keller, 2006). If the EEA is violated, higher similarity in MZ as compared to DZ twins emerges; the latter which is usually attributed to genetic factors and therefore inflates the estimate of genetic influences at the cost of underestimating common environmental influences.

There are several ways to test the EEA. First, twin resemblance can be assessed, which could be understood in terms of receiving similar treatments from the environment due to physical similarity. There is one study that applied this method across the schizophrenia

spectrum (Kendler, 1983), wherein no evidence for a substantial influence of physical resemblance on trait resemblance was found. Note that as the spectrum of colours encompasses various colours like violet and red, the term “schizophrenia spectrum” harbours different disorders and non-clinical schizophrenia-phenotypes (see also Schizophrenia Spectrum Disorders). Different parental treatment could be expected due to variations in physical similarity between MZ and DZ twins, yet parental influence was found to account for only 2% of the variation in behaviour (Turkheimer & Waldron, 2000).

Another way to test for the EEA is given by examining the impact of perceived compared to true zygosity on phenotypic similarity in twins as suggested by Scarr (1968). More MZ (than DZ) twins consider themselves on average, wrongly, as DZ twins. These misjudgements are however not based on physical appearance but rather on at birth misinformed parental explanation. If MZ twins are indeed more similar in terms of certain phenotypes, then perceived zygosity should have an impact on twin similarity. No evidence for the impact of being considered a MZ or DZ twin on twin resemblance has been found so far for major psychiatric disorders (Kendler, Neale, Kessler, Heath, & Eaves, 1993).

1.1.4.1.2. Gene-Environment Interaction

Classical twin studies further assume no gene-environment (GxE) interactions, i.e. that the effect of the environment does not depend on the genotype. GxE interactions are specifically defined as:

“A GxE occurs when the effect of exposure to an environmental pathogen on health is conditional on a person’s genotype (or

conversely, when environmental experience moderates genes' effects on health)" (Moffitt, Caspi, & Rutter, 2005, p. 473).

In case this assumption is violated, genetic or unique environmental effects will be overestimated. In GxE interactions wherein the environmental factors are shared between twins, these will be (falsely) attributed to h^2 , in GxE interactions wherein the environmental factors are unique to twins, these will be (falsely) attributed to E (Rutter, 2006). The assessment of GxE interactions can be performed by measuring the environmental effect and including it into the modelling (Neale & Maes, 2002).

1.1.4.1.3. Biological Typicality of Twins

The twin design is only of use if results can be extrapolated to the general (non-twin) population. It is therefore necessary to establish whether twins and singletons are comparable. Given the pre- and perinatal circumstances of twin pregnancies, this can be denied. Twins are in general prematurely born (Buselmaier & Tariverdian, 2007) yet, have also been found to catch up on these drawbacks by the age of 5 years (Christensen, Vaupel, Holm, & Yashin, 1995).

1.1.4.1.4. Random Mating

Another assumption of classical twin studies is random mating in the population. Random mating refers to the common saying of "opposites attract", whereas non-random mating or assortative mating relates to the commonly known statement of "birds of a feather flock together". Non-random mating leads to an increase in the amount of shared genetic variation

between DZ twins (and siblings) which is on average 50% and biases the estimates obtained from these participants.

1.1.4.2. Falconer's Formula

A straightforward way of estimating heritability is given by Falconer's formula (e.g. Falconer, Mackay, & Frankham, 1996). Heritability is hereby based on twin correlations:

$$h^2 = 2(r_{MZ} - r_{DZ});$$

$$\text{with } r_{MZ} = h^2 + c^2 \text{ and } r_{DZ} = \frac{1}{2}h^2 + c^2$$

The common environmental and unique environmental contributions can be calculated as:

$$c^2 = r_{MZ} - h^2 \text{ and } e^2 = 1 - (h^2 + c^2)$$

(Rijsdijk & Sham, 2002).

All of the additive genetic and common environmental components are supposed to contribute to r_{MZ} , as MZ twins share their genetic background as well as their common environment. Half of the additive genetic and all of the common environmental components are supposed to contribute to the r_{DZ} , as DZ twins share on average 50% of their genetic background and, similar to MZ twins, 100% of their common environment. The unique environmental component is by definition uncorrelated between twins. Figure 3 illustrates these contributions in a path diagram for univariate twin modelling. P thereby represents the observed or measured phenotype in each twin of a pair (here labelled as P1 and P2). A, C and E represent the variance components and a, c, and e the path coefficients (see also Structural Equation Modelling). The path from A1 to A2 is set to unity (.50) for MZ (DZ) twins to indicate the amount of genetic

variation shared between twins. The path from C1 to C2 is set to unity to indicate the similarity in common environmental influences (see Equal Environment Assumption).

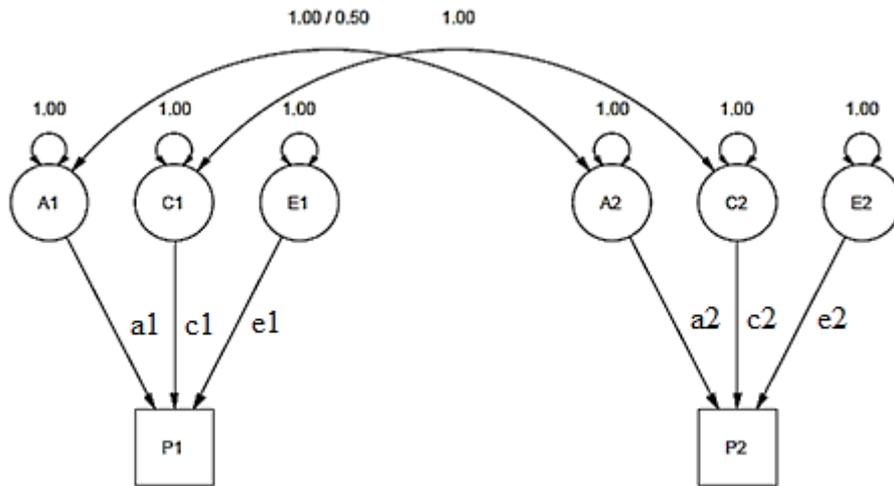


Figure 3 - Path diagram for univariate twin modelling.

P1 and P2 refer to the phenotype values in twins one and two of one twin pair, A, C and E (1 and 2 for twin one and two, respectively) refer to variance components for additive genetic, common environmental and unique environmental influences, respectively, a, c and e (1 and 2 for twin one and two, respectively) refer to the path coefficients for the respective components.

More sophisticated approaches such as twin modelling using structural equation modelling approaches are used today to test for heritability. These approaches also allow to test for sex differences in genetic effects (see Sex-limitation Modelling) and to incorporate multivariate data (see Structural Equation Modelling).

1.1.5. Structural Equation Modelling

Structural equation modelling (SEM) is rooted in (confirmatory) factor analysis and path analysis (Jöreskog, 1969; Schumacker & Lomax, 2004; Wright, 1920). The focus in this

analysis lies on modelling the variance-covariance structure of observed or measured variables and by using this data, estimate the underlying latent or unobserved variables. The overall aim of this approach is to minimize differences between the observed and expected (i.e. based on a model) variance-covariance structure. SEM results are usually depicted by path diagrams that follow certain conventions in how variables are represented. These conventions include that measured variables are shown in rectangles and latent or unobserved variables in circles. It is furthermore a convention to denote the paths in between variables as defining the connection strength between these variables. The single-headed arrows refer to variances and the two-headed arrows to covariances or correlations. Path coefficients (in lower case letters) along the paths correspond to the strengths of connectivity (Rijsdijk & Sham, 2002).

SEM calculations involve the following steps (Bollen & Long, 1993):

- Model formulation
- Model identification
- Model estimation
- Model evaluation and if necessary, modification.

1.1.5.1. Model Formulation

An application of SEM to the twin design is depicted in the path diagram in Figure 4.

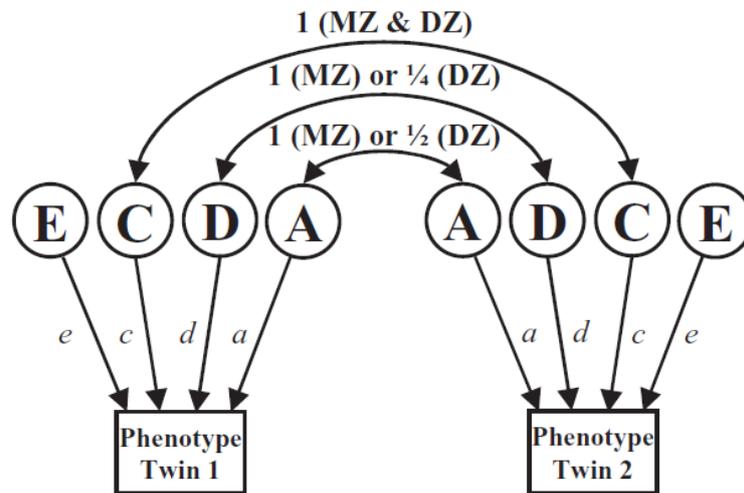


Figure 4 - Extended path diagram.

A, D, C, and E refer to variance components for additive genetic, dominance-related, common environmental and unique environmental influences, respectively, a, d, c and e refer to the path coefficients for the respective components, MZ=monozygotic, DZ=dizygotic twins. The paths between the additive genetic components indicate that MZ correlate at unity and DZ twins at .50 for additive genetic variation. The path between dominance-related components shows that MZ correlate at unity and DZ twins at .25 for dominance-related variation. The path between common environmental variance components shows that MZ and DZ twins both correlate at unity for common environmental influences as indicated by Rijdsdijk and Sham (2002).

The diagram depicted in Figure 4 cannot be estimated with reared-together twin data alone; rather an ACE or an ADE model can be specified. Scrutinizing twin correlations can help in determining which model to formulate. An ADE model is indicated by $r_{DZ} < \frac{r_{MZ}}{2}$ (Plomin, et al., 2008, p. 389), else an ACE model should be chosen. Figure 4 involves additive genetic, common environmental or dominance-related and unique environmental influences. The total variation in the phenotype can be rewritten as:

$$P = A + D + C + E$$

(Rijsdijk & Sham, 2002).

As indicated in Figure 4, MZ twins correlate perfectly for A, DZ twins correlate on average half. Dominance-related influences also correlate perfectly for MZ twins, and 25% for DZ twins. Common environmental influences correlate at unity for both MZ and DZ twins, as stated in the EEA, E influences are by definition uncorrelated between twins. The coefficients that indicate genetic and environmental relatedness between twins are represented by the two-headed arrows and indicate the correlations among variance components, r_g refers to the genetic correlation, r_d to the dominance-related correlation, r_c to the common environmental correlations and r_e to the unique environmental correlation (note that this applies to the multivariate case, wherein unique environmental effects can be shared between multiple phenotypes). The correlations among variance components indicate the strength of associations and can be interpreted as the degree to which the same additive genetic, dominance-related, common or unique environmental factors affect two or more traits.

1.1.5.2. Model Identification

Model identification is concerned with the plausibility of the model specified. The ACE and ADE models require that r_{MZ} is larger than r_{DZ} , that the covariance is positive and that there are as many values as there are parameters to be estimated. If these conditions are met, ACE/ADE models are said to be just “identifiable”. Identification of model parameters would be problematic if we were to estimate for instance, A, D, C, and E from reared-together twins, as the number of parameters we would want to estimate would be higher than the input statistics we would use to feed into the model, in that case the model is said to be “underidentified” (Neale & Maes, 2002).

1.1.5.3. Model Estimation

Model estimation is generally performed with statistical software packages which take the variance/covariance structure as input. The aim of model estimation is finding the best fitting parameter values for the variance components, in our case A, D or C, and E (Neale & Maes, 2002).

1.1.5.4. Model Evaluation and Modification

Parameter values obtained from model estimation are subsequently evaluated in terms of their fit, specifically the match between the obtained parameter values given by the input data and the expected values underlying the model that was specified. Model fit can be evaluated using several fit indices, the probably best known one being the likelihood-ratio test or χ^2 difference test (Neale & Maes, 2002). This test assesses the likelihood of obtaining the input data under the assumption that the parameter values that were provided during model estimation are true.

Acceptable fit is achieved if a p -value $>.05$ for a certain χ^2 value at a certain number of degrees of freedom (df) is obtained; it is then that the model can be considered to fit the data. In addition to fitting the data however, model fitting also aims to fulfil the criterion of parsimoniousness, that is finding the maximum fit with the maximum number of df possible (Plomin, et al., 2008). Parsimoniousness is partly indicated by the number of df, with a high number indicating more parsimoniousness. To increase parsimoniousness, components might be dropped from the model. By convention and common sense, the E component should be retained as this models measurement error as well and a model without error might realistically not fit the data well. Therefore, to further reduce the model, additive genetic, dominance-related or common environmental components could be dropped. Note, that after dropping components, models are generally compared to previously estimated ones. Evaluation between models is done by the difference (Δ) in χ^2 values, given by:

$$\Delta \chi^2 = \chi^2 \text{ constrained} - \chi^2 \text{ unconstrained},$$

whereby χ^2 constrained refers to the value of the constrained model (this could be an AE model, which assumes that similarity between twins is not due to common environmental influences for instance) and χ^2 unconstrained to that of the unconstrained model as for instance an ACE model (Cheung & Rensvold, 2002). Evaluation is also based on the difference in df between models, which is given by:

$\Delta df = df \text{ constrained} - df \text{ unconstrained}$,

again referring to the df of the constrained and the unconstrained model, respectively (Cheung & Rensvold, 2002). As the χ^2 tests depend on sample size, model fit is commonly evaluated by other goodness of fit indices, such as Akaike's Information Criterion (Akaike, 1987).

1.1.5.5. Sex-limitation Modelling

One benefit of SEM is the ability to model differences in heritability estimates between males and females. This can be accommodated in twin modelling through the inclusion of opposite-sex twin pairs. Qualitative or quantitative differences can emerge between genders, that is different genes can operate in males and females to influence a phenotypic trait or the same genes can act in both genders yet differ in strength of impact. The latter can be estimated using same-sex twins, the former requires the inclusion of opposite-sex twins into the classical twin design. Testing for qualitative differences is performed by modelling additive genetic effects separately for males and females and is also referred to as non-scalar sex-limitation modelling. Testing for quantitative differences, which is also called scalar sex-limitation modelling, is performed by allowing genetic effects to vary (as opposed to constrain them to be equal) across genders (Neale & Maes, 2002).

1.1.6. Summary Endophenotypes

The concept of endophenotypes is particularly useful to bridge the gap between genetic and phenotypic data and thereby facilitate the search for associations between genotypic and phenotypic variation. The use of endophenotypes to identify aetiological factors might be especially fruitful for psychiatric disorders which are assumed to be polygenic, that is caused

by multiple rather than single genetic variations, and under the influence of a large number of environmental factors (Cannon & Keller, 2006). One approach that relies on the endophenotype concept is imaging genetics. Imaging genetics uses endophenotypes that reflect brain structure or functioning to reveal aetiological factors of for instance psychiatric disorders. One of the main criteria for a valid endophenotype is its heritability, which can be estimated using the classical twin design. Latter makes use of the fact that MZ twins share all while DZ twins share on average 50% of their genetic variation. Similarity between MZ and DZ twins therefore allows us to estimate the amount of phenotypic variation that is due to genetic variation, also known as heritability. This estimation can be extended from univariate to multivariate, the former estimates the heritability of one trait, whereas the latter allows us to estimate multivariate heritability, that is the amount of genetic influences that are shared between multiple traits. The studies in chapter two and four make use of the classical twin design to estimate the amount of genetic influences. The study in chapter two estimates the univariate heritability of schizotypy as well as the multivariate heritability between schizotypy and the personality trait of neuroticism (see details in chapter two). The study in chapter four, in line with the concept of imaging genetics, estimates the amount of genetic influences on brain functioning.

1.2. Schizotypy

“An individual who displays the schizophrenic phenotype is considered to be a schizotype” (Rado, 1953, p. 410).

The following chapter provides a description of the construct of schizotypy on phenomenological, psychometric and neuro-cognitive levels. It will outline the definition of the construct of schizotypy, discuss its multidimensional nature and the factors that have been used to explain this multidimensionality. In addition, it will provide an overview of the theoretical accounts of the construct of schizotypy and its links to the schizophrenia spectrum. It will focus on the demographic and personality correlates of schizotypy and emphasize the association between schizotypy and the personality trait of neuroticism. Finally, it will consider the neurocognitive underpinnings of the construct of schizotypy and report on the advantages of studying schizotypy as a means of investigating the aetiology of schizophrenia.

1.2.1. The Construct of Schizotypy

The term “schizotype” originates from the term “*schizophrenic phenotype*”, which was originally used by Sandor Rado and later elaborated by Paul Meehl (Meehl, 1962; Rado, 1953) to characterize individuals with an underlying liability to develop schizophrenia. Characteristics of schizotypes include:

- Having unusual perceptions,
- Assigning significance to neutral events,
- Believing in magical abilities,
- Being suspicious,

- Showing little display of affect,
- Feeling highly anxious,
- Having impoverished social relations and
- An unusual use of language (Lenzenweger, 2010).

The list of characteristics already points to two main debates in the schizotypy literature: first, that schizotypy is not a unitary construct (Vollema & van den Bosch, 1995) and second and related to the first, that the precise number and quality of components to characterize the “*schizotype*” is diverse (Vollema & van den Bosch, 1995) and not well defined. The next sections will therefore refer to schizotypy as a multidimensional construct. Before dealing with the multidimensionality of the construct, it is important to get to the root of schizotypy and its theoretical background.

1.2.2. Theoretical Background to Schizotypy

Two main approaches comprise the theoretical background of schizotypy. One is the quasi-dimensional approach, put forward by Paul Meehl and colleagues, wherein schizotypy features are seen as dimensional, yet, as containing an indication for future psychopathology (Lenzenweger, 2010), hence the label quasi-dimensional. A second view considers schizotypy features as fully dimensional and is therefore addressed as the fully dimensional approach (Claridge & Beech, 1995; McCreery & Claridge, 1996). Proponents of latter view argue that, rather than functioning as a transitional construct indicative of future schizophrenia spectrum disorders, schizotypy features lie on a spectrum which covers “healthy” to “unhealthy” experiences and can therefore be found in the general population (e.g. McCreery & Claridge, 1996).

Both approaches are illustrated in Figure 5, which depicts the communality of both views, i.e. an underlying dimensional nature of schizotypy features. Both approaches share the notion that the expression of schizotypy traits in itself is not sufficient to indicate risk for psychopathology (Nelson, Seal, Pantelis, & Phillips, 2013; Rawlings, Williams, Haslam, & Claridge, 2008b). The quasi-dimensional view however makes predictions about the development of psychopathology, whereas the fully dimensional view remains neutral with regard to risk for future psychopathology in schizotypy.

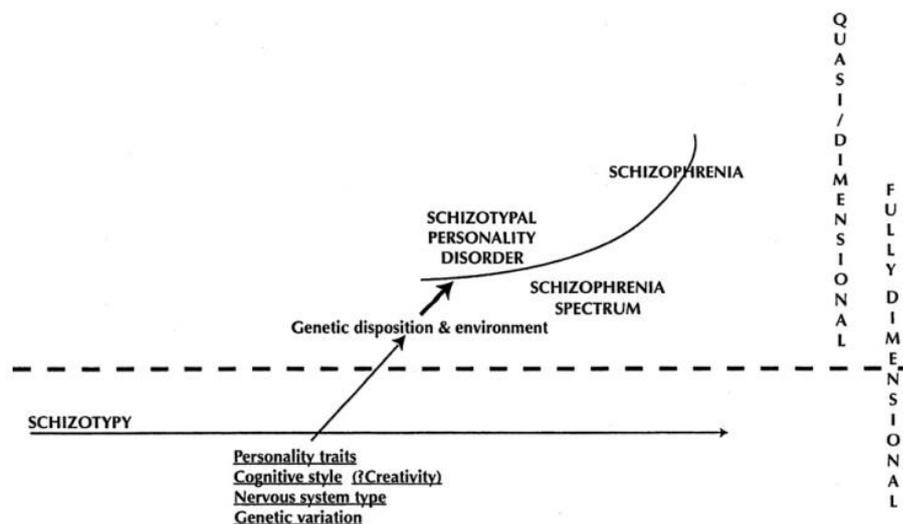


Figure 5 - Illustration of the quasi-dimensional and the fully dimensional view of schizotypy.

From Rawlings et al. (2008a).

1.2.2.1. Paul Meehl's Model of Schizotypy

Paul Meehl's account of schizotypy is based on clinical observations of Sandor Rado's work (1953). According to Rado, two cardinal features are present in the schizotype and define the schizotypal personality: pleasure deficiency and a proprioceptive (kinesthetic) diathesis, resulting in deviant perceptions of one's own body, which causes schizotypic body distortions (Lenzenweger, 2006). Rado further defined traits of the schizotype as schizotypal organization

and the behavioural manifestations as schizotypal behaviour (Lenzenweger, 2006). Meehl elaborated on this psychodynamically oriented view and proclaimed four core traits of schizotypy:

- Cognitive slippage
- Interpersonal aversiveness
- Anhedonia
- Ambivalence (Meehl, 1962).

Cognitive slippage is a mild form of loose association and can nowadays best be described as resembling thought disorder which at a behavioural level was thought to be detectable via neurocognitive measures such as eye tracking dysfunction (Lenzenweger, 2010). Interpersonal aversiveness would nowadays be conceptualised as social anxiety (Lenzenweger, 2010). Anhedonia, or a deficit in experiencing pleasure, was thought to play a major role in schizotypy, yet was later de-emphasized as a major aetiological component to the construct of schizotypy (Lenzenweger, 2010). Ambivalence draws back to the original core features of schizophrenia as noted by Eugen Bleuler, who described ambivalence as a “tendency of the schizophrenic psyche to endow the most diverse psychisms with both a positive and negative indicator at one and the same time” (Bleuler, 1950, p. 53) and refers, in short, to the capacity of simultaneously experiencing contradictory feelings and thoughts.

According to Meehl’s account, schizotypy is a disorder that originates from a Central Nervous System (CNS) abnormality called schizotaxia. The latter is a sine-qua-non for developing schizotypy and, in its decompensated form, schizophrenia. Prevalence rates of schizotaxia are, according to Meehl (1989), around 10% in the general population, with a smaller percentage developing some schizotypic disorder, e.g. .06-1.6% for Schizotypal Personality Disorder and .70-5.10% for Paranoid Personality Disorder (Lenzenweger, Lane,

Loranger, & Kessler, 2007). According to Meehl, schizotaxia leads to the development of clinical signs and symptoms via interactions with environmental (e.g. as social learning history) and genetic factors; the collection of mediating factors is what Paul Meehl called polygenic potentiators. Polygenic potentiators, e.g. personality features such as anhedonia and anxiety-proneness, might for the schizotypic population result in an enhanced risk for decompensation into schizophrenia (Lenzenweger, 2006). Genetic factors hereby include any kind of genetic variation that, given the presence of the schizotype and therefore the schizotypal personality organization, raises the likelihood of decompensation into schizophrenia. The account of schizotypy put forward by Paul Meehl is called quasi-dimensional as it is recognized that schizotypal traits are continuously distributed, yet there is a clear indication of risk for psychopathology.

1.2.2.2. The Quasi-Dimensional View of Schizotypy

Taxometric analysis (from Greek: “taxon”, meaning group) was initially created by Paul Meehl in order to resolve the disparity between dimensional and categorical profiles underlying important traits in psychiatric research (Haslam, Holland, & Kuppens, 2012). Current research failed to replicate a taxometric structure of schizotypy though. Rawlings et al. (2008b) reviewed taxometric studies and reanalysed data from studies that used taxometric analysis methods and did not replicate a taxometric structure of schizotypy. Reasons why previous studies were successful in producing results supporting a taxometric structure in schizotypy were the use of small sample sizes or of preselected (clinical) samples, which are not representative of the general population, and the use of skewed data that could have biased interpretation of the data as having a taxometric structure (Haslam, et al., 2012; Rawlings, et al., 2008b).

1.2.2.3. The Fully Dimensional View of Schizotypy

A different approach to schizotypy is given by the fully dimensional approach put forward by Gordon Claridge and colleagues (Claridge & Beech, 1995; Rawlings, et al., 2008b). The fully dimensional approach describes schizotypy features as lying on a spectrum that spans across the general population as opposed to the quasi-dimensional approach, which refers to a small proportion of the population. As shown in Figure 5, the fully dimensional approach emphasizes the dimensional nature of schizotypy. Support for the fully dimensional approach can be derived from work supporting the presence of schizotypy dimensions in the general population (Linscott & van Os, 2010; Verdoux & van Os, 2002; Verdoux, van Os, et al., 1998) and thereby indicating that schizotypy might rather be a feature present across the general population as opposed to being present in only a part of the population.

1.2.3. The Multidimensionality of Schizotypy

The multidimensionality of the schizotypy construct was first mentioned by Jean Chapman and colleagues (see e.g.: Chapman & Chapman, 1980; Vollema & van den Bosch, 1995). The term psychosis-proneness as a synonym for schizotypy was introduced subsequently, partly to reflect the fact that there is more than one component to the construct of schizotypy (see e.g. Chapman's Psychosis-Proneness Scales; Claridge et al., 1996). The broader construct of psychosis-proneness in fact embraces the construct of schizotypy (Giakoumaki, 2012), just as the psychiatric disorder cluster of psychosis embraces schizophrenia (American Psychiatric Association, 2000). In line with the characteristics introduced previously, various traits have been used to describe the phenomenology of schizotypy. Vollema and van den Bosch (1995) for instance reviewed schizotypy inventories and concluded that “schizotypy is a multidimensional construct consisting of three to four factors” (p. 19). They suggested the following factors:

- Positive schizotypy
- Negative schizotypy
- Disconformity and impulsivity and
- Cognitive disorganization and social anxiety

(Venables & Bailes, 1994; Vollema & van den Bosch, 1995).

Today, there is consistent evidence to support the multi-factorial nature of schizotypy (Claridge, et al., 1996; Raine et al., 1994; Wuthrich & Bates, 2006), yet inconsistent evidence as to the precise number of factors. Factor analytical studies investigated the factorial structure of schizotypy and reported evidence for a two factor, that is positive and negative schizotypy (e.g. Kwapil, Barrantes-Vidal, & Silvia, 2008), a three factor, that is positive, negative and disorganization-related features (Bentall, Claridge, & Slade, 1989; Compton, Goulding, Bakeman, & McClure-Tone, 2009) and a four-factor solution, that is positive, negative, disorganization-related and non-conformity-related features (Mason, Claridge, & Jackson, 1995; Rawlings, Claridge, & Freeman, 2001). Factors tend to overlap but the precise number of factors is said to depend largely on the scales used to describe the construct in various studies; the Schizotypal Personality Questionnaire (SPQ) for instance is said to be over-represented in studies assessing schizotypy (see e.g. Cicero & Kerns, 2010; Stefanis et al., 2004).

According to the review by Vollema and van den Bosch (1995), one factor that describes schizotypy is positive schizotypy, which covers aberrant perceptual experiences and unusual beliefs. Examples of aberrant perceptions are, for instance, altered sensations and perceptions of one's own body and the external world, hypersensitivity to sounds and smells, heightened sensitivity to the external environment, auditory hallucinations and pseudo-hallucinations (Mason, et al., 1995). Examples of unusual, magical beliefs include the

conviction that one's thoughts alone can influence or manipulate the environment. Eckblad and Chapman (1983) used the following definition to capture the feature of magical beliefs: "belief in forms of causation that are inconsistent with conventional standards" (p. 215). Aberrant perceptual experiences and magical beliefs are often described as representing the "unique, necessary element in the disposition to psychosis" (Claridge, et al., 1996, p. 113). This factor of schizotypy relates to the previously mentioned characteristics of "oddities in perception", "magical abilities", "suspiciousness" and "assigning significance to neutral events". It is labelled "positive" schizotypy as experiences and thoughts are added to the repertoire of "healthy" human functioning.

The second factor in schizotypy research is negative schizotypy ("negative" in the sense of reduced feelings, experiences and thoughts as compared to those found on average in the "healthy" general population). Negative schizotypy includes characteristics such as physical and social anhedonia (coming from Greek: "an" = "without" and "hedone" = "pleasure"). Physical and social anhedonia refer to a lack of enjoyment derived from physical pleasure or social interactions together with a preference for independence and solitary activities (Vollema & van den Bosch, 1995). Negative schizotypy can be captured by characteristics such as "little display of affect", "high anxious feelings" and "impoverished interpersonal relations". Negative schizotypy is linked to a reduced amount of affective responses in the absence of a total lack of emotional distress (Kwapil, Brown, Silvia, Myin-Germeys, & Barrantes-Vidal, 2012). Social and physical anhedonia indicated vulnerability to psychosis in college and community populations before (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994). Kendler et al. (1996) for instance showed that social anhedonia can separate relatives of individuals with schizophrenia from controls in a community adult sample. Similarly, physical anhedonia levels differentiate between relatives of schizophrenia patients and controls (Katsanis, Iacono, & Beiser, 1990). Moreover, physical anhedonia scores tend to be higher in

family members of schizophrenia patients with severe anhedonic symptoms (Berenbaum & McGrew, 1993; Fanous, Gardner, Walsh, & Kendler, 2001).

A third factor of schizotypy, according to Vollema and van den Bosch (1995), relates to cognitive disorganization and social anxiety. This factor is expressed by difficulties in attention, concentration and decision-making, alongside with moodiness and social anxiety (Vollema & van den Bosch, 1995). An example from the aforementioned list is “unusual use of language” for instance. The existence of both social and cognitive features in one dimension is intuitively peculiar (see Venables & Bailes, 1994, p. 292). It has been argued that cognitive disorganization precedes social impairments via a lack of communicative skills; this is at least true for schizophrenia (Venables & Bailes, 1994). Given that schizotypal characteristics and therefore both cognitive disorganization and social anxiety are usually assessed cross-sectional, it is not surprising that both co-occur.

A fourth factor which was extracted by Vollema and van den Bosch (1995) describes disconformity and impulsivity such as expressed in violent, (self-) abusive and reckless behaviours. The existence of this factor was taken as an indicator for the extension of schizotypy factors outside of the schizophrenia spectrum and led to a change in nomenclature from schizotypy to psychosis-proneness (Claridge, et al., 1996).

The number of factors derived in all of these studies is critically dependent on the data that is entered into the analysis. The dominant method used in most studies is principal component analysis (PCA) or exploratory factor analysis. Considering that the number of factors is determined by the data that is entered, it is not surprising that different studies produced similar but not completely overlapping results. The review by Vollema and van den Bosch is an important piece of work in that respect. Overall, the evidence points to a multi-

factorial nature of schizotypy, with the number of factors explaining variation in schizotypy scores ranging from two to four in the majority of studies.

1.2.4. Assessment of Schizotypy

There are numerous measures for assessing schizotypy (Bentall, Claridge, & Slade, 1989). Categories of these measures are based on the input that was used to construct the scales represented in these measures. These are the relevant categories for the current work:

- Symptom-based measures such as e.g. the Psychosis-Proneness Scales (PPS) or the Rust Inventory of Schizotypal Cognitions (RISC, Rust, 1988) and
- Syndrome-based measures such as e.g. the SPQ (Raine, 1991).

In line with the inventories used in the studies presented here, examples for the symptom- and the syndrome-based approach will be given. Despite their different theoretical roots, all these approaches conceptualize schizotypy as dimensional (Vollema & van den Bosch, 1995). The symptom-based scales allow the freedom to focus on certain dimensions of schizotypy and to investigate those more closely. The syndrome-based scales benefit from the fact that scale construction was based on covering the whole construct in one scale (it is therefore probably not surprising that the SPQ is said to be over-represented in schizotypy research).

1.2.4.1. The Psychosis-Proneness Scales

The PPS or Chapman Scales form one of the first attempts to assess schizotypy by self-report (Chapman et al., 1984; Chapman, Chapman, & Raulin, 1976, 1978; Chapman, Edell, & Chapman, 1980; Eckblad & Chapman, 1983). Psychosis-proneness is thereby supposed to reflect the sum of all possible psychosis-related features, including affective and impulsive

features (Claridge, et al., 1996). The scales are made up of four subscales and were guided by experiences and behaviours sampled from the non-clinical general population. Items for each scale were selected based on high item-scale correlations and low correlations with measures of social desirability. Psychometric properties of the scales were good with internal consistency measures of Cronbach's alpha $\sim .80$ and test-retest reliabilities between $.75$ and $.85$. Items are answered in a true/false response format and are usually administered intermixed with items from the several scales. The Psychosis-Prone Scales are:

- Perceptual Aberration and Magical Ideation scale
- (Revised) Social Anhedonia scale
- (Revised) Physical Anhedonia scale
- Hypomania and Impulsive-Nonconformity Scale

The Perceptual Aberration and Magical Ideation scales used to be separate scales (Chapman, et al., 1980; Eckblad & Chapman, 1983). Former scale taps schizophrenic-like perceptual distortions of the external world and the self, e.g. one's own body (a sample item from this scale is: "Occasionally I have felt as though my body does not exist."). This scale is made up of 35 items. The Magical Ideation scale was used to assess beliefs in irrational, mystic and magical forms of causation that are viewed as such by current cultural conventions (a sample item from this scale is: "I think I could learn to read other people's minds if I want to."). As both scales correlate highly with each other, i.e.: $.68-.70$, they have been combined into one, the Perceptual Aberration/Magical Ideation scale (e.g. Chapman, Chapman, Kwapil, et al., 1994).

The Revised Social Anhedonia scale contains 40 items and assesses indifference to social situations independent of social anxiety (Eckblad, Chapman, Chapman, & Mishlove, 1982). A sample item here would be: "I prefer hobbies and leisure activities that do not involve

other people”. The Revised Physical Anhedonia Scale consists of 61 true/false items that ask about sensory pleasures of any kind of physical activity such as eating or touching (Chapman, et al., 1976). Sample items here include: “I seldom care to sing in the shower”. Both scales tap the construct of anhedonia, a construct specified by a lack of or the presence of constricted or inappropriate affect. Both scales are usually used to describe negative schizotypy, yet frequently load onto different factors (Venables & Bailes, 1994).

The 51-item Impulsive Nonconformity Scale was designed to measure failures to conform to social norms and values alongside with a lack of empathy for the pain of others and a behavioural style dominated by impulsivity (Chapman, et al., 1984). Sample items here include: “I usually find myself doing things ‘on impulse’”. Finally, the Hypomania scale was developed as a tool to identify individuals at risk for bipolar disorders and separate these from the heterogeneous samples of psychosis-prone individuals (Eckblad & Chapman, 1986). The scale contains 48 items that assess features of hypomania-like traits such as an enhanced sociability, ambitiousness, speeded mood, increased energy and perceived uniqueness. Sample items include: “Sometimes ideas and insights come to me so fast that I cannot express them all” or “I would rather be an ordinary success in life than a spectacular failure” (scored in reverse).

1.2.4.2. The Schizotypal Personality Questionnaire

Adrian Raine’s measure can be considered a syndrome-based approach to assessing schizotypy. The SPQ is based on the symptoms of SPD as stated in the Diagnostic and Statistical Manual of Mental Disorders (*DSM-III*; American Psychiatric Association, 1987). Not surprisingly, therefore, it results in a three factor structure containing dimensions of reality distortion, negative symptoms and disorganization. Reality distortion covers unusual

perceptions, ideas of reference and magical beliefs, negative symptoms cover features such as constricted affect and disorganization that covers features such as eccentric odd speech (Raine, 1991). The questionnaire has good psychometric properties with high test-retest reliability (.82) and criterion validity (.68; Raine, 1991).

An advantage of the SPQ is that it was designed to capture other features of negative symptoms such as constricted affect and diminished social contacts (Venables & Bailes, 1994). The over-representation of the SPQ in the assessment of schizotypy (Venables & Bailes, 1994) is well-justifiable, as this scale is one of the few questionnaires which is based on diagnostic criteria, comes in a manageable format with 74 items (compared to the PPS, who is made up of >200 items) and most importantly covers the whole construct rather than single factors.

1.2.5. Schizotypy and Personality

One approach to the establishment of the construct of schizotypy is based on the assessment of differences (i.e. discriminant validity) and communalities (i.e. convergent validity) with existing personality constructs (Eysenck & Barrett, 1993). Hans Jürgen Eysenck initially investigated links between personality traits and schizotypy in an attempt to subsume schizotypy as part of the core traits of personality and thereby potentially allow us to conclude that schizotypy is no more than a facet of these. Originally, Eysenck's concept of personality was dominated by extraversion and neuroticism; psychoticism was later added as a third core trait in order to capture personality variation underlying psychosis (Eysenck, 1992). The construct of schizotypy however proves to be stable irrespective of whether personality traits such as extraversion, neuroticism or psychoticism are included in factor analyses (Claridge, et al., 1996). Extraversion as one core trait of personality is, in short, characterized by high sociability and impulsiveness (Eysenck & Eysenck, 1963). Neuroticism, which will be of

discussed in chapter two and three, is illustrated in Slater (1943), who talks about the “neurotic constitution”. He describes soldiers’ “neurotic symptoms”, who had been admitted to hospital after a brief period of service as follows:

“... the commonest symptoms were those of anxiety, hysteria, depression, hypochondriasis, etc., and tended to be shown by members of all diagnostic groups...The monotonous character ... was mirrored by a monotonous uniformity of the underlying personality. There were few who did not show to some degree a psychic asthenia, a feebleness of will and purpose, coupled with tendencies to worry, pessimism and moodiness or hysterical traits” (p. 1).

Eysenck’s concept of neuroticism relied on the descriptions of Slater (Eysenck, 1947) and will be applied throughout the studies reported here. Characteristics of neuroticism include high tension, irritability, dissatisfaction, shyness, low mood and self-confidence, emotional reactivity and solicitude (Eysenck & Eysenck, 1964). Given the focus in the studies reported subsequently, only neuroticism will be discussed here.

Neuroticism has consistently been linked to schizotypy (Barrantes-Vidal, Ros-Morente, & Kwapil, 2009; Ettinger et al., 2005). Barrantes-Vidal and colleagues (2009) for instance assessed the links between neuroticism and schizotypy and schizophrenia and concluded that “neuroticism is etiologically relevant for schizophrenia-spectrum psychopathology” (p. 303), thereby extending the importance of this personality trait to the whole schizophrenia spectrum.

Indeed, high levels of neuroticism have been found across the whole schizophrenia spectrum. For instance, schizotypal personality disorder was frequently associated with high levels of neuroticism (e.g. Blais, 1997; Costa & McCrae, 1990). Neuroticism was found to be

the strongest predictor of psychosis (Odds ratio (OR): 1.16), controlled for anxiety or depression levels (Krabbendam et al., 2002) and controlled for childhood adversity and comorbid mental illnesses (Goodwin, Fergusson, & Horwood, 2003). Additionally, neuroticism acts as a predictor of relapse in psychosis (Gleeson, Rawlings, Jackson, & McGorry, 2005). Depressed mood perpetuates the risk for psychosis given the presence of hallucinatory experiences (Krabbendam & van Os, 2005).

By taking a closer look at the nature of the association between neuroticism and schizotypy, it was revealed that, specifically positive schizotypy (e.g. features such as perceptual aberrations and magical thinking) is associated with neuroticism (Ross, Lutz, & Bailey, 2002). Kendler and Hewitt (1992) for instance found a correlation of .47 between positive features of schizotypy and neuroticism. Similarly, Claridge et al. (1996) examined a whole range of schizotypy measures and found substantial correlations between measures of positive features of schizotypy (as assessed by the Chapman Scales) and neuroticism ($r > .30$). More recent work confirmed the previously discovered associations (Missinne & Bracke, 2012; Rijdsdijk, Gottesman, McGuffin, & Cardno, 2011). However, neither of the previous studies has examined the nature of the association between (positive) schizotypy and personality in detail going beyond merely assessing correlations. This will be addressed in chapter two.

1.2.6. Schizotypy and its Heritability

Before investigating the nature of schizotypy and its correlations to personality traits, it is important to establish if schizotypy is genetically influenced. There is evidence for substantial genetic influences on the whole construct of schizotypy, with heritability estimated at 50-67% (e.g. Jang, Woodward, Lang, Honer, & Livesley, 2005; Kendler & Hewitt, 1992; Linney et al., 2003). These seem to be similar across features of the construct with positive schizotypy

showing 32-40% (Hay et al., 2001; Miller & Burns, 1995) and negative schizotypy showing 27-45% of genetic influences (Hay, et al., 2001; MacDonald, Pogue-Geile, Debski, & Manuck, 2001). Heritability estimates obviously vary depending on how much of the construct is captured and how much h^2 each of the dimensions contributes. The study outlined in chapter two deals with the heritability of schizotypy features and its link with neuroticism in more depth (see chapter two for details on the heritability of schizotypy).

1.2.7. Schizophrenia Spectrum Disorders

“...the symptoms of schizophrenia are not specific only to schizophrenia but are related to other human behaviours through continua” (Strauss, Carpenter, & Bartko, 1974, p. 64).

Various psychotic disorders are included in the schizophrenia spectrum, amongst them those of schizophrenia and schizotypal personality disorder, upon which we will focus in the following paragraphs. For reasons of completeness, other psychotic disorder will be briefly introduced in the following paragraphs as well. The category of psychotic disorders, according to the *DSM* at least, harbours clinical syndromes such as schizophrenia, as well as schizoaffective and delusional disorder. The category of personality disorders specifies three psychosis-based personality disorders: paranoid, schizoid and schizotypal personality disorder (*DSM-IV-TR*; American Psychiatric Association, 2000). Schizotypy builds on the definition of schizophrenia. It needs to be stressed however that the participants involved in the empirical studies presented here are derived from the general, non-hospitalized, population.

1.2.7.1. Schizophrenia

Two cardinal figures are linked with the term “Schizophrenia”: Kraepelin in 1919 (Kraepelin, 1971) and Bleuler in 1908 (Bleuler, 1950). The recognition of psychotic disorders as a group of disorders with similar symptoms dates back to Bleuler, who referred to a “disease group” (Bleuler, 1924, p. 373). Symptoms of schizophrenia can be categorized as positive or negative symptoms, “positive” meaning that these symptoms add experience to the regular repertoire of perceptions and experiences and “negative” meaning that these symptoms lack features of the regular repertoire of experiences and behaviour. Positive symptoms of schizophrenia include:

delusions and hallucinations (American Psychiatric Association, 2000; Crow, 1980a, 1980b). Negative symptoms of schizophrenia consist of apathy, blunted affect, alogia, avolition and anhedonia (American Psychiatric Association, 2000; Crow, 1980a, 1980b). It has been argued that this dichotomization of symptoms is overly simplistic (Liddle, 1987). Symptoms are nowadays thought to be tripartite. In addition to the positive or cognitive-perceptual (e.g. delusions and hallucinations) and negative or interpersonal (e.g. anhedonia) cluster, a third cluster has been added, labelled the disorganization syndrome (Liddle, 1987). The latter includes bizarre behaviour and speech, formal thought disorder, inappropriate affect (such as laughing at bad news) and attentional difficulties (American Psychiatric Association, 2000; Venables & Bailes, 1994).

With a lifetime prevalence rate of 1% across all cultures, an onset during the late teens or early twenties and a tendency for chronicity, schizophrenia is a devastating long-lasting disorder that costs 1.5-3% of the total national health care system (Kessler et al., 2005; Knapp, Mangalore, & Simon, 2004). The disorder is unevenly distributed between genders. Males tend to withdraw more frequently and show greater level of social isolation possibly due to less developed social interaction skills prior to the age of onset (Häfner, 2003), whereas females tend to express lower levels of the deficit syndrome, that is less negative symptoms, which altogether indicates a more severe course and poorer outcomes in males (Carpenter, Heinrichs, & Wagman, 1988; Goldstein, 1988).

1.2.7.2. Schizoaffective and Delusional Disorder

The co-occurrence of affective symptoms together with psychotic symptoms has been formalized in the diagnostic criteria of schizoaffective disorder (American Psychiatric Association, 2000). Diagnosis requires patients to fulfil the criteria of schizophrenia as well as

those of depressive or manic episodes. However, the reliability and clinical utility of the diagnosis has been questioned before (Wilson, Nian, & Heckers, 2014). It has also been suggested that schizoaffective disorder should rather be assigned to affective than psychotic disorders however evidence from systematic reviews shows that schizoaffective disorder and schizophrenia are more similar in terms of demographic features (e.g. marital status, years of education, number of hospitalizations, years of illness) than schizoaffective and affective disorders are (Pagel, Baldessarini, Franklin, & Baethge, 2013), favouring the inclusion of schizoaffective disorders to the schizophrenia spectrum.

The diagnosis of delusional disorder is given when non-bizarre delusions have been present for at least one month; hallucinations, auditory, visual, olfactory or tactile in nature might be present but have to be linked to the delusion (American Psychiatric Association, 2000). The symptom structure of delusional disorder has been found to be composed of dimensions similar to schizophrenia and cover paranoia, cognitive deterioration, schizoid as well as affective features. In delusional disorder however, paranoia and affective symptoms were said to be at the forefront (de Portugal et al., 2013).

1.2.7.3. Schizotypal Personality Disorder

Schizophrenic patients' treatment is generally stationary, which allowed psychiatrists and staff members to observe patients' families. The definition of schizotypal personality disorder arose from the observation that relatives of schizophrenia patients show schizophrenia-like symptoms (Kety, Rosenthal, Wender, & Schulsinger, 1968) and was included in the *DSM-III* and *DSM-IV* (American Psychiatric Association, 1987, 2000). SPD is said to lie on a dimension between schizotypy in healthy populations and full-blown psychotic disorders (Nelson, et al., 2013) which further substantiates a spectrum view of schizophrenic disorders.

1.2.7.4. Paranoid and Schizoid Personality Disorder

Paranoid personality disorder is characterized by pervasive suspiciousness and distrust which are expressed in adolescence and persist into adulthood (American Psychiatric Association, 2000). The reliability and validity of the diagnosis of paranoid personality disorder however has been called into question which partly explains why there is little research today focussing on paranoid personality disorder despite its inclusion into the *DSM* from the first *DSM* edition on (Triebwasser, Chemerinski, Roussos, & Siever, 2013).

Similar to paranoid personality disorder, the construct validity of schizoid personality disorder has been questioned (Hummelen, Pedersen, Wilberg, & Karterud, 2014). The term “schizoid” was elaborated on by Kretschmer (1921) to characterize individuals who present with blunted affect and appear aloof and indifferent to interpersonal stimuli. Kretschmer stressed the similarity between these traits to symptoms of schizophrenia and mentioned that this similarity might have its origin in common brain pathology. Features nowadays are supposed to occur in adolescence and include social detachment, withdrawal, and restricted display of emotions (American Psychiatric Association, 2000).

1.2.8. The Continuum Model

Research on perceptual aberrations in healthy individuals dates back to Sidgwick, Johnson Myers, Podmore and Sidgwick (1894) who found that 9.9% of individuals reported full-blown hallucinations in a sample of 17,000 people. These findings have since then been replicated. For instance, Posey and Losch (1983) showed that 71% of students reported having experienced brief auditory hallucinations in wakeful situations. Hanssen et al. (2005) reported an incidence of positive subclinical psychotic experiences that is higher than the 10% incidence assumed by Paul Meehl in a Dutch population. Similarly, Verdoux et al. (1998) assessed experiences that mimic hallucinations and delusions (with items such as “Do you ever feel as if there is a conspiracy against you?”, “Do you ever feel as if people are looking oddly at you?”, or “Do you ever think that people can communicate telepathically?”) and found an item endorsement of 5 to 70%. Overall, roughly half of the participants (46.9%, N=462), who had never been diagnosed with a psychiatric disorder, believed in telepathic communication, 25.5% in being persecuted and 4.8% in hearing voices (Verdoux, Maurice-Tison, et al., 1998). In short, there is consistent evidence showing that schizophrenia-like features are present in the general population.

Findings as these have led to a change in the way schizophrenia is perceived. The International Schizophrenia Consortium (2009) indicated for instance that schizophrenia can be viewed as physical conditions such as diabetes or heart disease. This continuum view of psychotic disorders involves a multi-factorial aetiology to the disease, with multiple genetic and environmental risk factors (Allardyce, Suppes, & van Os, 2007; International Schizophrenia Consortium, 2009). Several studies favour such a view. For instance, increased levels of schizotypy and schizotypal traits were found in first degree relatives of schizophrenia patients (Kendler, 1985; Kendler & Walsh, 1995). The same picture emerges for offspring of schizophrenic patients, who show higher levels of schizotypal traits (Tienari et al., 2003) and

schizotypal personality disorder than the prevalence rate found in the general population (Baron, Gruen, Asnis, & Lord, 1985; Kendler et al., 1993). Thus, schizotypy and schizophrenia might, just as siblings belong to the same family, originate from the same source, at least at the phenotypic level.

1.2.9. The Schizophrenia Spectrum and its Neural Correlates

What about the link between schizophrenia and schizotypy at the level of the “neurome”? Briefly, the main deficits found in schizophrenia have been focussing on reduced activation in the frontal areas, hence the term “hypofrontality”. Findings on the functional differences across the schizophrenia spectrum, including schizotypy, are however mixed. The next sections will therefore outline functional aberrations across the spectrum to provide an introduction to the fMRI findings discussed in the empirical chapters. The following paragraphs summarize functional evidence in various tasks to assess the neural correlates underlying the schizophrenia spectrum and its features, the following chapter (on the antisaccade task) will specifically focus on the functional evidence using the antisaccade task that has been gathered across the spectrum.

1.2.9.1. Spectrum Disorders - Functional Evidence

In schizophrenia, deviations in prefrontal cortex functioning are most prominent (Hill et al., 2004). Different symptoms of schizophrenia seem to be related to different brain areas, with negative associations found for positive symptoms and blood flow in right temporal areas, for symptoms of disorganization and blood flow in left dorso-lateral prefrontal cortex (DLPFC) and right temporo-occipital areas and for negative symptoms and blood flow in bilateral

occipital areas (Liddle et al., 1992). Symptom-specific links seem to cover areas in frontal, temporal and occipital cortical areas. Frontal areas were initially probed with tasks such as the Wisconsin Card Sorting Test (WCST), which revealed decreased left as well as increased right prefrontal activation in the schizophrenia spectrum (Buchsbaum et al., 1997) and thereby indicated an irregular pattern of activation at frontal sites and supporting the notion of hypo- as well as hyperfrontality. Increased medial frontal activation has also been reported across the spectrum in schizotypal personality disorder during a verbal learning task (Buchsbaum et al., 2002). Increased activation might be interpreted as a compensatory mechanism to e.g. disruptions in prefrontal-subcortical circuitries. Schizotypal personality disorder patients seem to place intermediate between healthy controls and schizophrenia patients, both patient groups however demonstrate similar impairments in superior temporal gyrus, prefrontal cortex and the thalamus (Buchsbaum, et al., 2002; Siever & Davis, 2004). Studying populations across the spectrum like those with schizotypal personality disorder can give insight into the “protective” mechanisms that operate in SPD and might point to the factors that protect SPD patients from transgression to schizophrenia. Protective candidate areas hereby include the hippocampus and amygdala (Mohanty et al., 2005) and sub-regions of the prefrontal cortex (Buchsbaum, et al., 2002).

Some differences in activity patterns however were reported to be state- rather than trait-dependent and to remit with treatment (Spence, Hirsch, Brooks, & Grasby, 1998) pinpointing to difficulties such as treatment effects which are encountered when assessing functional deviations in schizophrenic patient populations. It might therefore be useful to take findings from the schizotypy literature into account to approach the aetiology of brain pathology in schizophrenia.

1.2.9.2. Schizotypy - Functional Evidence

Evidence from functional magnetic resonance imaging (fMRI) used a broad range of tasks to probe brain activation and link that with schizotypy (note that the method of fMRI will be discussed in depth in the section on fMRI). Schizotypy, as mentioned previously, refers to an attenuated form of schizophrenia-like features that are present in the general population, whereas the psychosis-proneness relates to the whole cluster of features that are present in a wide range of psychoses; schizotypy is therefore thought to be a specific construct within the frame of psychosis-proneness (Giakoumaki, 2012). Studies here can be differentiated based on the measures they used to assess schizotypy, i.e. whether they relied on symptom- or syndrome-based measures.

1.2.9.2.1. Symptom-based Measures

Corlett and Fletcher (2012) used a causal learning task in order to reveal links between schizotypy (as assessed with the PPS and Peters et al. Delusions Inventory, PDI, N=18). The task, a food-allergy causal learning task, wherein participants were asked to predict whether a patient would develop an allergy upon eating certain types of food, was preceded by a sequence of trials. In this sequence, it was shown if a certain type of food would predict an allergy or not. These trials however contradicted each other. The participants' responses throughout these trials were summed up to calculate a measure of predictive confidence. Healthy participants reporting unusual beliefs showed a relative attenuation of brain responses to events that, on the basis of prior experience, ought to be relatively surprising. Unusual beliefs were linked to variation in right frontal prediction error signal. Activation in the striatum was negatively associated with positive schizotypy, specifically magical thinking. Findings in both areas were thought to be in line with findings from the schizophrenia spectrum, providing evidence for an

approach that includes schizotypy as well as for the implication of the striatum and frontal areas in positive features such as unusual beliefs (Corlett & Fletcher, 2012).

Soliman et al. (2005) similarly investigated the striatum and its role in schizotypy. These authors assessed stress-induced patterns of brain activation and their association with positive (perceptual aberration, N=9) or negative schizotypy (physical anhedonia, N=7) or healthy controls (N=10). Upon stress induction, the negative schizotypy group in particular showed a significant increase in dopamine release in the striatum. The latter finding is in contrast to Corlett and Fletcher, who found association with positive schizotypy, yet highlights a dysfunctional pattern of activation in the striatum in schizotypy in general. Soliman et al. however relied on perceptual aberrations to operationalize positive schizotypy, not magical thinking (as Corlett & Fletcher, 2012). Though both features form part of the positive dimension of schizotypy and correlate highly on psychometric levels ($r=.78$, Ross, et al., 2002), they might act differently at the level of the brain, which will be examined more closely in chapter three.

Mohanty et al. (2005) used both perceptual aberrations and magical ideations to classify their participants as high schizotypy scorers (specifically “Individuals with a score at least 1.5 standard deviations above the mean on either the Perceptual Aberration Scale (Chapman, Chapman, & Raulin, 1978) or the Magical Ideation Scale (Eckblad & Chapman, 1983) were included in the positive-schizotypy group”, p. 18). These authors asked participants to perform an emotional Stroop task. High schizotypal individuals showed reduced activation in the left DLPFC and enhanced in the right DLPFC as compared to controls (N=32). High schizotypy individuals also showed decreased activity in the nucleus accumbens, that is the ventral striatum, in line with the findings from Corlett and Fletcher. Mohanty et al. (2005) also report increased activity in the hippocampus and amygdala. Both findings are consistent with the

emotional-cognitive deficits found in schizophrenia (Barch et al., 2001; Taylor, Liberzon, Decker, & Koeppe, 2002).

Further exploration of the emotional-cognitive domain comes from Premkumar et al. (2013), who found that high schizotypic individuals are less sensitive to positive comments. Their high schizotypy group, who showed lower mood as contrasted with the low schizotypy group, showed decreased activation in thalamus, insula, putamen and brain stem during positive, compared to neutral, comments. The latter was interpreted as an inability “to respond to rewarding aspects of positive comments” (p. 57). An insensitivity to social rejection was also demonstrated. Premkumar et al. (2013) found that during social rejection high schizotypy scorers (N=12; operationalized by the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE), specifically the unusual experiences scale) deactivated the bilateral dorsal anterior cingulate cortex (dACC), right superior frontal gyrus, and left ventral prefrontal cortex whereas low schizotypy scorers (N=14) showed activation in these areas. These findings indicate that upon social rejection, high schizotypy individuals seem to detach salience from the social rejection stimuli (Premkumar, et al., 2013).

Altogether the pattern of deviant brain activations in schizotypy is diverse, covering frontal, parieto-occipital and various subcortical structures. Most of these symptom-based studies however addressed single schizotypy features; syndrome-based measures, as the SPQ that was applied in the study reported in the empirical chapter, helps to provide a broader assessment of schizotypy and to better elucidate the neural correlates underlying the whole construct.

1.2.9.2.2. Syndrome-based Measures

Ettinger et al. (2013) used a procedural learning task in healthy adults (N=26) from the general population and the Schizotypal Personality Scale (STA) to probe schizotypy. These authors found positive associations with activity in the right middle temporal gyrus and positive features of schizotypy, in line with the notion of a dysfunctional activity pattern in the temporal lobe in schizophrenia. Debbane et al. (2014) used a self-reflection task during fMRI wherein female adolescents (N=19) were asked to evaluate trait adjectives referring to themselves or to their best female friends. Positive schizotypy (as assessed with the SPQ) correlated with activation in cortical structures such as in the dorso-medial prefrontal cortex (dmPFC), posterior cingulate cortex (PCC), DLPFC and lingual gyrus. These findings show that activation patterns associated with schizotypy, in particular positive features, are present in adolescence already and might, as the authors put it, lead to “faulty self-development and/or anomalous self-experiences such as those observed in adults suffering from schizophrenia” (Debbane, et al., 2014, p. 7). Brain activity pattern underlying schizotypy will be further scrutinised in chapter three.

Overall, findings of dysfunctional brain activation patterns in schizotypy mimic those found in schizophrenia spectrum disorders, supporting a view that extends to evidence from fMRI data, or as reported in a recent review on similarities between schizophrenia and schizotypy: “It would appear that it is no longer a question of whether or not the two constructs are related” (Nelson, et al., 2013, p. 324).

1.2.10. Summary Schizotypy

The construct of schizotypy has undergone some conceptual changes throughout the years; initially referring to a clinical condition that predisposes to developing full-blown psychosis, it is nowadays conceptualized as a collection of traits that are present in the general population and can be seen as part of the schizophrenia spectrum. It is not a unitary construct but consists of several factors that depending on the measures used include two to four factors, usually labelled as positive, negative, disorganization-related schizotypy as well as a temperamental component best described as covering low conformity and high impulsivity. One way of revealing pathways to psychopathology might be given by investigating the aetiology of schizotypy in depth (as in the study reported in chapter two) and additionally supporting the construct of schizotypy by revealing its underlying neural correlates (as in the study reported in chapter three). Studying schizotypy offers the possibility to examine traits linked to clinical pathology free of the confounding effects of medication, deterioration due to illness onset or effects caused by institutionalization. It therefore appears that “the value of schizotypy is not found in its use as a screening measure for specific psychotic disorders. Rather, the value of schizotypy lies in what it can tell us about normal human experience, and the possible pathways from psychological health to psychological dysfunction” (Nelson, et al., 2013, p. 324).

1.3. The Antisaccade Task

“... while strolling down a crowded sidewalk, you might notice an attractive person in the distance. Under most circumstances, an admiring glance towards that person would be appropriate. Except, however, when you are with your partner. In this instance, it might be wise to avoid looking in that direction and instead to orient in the opposite direction. This ability to control behaviour flexibly, responding automatically to stimuli in one situation and suppressing this automatic response in favor of an alternative response in a different situation, is the hallmark of executive control” (Munoz & Everling, 2004, p. 218).

Perception and action planning are necessary to navigate through life successfully. Behavioural studies of eye movements have the potential to provide crucial insights into how perception and action control work at the neurocognitive level (Sweeney, Luna, Keedy, McDowell, & Clementz, 2007). The next section will describe one measure of eye movements and focus on its neural correlates, as these were of relevance for the studies discussed in the empirical chapters.

1.3.1. *Definition of Antisaccades*

The study of the ocular reactions of psychiatric patients from photographic records goes back to Diefendorf and Dodge (1908). The performance shown by these patients was characterised as showing:

- “[a] lack of comprehension of the experimental test,
- [a] lack of ability to execute it,
- a lack of interest,
- [a] of cooperation and of endurance” (Diefendorf & Dodge, 1908, p. 451f).

Here, we will be focussing on the “lack of ability to execute” the task. Advantages of “studying the reactions of the eyes” (p. 452) as Diefendorf and Dodge called the method, included that the technique was simple to apply and that it was inaccessible to introspection and therefore less distorted by biases imposed through psychiatric conditions.

Antisaccades are one type of eye movements and were only later introduced by Hallett (Hallett, 1978). Antisaccades involve the suppression of a reflex-like saccade towards a visual stimulus (a pro-saccade or reflexive saccade) that is presented and the concurrent initiation of a voluntary anti-saccade to the mirror location of the visually presented stimulus. A saccade thereby is a quick eye movement directed at a (new) stimulus wherein the entire eye is repositioned and serves to keep the fovea on the stimulus (Duchowski, 2007).

1.3.2. *Antisaccade Task Description*

There are various designs of the antisaccade task. The step antisaccade task design was the one that was used throughout the studies presented in the empirical chapters and therefore will be

focussed on here. In the step design, depicted in Figure 6, the peripheral target occurs directly with the extinction of the central fixation stimulus, contiguous in time in a step-like fashion.

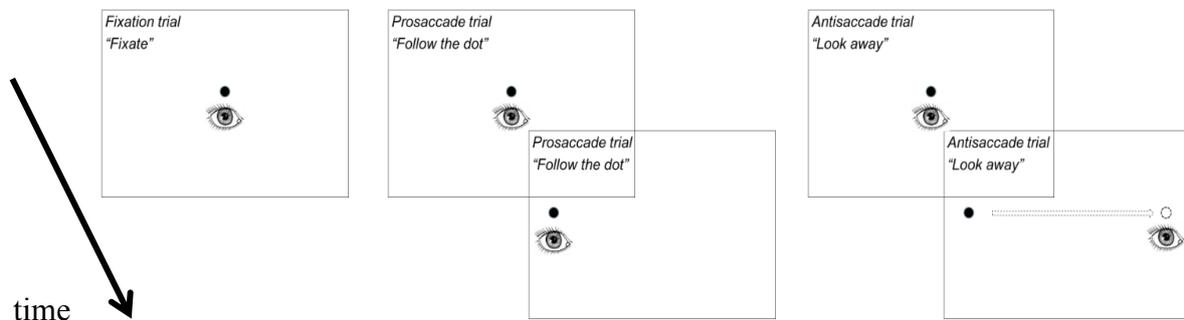


Figure 6 - Illustration of the outline during fixation, prosaccade and antisaccade trials, respectively.

As illustrated in Figure 6, in fixation trials, a central fixation stimulus (centrally at 0°) is displayed and the participant is required to focus on the central stimulus for the duration of the trial.

In prosaccade trials, participants view the central fixation stimulus, again for a certain period of time (usually the duration of the central fixation stimulus is variable to counteract anticipation of the target stimulus) and subsequently, in horizontal saccade tasks, this stimulus jumps into the periphery (at e.g. 8° or 14°, either to the left or right side). The participant is instructed to “follow the dot”, that is to perform a saccade towards the target. The “visual grasp reflex” facilitates directing gaze towards the peripheral target and allows for intact performance on prosaccade trials in non-clinical participants (Sweeney, et al., 2007).

Antisaccade trials show the same visual input as prosaccade trials, yet present different instructions; during antisaccade trials, the participant is instructed to “look away” to the mirror location of the stimulus, i.e. perform an anti-saccade (see Figure 6). Correct performance on the antisaccade task requires two processes: the suppression of the reflex-like response to look

at the target (i.e. the pro-saccade) and the transformation of “the location of the stimulus into a voluntary motor command to look away from the target (anti-saccade)” (Munoz & Everling, 2004, p. 218).

There are numerous ways in which trials can be arranged in eye movement tasks. Trials can be presented in blocks or in an event-related fashion. During block designs, equal numbers of antisaccade or prosaccade trials are presented after each other. In event-related designs, antisaccades are presented in an interleaved way with prosaccades trials (Brown, Goltz, Vilis, Ford, & Everling, 2006; Ford, Goltz, Brown, & Everling, 2005), or occur intermittently as an oddball trial (Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007). Event-related designs are supposed to put greater demands on switching between stimulus-response mapping from trial to trial (Hodgson et al., 2007), yet it was shown that the design of the task, be it event-related or a block design, had no impact on main performance indicators such as the error rate (Hallett & Adams, 1980). The studies presented here in the empirical chapters relied on a block design.

1.3.3. Antisaccades as Measures of Oculomotor Inhibition

Antisaccades can be subsumed under the umbrella term of measures of executive functioning. Executive functions refer to “a collection of correlated but separable control processes that regulate lower-level cognitive processes to shape complex performance” (Friedman et al., 2008, p. 201). These functions are considered to be crucial for adaptation in everyday life and found to be impaired in disorders such as schizophrenia (Frith, 1992) or attention-deficit/hyperactivity disorder (ADHD; Nigg, 2000). Inhibition, one of the most widely studied executive functions can be described as the “ability to suppress irrelevant stimuli or impulses” (Garavan, Ross, & Stein, 1999, p. 8301).

Inhibition is crucial for adapting behaviour and guiding through life without being driven by bottom-up or exogenously triggered processes. Inhibition is not a unitary construct, as Friedman and Miyake (2004) showed, it can be decomposed into three components, which are: prepotent response inhibition (suppressing an automatic response), resistance to distractor interference (i.e. ignoring task-irrelevant information), and resistance to proactive interference (i.e. preventing intrusions into memory by irrelevant information).

The antisaccade task can be seen as a measure of prepotent response inhibition (Aichert et al., 2012; Friedman & Miyake, 2004). In particular, this task represents oculomotor inhibition which is defined as “the suppression of an unwanted eye movement” (Van der Stigchel, van Koningsbruggen, Nijboer, List, & Rafal, 2012, p. 198). The stop signal, Stroop or go-no-go task can also be taken as measures of response inhibition (Aron, Robbins, & Poldrack, 2004). For the empirical fMRI studies reported in the following, data was collected on the stop signal and go/no-go task as well; given that the focus of the current work lies on schizotypy and schizophrenia-related endophenotypes, i.e. antisaccade task performance (Greenwood et al., 2012), the antisaccade task will be discussed in depth subsequently (see empirical chapters).

1.3.4. Measures of Antisaccade Task Performance

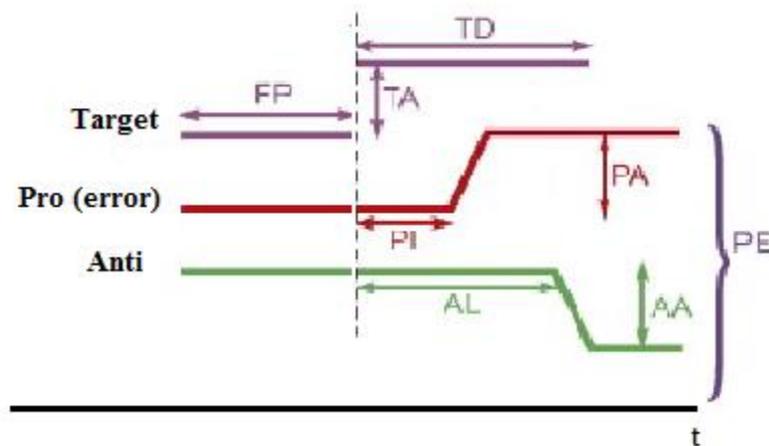


Figure 7 - Illustration of the measures of the antisaccade task.

The course of the target stimulus (violet), the prosaccade (red) and the antisaccade (green) in a step design. The target stimulus is first shown centrally, then jumps into the periphery after a certain period of time (FP=foreperiod). This course is defined by the target amplitude (TA) and the target duration (TD). The latency of pro- and antisaccades is indicated by PL and AL, respectively; their amplitudes by PA and AA, respectively. PE indicates the proportion of errors during an antisaccade trials, which is given by the number of (erroneous) prosaccades performed/number of antisaccade trials, t =time. Adapted from Antoniadou et al. (2013).

The antisaccade task offers several measures of performance, amongst them are: the latencies of incorrect pro- and correct antisaccades (see Figure 7), the percentage of errors (labelled as antisaccade error rate or rate of direction errors on the antisaccade task) and the percentage of antisaccade errors that are corrected (labelled as correction rate). Errors on the antisaccade task can be defined as initial saccades towards the peripheral target (Klein, Brugner, Foerster, Müller, & Schweickhardt, 2000).

The latency on antisaccade trials is usually subject to a cut-off, in order to exclude saccades that occurred in anticipation of as opposed to in response to the peripheral target. These are accordingly labelled anticipatory saccades (Fischer & Weber, 1993) and are excluded

from analyses as they occur at a latency of <100 ms, which does not represent a valid response to the target (Fischer & Breitmeyer, 1987).

Error rates in healthy individuals vary between 2 to 30% (Smyrnis, 2008), the average is said to be approximately around 20% (Hutton & Ettinger, 2006). Healthy participants and patients suffering from conditions such as schizophrenia correct the vast majority of errors, suggesting that they understand task instructions yet, due to a deficit in inhibition and possibly also response generation, fail to fulfil task requirements correctly throughout the task (Crawford, Bennett, Lekwuwa, Shaunak, & Deakin, 2002; Hutton & Ettinger, 2006). The antisaccade task therefore offers the potential to reveal a range of deficits which are approached in a non-intrusive way. Antisaccade task performance provides various measures as indicators of performance; the crucial measure of successful performance on the task however is the antisaccade error rate as an indicator for unsuccessful oculomotor inhibition.

1.3.4.1. Effects on the Antisaccade Error Rate - Age

Antisaccade error rates vary across the lifespan, with high error rates found during childhood, improvements until early adulthood, and a slow decline again with old age until around 60 years, upon which the decline becomes steeper (Fischer, Biscaldi, & Gezeck, 1997; Klein & Foerster, 2001).

These variations in the error rate are due to the developmental changes that take place across the lifespan, particularly at the neurocognitive level. Adolescents who perform similar to adults on response inhibition tasks have been found to show greater activation in inhibition-related brain areas (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002). Increased inhibitory control over the saccade circuit was suggested to lie at the heart of these improvements in antisaccade performance across adolescence (Klein & Foerster, 2001; Munoz

& Everling, 2004). Young children for instance (<8 years) show low performance due to an inability to suppress prosaccades on antisaccade tasks, yet correct these errors, indicating that they understand task instructions (Munoz & Everling, 2004). In childhood, inhibition is unsuccessful on 50-60% of trials, which significantly improves until adulthood, when the error rate drops to 10-20% (Fischer, et al., 1997; Luna, Velanova, & Geier, 2008). Error performance is supposed to reach stability at the age of 15 (Luna, Garver, Urban, Lazar, & Sweeney, 2004), similar to response latency, which is also subject to improvements throughout puberty and suggested to reach stability in late adolescence (Fischer, et al., 1997). With old age (55 to 72 years), performance declines, possibly due to changes in the link between frontal and parietal eye fields (Raemaekers, Vink, van den Heuvel, Kahn, & Ramsey, 2006). Given these effects of age on task performance, we included participants aged 18 to 55 years in the antisaccade studies presented here.

1.3.4.2. Effects on the Antisaccade Error Rate - Lateralization

The brain is set up bilaterally symmetrical, yet differences were noted between left and right hemispheres in structure and function. The asymmetry in functioning is referred to as lateralization of the brain. The left hemisphere for instance is responsible for language processing whereas the right hemisphere is supposed to be involved in visuo-spatial information processing (e.g. Pinel, 2009). Lateralization effects have to be taken into account when examining brain activity in respect to handedness for instance. We chose to include only right-handed participants in the fMRI scanning sessions that are outlined in the current fMRI studies in the empirical chapters.

1.3.5. Models of Antisaccade Errors

Models of antisaccade performance are concerned with the question: Why do prosaccades occur in the antisaccade condition? One way of explaining the occurrence of erroneous prosaccades assumes that antisaccade performance relies on parallel processing of pro- and antisaccades and that the result of the “race” between the exogenously triggered pro- and the endogenously triggered antisaccades determines if an error occurs (Massen, 2004; Munoz & Everling, 2004).

Prosaccades as opposed to antisaccades do not require learning, memorizing new stimulus-response mapping in the absence of a visual stimulus or the inhibition of a prepotent response (Munoz & Everling, 2004), which altogether facilitates the performance of prosaccades above that of antisaccades. Evidence supporting a competition between processes favouring pro- and those favouring antisaccades can be derived from the study of incorrect prosaccade and corrective antisaccade latencies. These latencies are too close together in time to be processed in a serial manner. Incorrect prosaccades take on average 95 ms, corrective antisaccades 145 ms (Hutton, 2008) to perform. Further evidence favouring parallel processing is given by the finding that slowing the exogenously triggered prosaccade lowers the error rate (possibly by allowing the antisaccade processes to “win the race”), and slowing the endogenously triggered antisaccades increased the error rate (Massen, 2004).

Additional evidence supporting parallel processing comes from neurocognitive accounts of eye movements. To inhibit a prepotent motor response, top-down and bottom-up control mechanisms compete and recruit distinct cortical and subcortical areas. The basic neural underpinnings of the saccade circuits will be outlined the following section.

1.3.6. Neural Correlates of Antisaccade Task Performance

Information on the neural correlates that underlie eye movements comes from several sources. The first findings were derived from lesion studies, later studies made use of fMRI to reveal neural underpinnings and circuits involved in saccade generation. Studies on the neural sites of eye movement control were initially dominated by studies in non-human primates. Nowadays, this work has been extended to humans on whom we will focus in the following.

1.3.6.1. Evidence from Lesion Studies

Early evidence into the working of eye movements on a neural level comes from human lesion studies. Guitton, Buchtel and Douglas (1985) for instance examined the role of the frontal eye fields (FEF) and superior colliculi (SC) in the brain stem in the generation of saccadic eye movements and hypothesized that the FEF exert top down control onto the visual grasp reflex which is supposed to be represented in the SC. The visual grasp reflex is a quick response that is thought to result from the “direct transformation of the incoming visual signal into the motor command to drive the eyes to the stimulus” that happens to novel visual stimuli (Munoz & Everling, 2004, p. 220). Patients with unilateral removals of frontal lobe tissue were compared with those with unilateral temporal lobe removals and healthy controls. These groups performed a prosaccade and an antisaccade task. Patients with frontal lesions in dorso-lateral or medial areas were impaired in suppressing glances at stimuli that occurred in the periphery. Glances away from the target were hardly generated spontaneously. Results indicated the importance of the frontal lobes in eye movements specifically that of the FEF in suppressing reflex-like saccades and initiating a volitional movement (Guitton, et al., 1985).

In line with this finding, lesions to further frontal areas besides the FEF, i.e. the DLPFC, have been found to increase the antisaccade error rate (Pierrot-Deseilligny, Ploner, Müri, Gaymard,

& Rivaud-Pechoux, 2002). DLPFC lesions in particular led to an increased failure in inhibiting prosaccades (Gaymard, Ploner, Rivaud-Pechoux, & Pierrot-Deseilligny, 1999). It has therefore been suggested that another part of the saccade circuit consists of the DLPFC, as lesions in the latter produced diminished inhibition of the saccade generating neurons in the FEF and SC (Munoz & Everling, 2004).

Similarly, lesions to ventral prefrontal and anterior cingulate cortices increase the antisaccade error rate. Dorsal ACC lesions increase antisaccade errors (Milea et al., 2003) and latencies of pro- and antisaccades (Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1998), adding further areas to the saccade generating circuit.

The posterior parietal regions, which involve the parietal eye fields (PEF), are supposed to be involved in spatial programming of antisaccades (Pierrot-Deseilligny, et al., 2002). Patients with lesions in these areas were not able to correctly select between two competing visual stimuli and still failed to do so if they received feedback on their error, suggesting the crucial role of the PEF in performing the requested saccade (Braun, Weber, Mergner, & Schultemonting, 1992).

Lesion studies provide crucial insights into the working of the brain, yet lesions across patients often differ in nature and severity and are therefore difficult to compare. Neuroimaging studies of brain functioning help to give more fine-tuned information on the neural substrates of eye movements.

1.3.6.2. Evidence from fMRI Studies

Studies on neural networks and circuits involved in saccade generation and inhibition allow us to dissect the individual motor commands involved in anti- and prosaccades. Information on the latter is most likely to come from fMRI (Hutton & Ettinger, 2006). The main neural sites of complex saccadic eye movements such as the antisaccade include the FEF, SEF, DLPFC, ACC, the posterior parietal cortex, the thalamus and the striatum (Hutton & Ettinger, 2006).

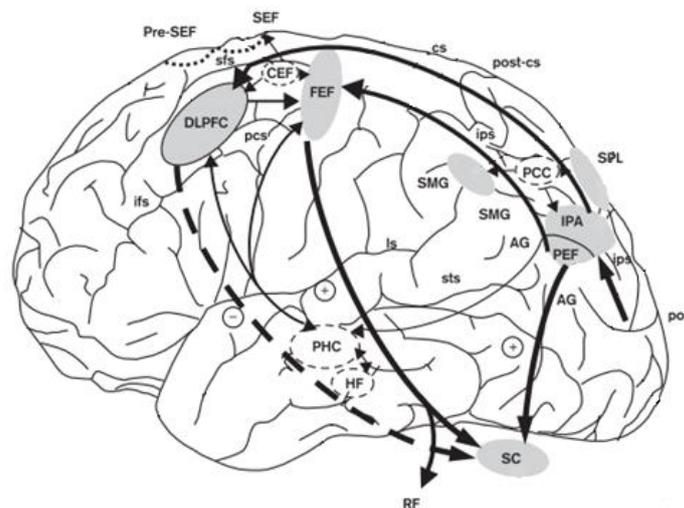


Figure 8 - Illustration of the main cortical areas and projections involved in saccadic eye movements.

SEF=supplementary eye field, sfs=superior frontal sulcus, CEF=cingulate eye field, cs=central sulcus, DLPFC=dorso-lateral prefrontal cortex, pcs=precentral sulcus, FEF=frontal eye field, ips=intraparietal sulcus, ifs=inferior frontal sulcus, SMG=supramarginal gyrus, PCC=posterior cingulate cortex, SPL=superior parietal lobe, IPA=intraparietal areas, ls=lateral sulcus, AG=angular sulcus, PEF=posterior eye field, sts=superior temporal sulcus, pos=parieto-occipital sulcus, PHC=parahippocampal cortex, HF=hippocampal formation, SC=superior colliculus, RF=reticular formation.

Adapted from Pierrot-Deseilligny et al. (2004).

1.3.6.2.1. Frontal Eye Fields

The competition between stimuli of different importance, i.e. relevant stimuli vs. distractors recruits the FEF (Clementz, Brahmhatt, McDowell, Brown, & Sweeney, 2007). The FEF are located in the precentral sulcus, specifically they were defined as “vertices in and around the precentral sulcus, beginning approximately at the level of the superior frontal sulcus” (p. 339, Agam, Joseph, Barton, & Manoach, 2010; Koyama et al., 2004; Paus, 1996). They are included in the cortical network that is responsible for saccadic eye movements (Gaymard et al., 1998) and are play an important part the generation of saccades. Enhanced FEF activity therefore occurs during both antisaccade and prosaccade trials (e.g. Connolly, Goodale, Menon, & Munoz, 2002; Ford, et al., 2005; Manoach et al., 2007; O'Driscoll et al., 1995; Sweeney et al., 1996). When comparing the BOLD response in the FEF between anti- and prosaccades, an increased BOLD signal in the FEF is commonly demonstrated and interpreted as reflecting a heightened degree of inhibition during antisaccade as compared to prosaccades trials (e.g. Ford, Gati, Menon, & Everling, 2009). Specifically, the inhibition of saccade neurons in the FEF is suggested to be critical for the suppression of the prepotent response in antisaccade trials (Munoz & Everling, 2004), which in line with evidence from human lesion studies. The key to successful antisaccade performance has been supposed to lie in the activation that precedes antisaccades in frontal areas, amongst these the FEF (Connolly et al., 2002; DeSouza, Menon & Everling, 2003).

This body of evidence supports the hypothesis that the inhibition of saccade-related neurons in the FEF is crucial for suppressing the prepotent response during antisaccade trials and successful performance on these trials.

1.3.6.2.2. Supplementary Eye Fields

Other frontal areas included in the oculomotor circuit are the supplementary eye fields (SEF). The SEF are located in the medial frontal cortex (Luna et al., 1998). Anatomically, the SEF are connected to FEF and SC (Shook, Schlag-Rey, & Schlag, 1990). Schlag-Rey et al. (1997) demonstrated mechanisms by which neurons responsible for vision and movement in the SEF show enhanced activity during antisaccades than during prosaccades using single-unit recordings in monkeys. Thereby, these authors helped in explaining why neurons that usually activate prosaccades also activate oculomotor neurons to successfully performed antisaccades. In humans, the SEF in interaction with saccade neurons in the FEF and the SC contribute to motor commands for antisaccades (Munoz & Everling, 2004). SEF responses are increased during antisaccade trials, indicating that this area helps to facilitate antisaccade responding in humans as well (Schlag-Rey, et al., 1997).

Curtis and D'Esposito (2003) for instance showed differences in SEF activation between pro- and antisaccade trials during the preparatory periods before stimulus presentation and saccade initiation and suggested that this difference might contribute to successful performance on the antisaccade task. The precise mechanisms, which take place in the FEF, SC and SEF, and determine if an antisaccade command wins the “race”, are however not precisely defined. It is suggested that the SEF sends input to the FEF and SC and that “SEF efferents could excite local inhibitory interneurons to exert inhibition of saccade neurons” in FEF and SC (Munoz & Everling, 2004, p. 223).

1.3.6.2.3. Dorso-lateral Prefrontal Cortex

Other parts of the oculomotor system in the brain extend into Brodmann areas nine and 46, the DLPFC. The DLPFC is interconnected with several eye fields in frontal (Selemon & Goldman-

Rakic, 1988), cingulate and parietal cortices as well as with the superior colliculi in the brainstem (Goldman & Nauta, 1976; Leichnetz, Spencer, Hardy, & Astruc, 1981). The role of the DLPFC in inhibition has been discussed before (e.g. MacDonald, Cohen, Stegner & Carter, 2000) and its importance for processes such as task-relevant representation and maintenance of information in working memory stressed (MacDonald et al., 2000). MacDonald et al. (2000) for instance found that the magnitude of the left DLPFC activation during an inhibition task was linked to successful inhibition. Similarly, activation in the DLPFC is specifically found in trials wherein correct antisaccade task performance is shown (e.g. Ford, et al., 2005; McDowell et al., 2005). Consistent with findings in other areas of the oculomotor system, the DLPFC shows enhanced activity before antisaccades, in the preparatory period (Connolly et al. 2002; Curtis and D'Esposito, 2003; DeSouza et al. 2003). The DLPFC was also found to be activated during stimulus-response mappings, as evidenced in monkey studies, wherein neurons responsible for stimulus location encoding and those for response direction encoding were found (Funahashi, Bruce, & Goldman-Rakic, 1993). Due to the connections between DLPFC and the eye fields, it has been suggested that the DLPFC activity could be interpreted as contributing to the response selection phase during antisaccades (Miller & Cohen, 2001).

1.3.6.2.4. Anterior Cingulate Cortex

The anterior cingulate cortex is, in addition to the DLPFC, relevant for successful inhibition (MacDonald et al., 2000). Both areas have been suggested to be recruited rather during “presetting the saccade network” for a volitional saccade than during response execution (Brown, Vilis, & Everling, 2007, p. 1751).

The cingulate cortex can be separated into an anterior and a posterior part. The ACC can be further separated into dorsal and rostral segments (Devinsky, Morrell, & Vogt, 1995). The

cingulate eye field refers to an area located in the dorsal part of the ACC, as it was found to be involved in generating volitional saccades (Gaymard et al., 1998; Paus, Petrides, Evans, & Meyer, 1993; Pierrot-Deseilligny, et al., 2004). The dACC spans an area between the genu of the corpus callosum and the anterior commissure and shares connections with the DLPFC to coordinate highly-demanding cognitive processes. The ACC is known to be recruited during error monitoring and conflict detection (Polli et al., 2005). Its role has more recently been extended to performance monitoring, in specific to discrepancies between expected and observed outcomes (Brown, 2013). The ACC is well connected to motor and pre-motor areas including the oculomotor regions, e.g. FEF, aids in providing top-down control upon these regions (Johnston, Levin, Koval, & Everling, 2007) and facilitates inhibition in coordination with the FEF (Agam, et al., 2010).

The rostral ACC has also been found to be implicated in the oculomotor network. It can be located at anterior and ventral sites around the genu of the corpus callosum. Polli et al. (2005) for instance demonstrated both task-induced deactivation of the rostral ACC sub-region early in correct antisaccade trials as well as increased activation of a different rostral ACC sub-region later in the trial, following an error, highlighting enhanced sensitivity of the (rostral) ACC to error-evaluation. The ACC has been mentioned in connection with error-monitoring in inhibition before (Hester, Fassbender, & Garavan, 2004).

1.3.6.2.5. Parietal Areas

The parietal eye field is located in the IPS (Andersen, Brotchie, & Mazzoni, 1992). Previous evidence showed an involvement of this region in the processing of visual information and in the triggering of saccades (e.g. Brown et al., 2006; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991). Enhanced activation in this area during antisaccades as compared to prosaccades has been demonstrated before (e.g.: Ettinger et al., 2008). Mort and colleagues (2003) reported

that “relative to reflexive saccades, voluntary saccades produced greater activation within ... the intraparietal sulci” (p. 231). In addition, a role for the IPS in spatial attention and spatial coordinate transformations was also proposed (Merriam et al., 2001). Consistent with the latter proposition is that the transformation is represented by posterior parietal cortex activation and is suggested to help in generating a correct antisaccade, which explains why this area shows activation during antisaccades too (Zhang & Barash, 2000).

1.3.6.2.6. Subcortical Areas

Subcortical areas involved in the saccade generation circuit involve the thalamus and striatum (McDowell, Dyckman, Austin, & Clementz, 2008).

The thalamus has various connections to cortical areas such as the frontal and parietal lobes, as well as to brain stem areas such as the superior colliculi, information travels specifically from the lenticular nucleus indirectly via the subthalamic nucleus to the brainstem nuclei (Alexander & Crutcher, 1990). Activation in the thalamus in response to antisaccades has been documented before (Ettinger et al., 2008; Sweeney et al., 1996). Its largest nucleus, the pulvinar, has previously been found to be involved in successful guidance of eye movements and assumed to be the site that coordinates top-down information from the cortical areas with bottom-up information generated by the brain stem (Van der Stigchel, Arend, van Koningsbruggen, & Rafal, 2010).

The striatum is part of the basal ganglia, the latter which is crucially involved in the steering of movements. The basal ganglia receive numerous inputs from cortical sites, amongst them the frontal eye fields; the striatum is hereby the main input site amongst the basal ganglia (McDowell, et al., 2008). The striatum can be differentiated into two parts, the dorsal and ventral striatum. The dorsal part includes the putamen and the caudate nucleus, the ventral part

consists of the nucleus accumbens. Enhanced BOLD responses to antisaccades were demonstrated in the striatum, particularly in the caudate nucleus (Dyckman, Camchong, Clementz, & McDowell, 2007; Ettinger et al., 2008; Matsuda et al., 2004). Its role in the generation of reflexive saccades is less consistent, with some support for activity in the striatum in some studies (e.g. Matsuda, et al., 2004), while others failed to find supporting evidence (Brown, et al., 2006; McDowell et al., 2002), indicating that the role of the striatum might lie mainly in inhibition (e.g. McDowell, et al., 2008).

Altogether, visual information processing in the brain during eye movement tasks can be summarized as follows: Basic visual stimulus features are processed in the visual cortices located in the occipital cortex. The latter regions receive input from the thalamus, specifically from the lateral geniculate nucleus of the thalamus, which in turn derives its information from the projections of the retinal ganglion cells. Information on the relevance of saliency of the visual stimulus is transferred to the parietal lobe, specifically the posterior regions of the IPS, where the parietal eye fields can be located. The parietal eye fields are responsible for triggering a reflexive saccade towards the visual stimulus. The latter is accomplished by a direct connection between parietal and collicular regions, the parieto-collicular tract. Information is also sent from the PEF to the FEF for active fixation of the visual stimulus and to the DLPFC for the inhibition of reflexive responses. Inhibition can be directly performed through connections between the DLPFC and the SC. Further contributions to successful inhibition come from basal ganglia sites such as the striatum. The antisaccadic response is initiated by the FEF in coordination with other frontal areas such as the SEF which are responsible for antisaccade execution together with the cingulate eye fields in the ACC, which are responsible for error monitoring and motivational processes.

1.3.7. Antisaccade Performance across the Schizophrenia Spectrum

Identifying markers of schizophrenia that are independent of psychometric assessments has long been a core goal of research in schizophrenia. One promising intermediate phenotype candidate for schizophrenia are eye movement dysfunctions (Ettinger et al., 2004; Light et al., 2012). Behavioural and fMRI antisaccade task findings across the spectrum will be discussed in the following. Antisaccade performance (behavioural or fMRI-based) has been discussed mainly in schizophrenia, to cover the spectrum findings in various disorders as well as in schizotypy will be mentioned.

The first ones to show dysfunctional antisaccade task performance in schizophrenia were Fukushima et al. (1988) who demonstrated an increased antisaccade error rate in schizophrenic patients. This finding as well as further behavioural abnormalities on this task in schizophrenia, e.g. increased latencies for antisaccades, has been replicated since then (Camchong, Dyckman, Austin, Clementz, & McDowell, 2008; McDowell, et al., 2002; Reuter, Herzog, & Kathmann, 2006; Müller, Riedel, Eggert, & Straube, 1999). These behavioural differences were altogether linked to frontal cortex dysfunction, including that of the DLPFC (McDowell, et al., 2002), however also to regions such as the striatum (Crawford et al., 1996; Polli et al., 2008; Raemaekers et al., 2002) and the anterior cingulate cortex (Crawford et al., 1996; Polli et al., 2008). Fukumoto-Motoshita et al. (2009) showed that patients show abnormal levels of activation in the DLPFC and thalamus during antisaccades as contrasted to fixations and interpreted this dis-proportional response in schizophrenia as a failure to appropriately engage task-relevant areas. Task-related activation was further found to be reduced in various areas of the saccade generating networks including frontal, supplementary, and parietal eye fields, cingulate cortex and precuneus as evidence generated in un-medicated first episode schizophrenia patients shows (Keedy, Ebens, Keshavan, & Sweeney, 2006). Studies of medicated schizophrenia patients have been mixed with some reporting less activation with

medication in schizophrenia (Raemaekers et al., 2002) and others showing no altered pattern of activation within the saccade generating network (McDowell, et al., 2002). Dyckman et al. (2011) for instance targeted the FEF in medicated schizophrenia patients and found a prolonged response in the FEF for antisaccades. Polli et al. (2008) demonstrated reduced recruitment of the ACC in schizophrenia indicating a reduced sensitivity to errors. These authors suggested that this lower activation might be interpreted as a deficit in stimulus-response mapping, this combined with a reduced ability to monitor own performances might contribute to the commonly observed rigid behaviour in schizophrenia (Polli et al., 2008). Other areas of reduced activation include the striatum. Raemaekers et al. (2006) for instance focussed on antisaccade performance in first degree relatives of schizophrenia patients and found differences in fronto-striatal network activity, specifically in the caudate nucleus, compared to healthy controls. Camchong et al. (2008) similarly investigated schizophrenia patients, their relatives and healthy controls (N=15, N=13 and N=14, respectively) on antisaccade task performance and found that both patients and relatives made more antisaccade errors on a behavioural level and showed decreased activation in a network of oculomotor inhibition related areas such as the middle occipital gyrus, insula, cuneus, anterior cingulate and prefrontal cortex. The schizophrenia group however was the only one to show decreased activity in FEF and SEF, indicating a deficit in early sensory and attention processing areas, as well as a specific rather than a global pattern of dysfunctional activation in schizophrenia (Camchong, et al., 2008).

Patients with schizoaffective disorder have, similar to schizophrenia (and bipolar) patients, been found to show elevated error rates on the antisaccade task (Martin et al., 2007; Reilly et al., 2014) compared to healthy controls. Schulze et al. (2006) investigated the links between volume abnormalities across the whole brain as well as in the prefrontal cortex, lateral ventricles, third ventricle, hippocampus, and cerebellum across schizophrenia patient

populations and antisaccade task performance. These authors found links between longer antisaccade latencies and smaller prefrontal cortex volume; included however only 7 schizoaffective patients into the patient sample which makes it difficult to draw cogent conclusions for schizoaffective disorder from this study. Altogether there is tentative behavioural evidence for elevated antisaccade error rates in schizoaffective disorder, indicating similarity with task performance in schizophrenia.

Schizotypal personality disorder however has not consistently been linked with reduced performance on the antisaccade task. Studies in patient populations, especially fMRI studies, have been scarce and hampered by small sample sizes, making interpretability of the findings difficult. For example, Brenner, McDowell, Cadenhead and Clementz (2001) tested 29 patients, who met *DSM-IV* criteria for schizotypal personality disorder on the antisaccade task and found that this patient group did not differ significantly from health controls on correct performance on the antisaccade task. However, a subset of patients showed abnormal performance scores, which tentatively indicate similarity across the schizophrenia spectrum including SPD (Brenner et al., 2001). Similarly, Cadenhead, Light, Geyer, McDowell and Braff (2002) investigated 21 patients diagnosed with schizotypal personality disorder on task performance and found preliminary evidence for “inhibitory deficits measured by the ... antisaccade paradigms ... in a significant subgroup of subjects with schizotypal personality disorder” (p. 870). This study however had no control group and a small sample size (N=21 of which N=7 showed antisaccade task performance deficits). Research on antisaccade task performance (during fMRI) in other schizophrenia spectrum disorders, such as paranoid or schizoid personality disorders is rare, possibly due to diagnostic difficulties with these disorders.

Studying patient groups in addition comes with certain drawbacks, such as the confounding effects of illness manifestation, hospitalization or medication and their differential

effects on behavioural performance and brain activity during antisaccades. One way to circumvent these drawbacks is given by approaching spectrum deficits by studying schizotypy level in the general population.

Ettinger and colleagues (2005) assessed 115 non-clinical participants on the RISC and found positive correlations between positive schizotypy and enhanced errors on the antisaccade task. These effects were present when controlling for neuroticism, leading to the conclusion that antisaccade performance in schizotypy is “not due to negative emotionality or general psychopathology, but specific to schizophrenia spectrum signs and symptoms.” (Ettinger et al., 2005, p. 61). Similar findings of elevated antisaccade errors in individuals with high scores on schizotypy measures were reported throughout (Holahan and O'Driscoll, 2005; Larrison, Ferrante, Briand, & Sereno, 2000) indicating support for a pattern of antisaccade performance dysfunction in schizotypy that is consistent with the patterns found in schizophrenia. Aichert et al. (2012) provide evidence for neural correlates of schizotypy by investigating a neurocognitive deficit common in schizotypy and schizophrenia, poor antisaccade performance. As poor performance is evident in schizophrenia and as schizotypy can be seen as a multi-factorial trait similar to but less severe than the clinical picture of schizophrenia, these authors suggest that high schizotypy as found in the general population might activate similar brain areas during the antisaccade task as found in schizophrenia. They assessed participants (N=54) on positive schizotypy by means of the RISC and antisaccade performance during fMRI. Results showed that indeed higher schizotypy scores were associated with worse performance on the antisaccade task. During prosaccades (as assessed with the contrast prosaccades vs. fixation), schizotypy was associated with activity in the left posterior intraparietal sulcus (IPS) and left supplementary eye fields (SEF) and visual cortex. In the antisaccade contrast (antisaccades vs. fixation), schizotypy was associated with activity in right putamen, left cerebellum, right thalamus and visual cortex. Overall, the visual cortex was the

best predictor of schizotypy scores and explained up to 19% of variance in schizotypy scores. Latter finding was linked to alterations in early visual processing in schizotypal individuals. Disturbances in early visual processing in schizophrenia have been proposed to play an important role in the pathophysiology of schizophrenia before (Andreasen, Paradiso, & O'Leary, 1998), indicating similarity of brain activation patterns across the spectrum.

The study presented in chapter three builds on the work of Aichert and colleagues. The latter did not find evidence favouring a link between brain activation during the contrast antisaccades vs. prosaccades and schizotypy; however they covered only part of the schizotypy construct. The study presented here provides an assessment of all schizotypy features, assesses important confounders (e.g. neuroticism) and relies on a larger sample size.

1.3.8. Summary the Antisaccade Task

The antisaccade task and the performance measures derived from it assess prepotent response inhibition and were said to be particularly useful markers of psychiatric disorders, in specific schizophrenia and schizophrenia spectrum disorders. In order to investigate the link between schizophrenia spectrum disorders and schizotypy further, the antisaccade task offers potential. As listed in the chapter on “Endophenotypes”, the establishment of a feature as endphenotype requires the fulfilment of various criteria such as: an association between the candidate endophenotype with the disorder in the population; heritability of the candidate endophenotype; the candidate endophenotype being a trait of the disorder; among affected relatives, who present with the candidate endophenotype, the prevalence of the disorder must be higher than among relatives who do not present with the candidate endophenotype and among non-affected relatives the candidate endophenotype must be present at a higher rate than in the general population. The studies presented here in chapters three and four used the antisaccade task during fMRI first to reveal the neurocognitive underpinnings of schizotypy

and second to investigate the amount of genetic influences on the brain activity underlying task performance, which provides further establishment for antisaccade task performance and its related brain activity as an endophenotype.

1.4. Functional Magnetic Resonance Imaging

"Blood very likely may rush to each region of the cortex according as it is most active" William James (1890).

The following section will outline the basics of functional magnetic resonance imaging (fMRI) as they were applied throughout the fMRI studies presented in chapters three and four.

1.4.1. Introduction to Functional Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a technique used to display in vivo brain structure in a non-invasive fashion. fMRI, as the name indicates, allows examination of functional neural correlates of behavioural phenotypes. The method's main benefit is good spatial resolution, which comes at the price of poor temporal resolution. In brief, the aim in fMRI is to locate areas of the brain that are significantly "activated" by different conditions of a task for instance. Results are generally reported as contrasts between conditions, i.e. activation during one condition is compared to activation during a control or baseline condition; the underlying assumption thereby being that more activation is produced by one condition relative to its baseline or to the activation derived during a control condition. Results are therefore always relative and provide an answer to the question: Which parts of the participant's brain were more activated during one condition of the experiment relative to another condition?

Figure 9 shows the main components of a scanning session. The set-up includes a strong magnet, the scanner bore as well as a number of coils, i.e. the radio frequency coil (or head coil) and the gradient coil. Participants are generally scanned in a supine position, i.e. on their back. The magnet produces a strong, static magnetic field, of which the strength is given in

Tesla (T) (participants in the current studies were scanned at 3T, this is 60,000 times the strength of the Earth's magnetic field or 1/3 of the magnets used to recycle cars at scrap-yards). The static magnetic field of the scanner is strong enough to pull heavy objects towards it; this is known as projectile effect and is the main reason for MRI safety (Huettel, Song, & McCarthy, 2004). Due to reasons of safety, participants in the current studies were screened for MRI compatibility. Participants, who had e.g. non-removable metal pieces in or on their body, had to be excluded from participation.

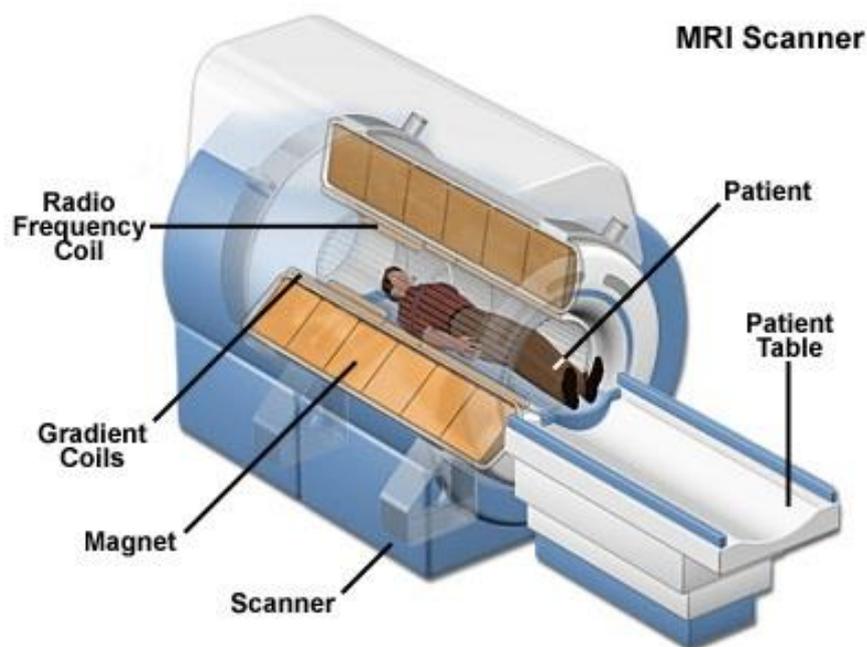


Figure 9 - Illustration of Magnetic Resonance Imaging (MRI) scanner set-up.

Adapted from <http://www.themesotheliomalibrary.com>.

The magnetic field created by the magnet is supposed to fulfil certain criteria: first, it should produce a homogeneous magnetic field. This is important because the way the body is positioned in the magnetic field should not affect the signal that can be measured (which it would if the magnetic field was inhomogeneous). Second, the field strength needs to be large.

The latter can be achieved with superconducting electromagnets, that consist of wires of metals such as titanium for instance, which can generate a strong magnetic field with minimal power requirements, the latter in turn is achieved by cooling the wires which reduces the amount of resistance and thereby can achieve minimal power requirements (Huettel, Song, & McCarthy, 2004).

The magnet in itself does not produce a magnetic resonance (MR) signal, it is through the use of coils that latter can be generated. These send and receive pulses in certain frequency ranges, to which atomic nuclei respond. The strong magnetic field facilitates the alignment of hydrogen atoms in the body. Each hydrogen atom, which is present in water molecules in the brain, has a spin. The characteristics of this spin (i.e. an angular and a magnetic moment) allow the atoms to behave like rotating magnets. If exposed to a strong magnetic field, these atoms (or rather the electrons of the atom) precess to the magnetic field. This precession takes place at a certain frequency, the Larmor frequency, and is proportional to the strength of the magnetic field (Lauterbur, 1973). The hydrogen atoms align to the magnetic field, either parallel to the magnetic field, i.e. in B_0 -direction, or anti-parallel, whereby the former alignment gives a higher energy state than the latter. The difference in energy increases with higher field strength. Once the spins reach an equilibrium state, energy in the magnitude of the Larmor frequency is added in order to “excite” the atomic nuclei. This perturbation is induced by the radiofrequency coil and causes a phenomenon called resonance and gives MRI its name. When atomic nuclei return to their original state, they release energy and this release can be picked up by the coil. The sensitivity of the radiofrequency coil is determined by the strength of the magnetic field.

MRI is a tomography-based procedure; images of the body are therefore sampled in slices. A volume of the brain which is captured in slices can be acquired continuously (e.g. with a brain sliced up in 38 slices). The slice order could thereby increase steadily from 1 to 38 or it could be interleaved (i.e. the slice order thereby would be 1, 3, 5... 37 and 2, 4, 6 ... 38).

With use of the gradient coil, localising the origin of the slices following acquisition is made possible. Localisation is accomplished by inducing inhomogeneity into the magnetic field in a controlled fashion.

1.4.2. Imaging Parameters

A number of parameters such as repetition time, echo time, sequence type, flip angle, matrix size and field of view define the way in which the brain is scanned and the MR image created. Repetition time (TR) is the time it takes to acquire one volume of the brain, i.e. all slices that make up the whole brain, and is usually set between 2-3 s. This parameter determines the time interval between successive excitation pulses (see Figure 10). The MR signal is recorded at every TR. A TR of >3 s is considered as a long TR, a TR of <2 s is considered to be a short TR (Weishaupt, Köchli, & Marinček, 2001). A short TR leaves little time for the spins to recover; therefore another parameter is adapted to ensure a good signal, the echo time. The echo time (TE) determines the time interval between the excitation pulse and data acquisition and is substantially shorter than the TR (e.g. 30 ms). The angle of the pulse is also referred to as flip angle and is generally set at <90° (e.g. at 80° as in the current fMRI studies). Each volume is made up of a number of slices of a certain thickness. The smallest feature of the volume, the voxel, is a 3D extension of a pixel. In addition to the slice thickness, the voxel size is determined by the matrix size and the field of view (FOV). Given a certain FOV, a higher matrix size leads to a better resolution (see Figure 11 as a 2D illustration of the interplay between FOV and matrix size). Overall, the slice thickness provides one dimension and the FOV and matrix size provide the other two dimensions for the voxel size.

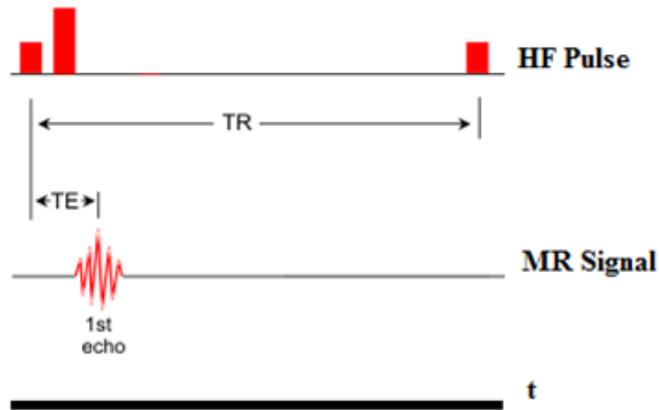


Figure 10 - Illustration showing the relationship between repetition time (TR) and echo time (TE).

HF Pulse=high frequency pulse, MR signal=Magnetic resonance signal, t=time, adapted from

<http://spinwarp.ucsd.edu/neuroweb/Text/br-100/br-1002.gif>.

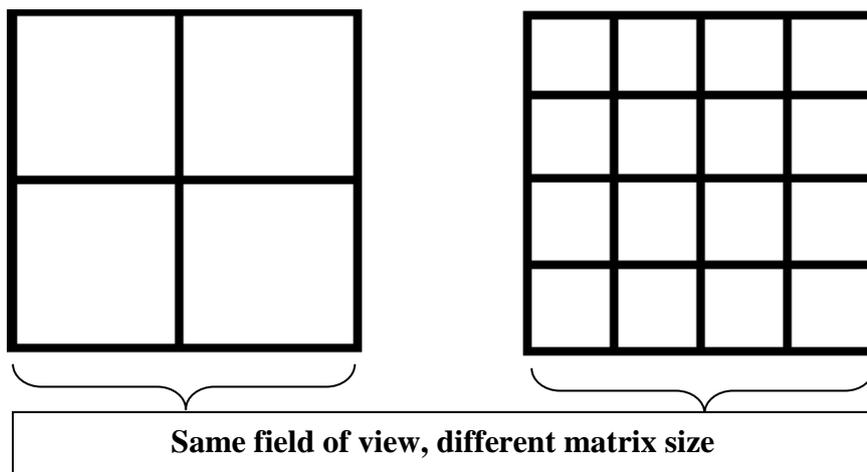


Figure 11 - Illustration of field of view and matrix sizes 2x2 and 4x4.

Three parameters determine the contrast in the MR image: proton density, T1 and T2 times. The proton density reflects the maximum MR signal that can be obtained which in turn is determined by the number of spins that are available to be stimulated in a certain volume. The T1 time determines the recovery time of spins after excitation. The T2 time determines how

quickly the MR signal decays. T1-weighted images or anatomical images take a long time to acquire, have a small resolution and a good grey-to-white-matter contrast. The TR sets an upper limit on the T1 time as it restricts the time for recovery of the spins (to the duration of the TR). A TR of >1.5 s ensures that all types of tissues can recover (Weishaupt, et al., 2001). The TE, the time between excitation by a high frequency pulse and the recording of the MR signal, determines the T2 image contrast. A long TE, i.e. >60 ms ensures that differences in signal contrast between different types of tissue are visible (Weishaupt, et al., 2001). Cerebro spinal fluid (CSF) for instance has a short T2 time and appears light on MR images. The T2-weighted images form the basis for the BOLD response.

Image acquisition requires several steps: excitation, phase coding, echo and recoding. There are a number of sequences that can be used to perform these steps. The echo planar imaging (EPI) sequence with its short acquisition time makes this type of sequence especially suitable for fMRI experiments. EPI relies on a single excitation pulse and a rapid switching of gradients (Mansfield, 1977).

1.4.3. The BOLD signal

In 1990, Ogawa and colleagues showed that functional brain mapping is possible by using the venous blood oxygen level-dependent (BOLD) signal (Ogawa, Lee, Kay, & Tank, 1990). It is linked to neural activity and is nowadays the main measure used in fMRI (Logothetis, 2003; Logothetis & Pfeuffer, 2004). The basic concept for brain imaging techniques capitalize on the coupling of cerebral blood flow (CBF) and volume, metabolic changes accompanied by changes in energy demands and neural activity (Logothetis, 2003; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). Following a period of neural activity, blood flow is increased in the region that is activated; this increase gives rise to the haemodynamic response (Figure

12). The precise neurobiology underlying the link between neural activity and the haemodynamic response, also referred to as neurovascular coupling, yet remains to be understood completely (Arthurs & Boniface, 2002). CBF and the cerebral metabolic rate of oxygen consumption interact in producing the BOLD signal. As the name already indicates, the BOLD signal relies on changes in oxygen levels in the haemoglobin (Hb) molecule. The magnetic properties of Hb are altered depending on the level of oxygenation (Pauling & Coryell, 1936). Upon neural activity, oxygen is consumed and the Hb molecule becomes deoxygenated, i.e. oxygen-free. Oxygenated Hb is diamagnetic, whereas deoxygenated Hb is paramagnetic, i.e. magnetic. It is the ratio between these two types of magnetic susceptibilities that allows a signal to be measured during MRI (Weishaupt, et al., 2001). As shown in Figure 12, neural activity initiated by a stimulus, triggers neurovascular coupling. The haemodynamic response is at the heart of the BOLD signal, the former which is produced by increases in local blood flow and concurrent, yet smaller, increases in blood oxygenation which produces a change in the ratio of deoxygenated to oxygenated blood. Former is also affected by the blood volume.

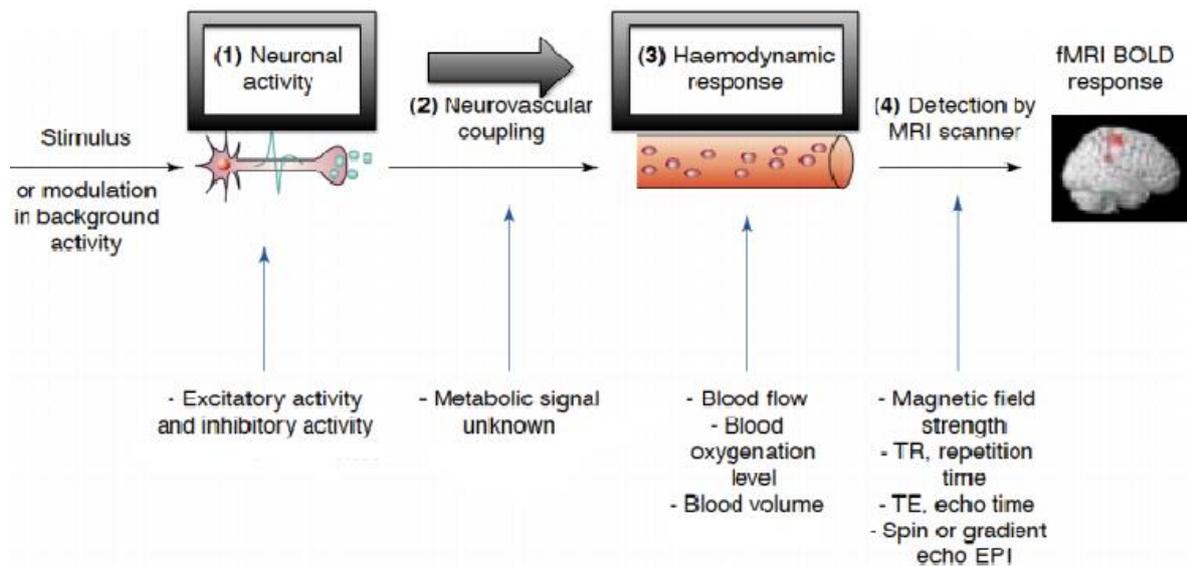


Figure 12 - Illustration of the way from neural activity to the blood oxygen level-dependent (BOLD) response as assessed with fMRI.

fMRI=functional Magnetic Resonance Imaging, TR=repetition time, TE=echo time, EPI=Echo planar imaging, adapted from Arthurs and Boniface (2002).

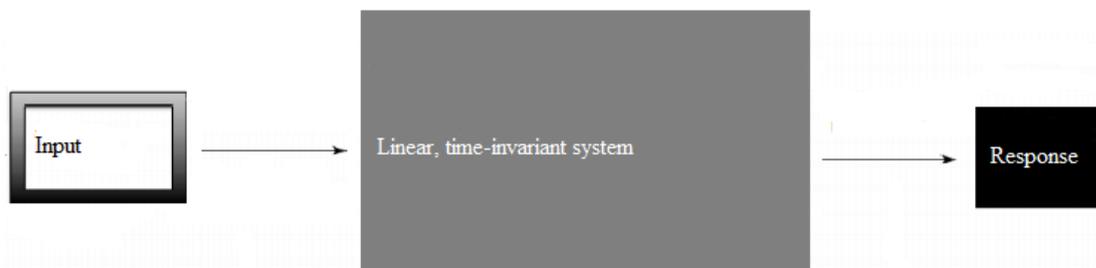


Figure 13 - Simplified illustration of the mathematical assumptions underlying the pathway from neural activity (input) to the blood oxygen level-dependent (BOLD) response.

Adapted from Arthurs and Boniface (2002).

Figure 12 could be dramatically simplified by leaving out the processing steps from neural activity to the BOLD signal and replacing these with components that allow for the mathematical decomposition of the BOLD signal (see Figure 13). The BOLD response can be

seen as a linear, time-invariant system (e.g. Boynton, Engel, Glover, & Heeger, 1996; Cohen, 1997). In any time-invariant system the (BOLD) response of that system to any kind of input can be predicted once the reaction of the system to an impulse is known, this in turn can be used to predict responses of the systems to future inputs (Ashby, 2011). The linearity characteristic of the system offers the chance to create a straightforward statistical model that models the time course of the BOLD signal which would be expected given some particular time course of neural activity, using the mathematical operation of convolution (Poldrack, Mumford, & Nichols, 2011). The application of convolution to a linear, time-invariant system results in an impulse response function, also known as haemodynamic response function (HRF) in neuroimaging (Poldrack, Mumford, & Nichols, 2011). It is important to point out that the HRF is a model of the BOLD signal under ideal circumstances.

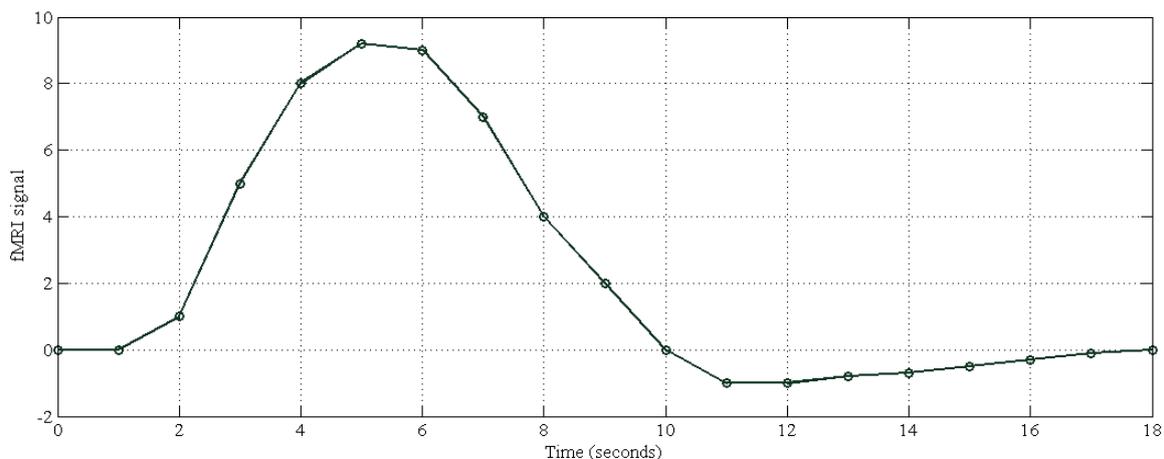


Figure 14 - Illustration of the haemodynamic response function (HRF).

fMRI=functional Magnetic Resonance Imaging, adapted from Glover et al. (1999).

The typical time course of the HRF is depicted in Figure 14. Its' onset starts roughly at 2 s post-stimulus (Kwong et al., 1992) which is the time it takes blood to travel from arteries to capillaries and veins. The HRF reaches its peak after 6–12 s and returns to baseline following

a post-stimulus undershoot (Buxton, Wong, & Frank, 1998; Logothetis, Guggenberger, Peled, & Pauls, 1999).

1.4.4. *Pre-processing*

The goal in any fMRI analysis is to reveal the neural correlates of the task at hand. Raw data, as it comes out of the scanner is not suited for this goal. Pre-processing of the data is performed to clear the signal from non-task-related sources of variability. Noise in statistical terms can be seen as any kind of variability in data that is not explained by the statistical model. There is systematic and un-systematic variability, here we are concerned with systematic noise for which we correct the data. Scanning offers various sources of systematic noise, e.g. head movements. To reduce the amount of noise and allow for group-level comparisons and relevant statistical inference, spatial pre-processing is applied. Here, the data was re-sliced, realigned, normalised and smoothed (see Figure 15, note that spatial pre-processing is performed on the single-subject-level, thus for every participant).

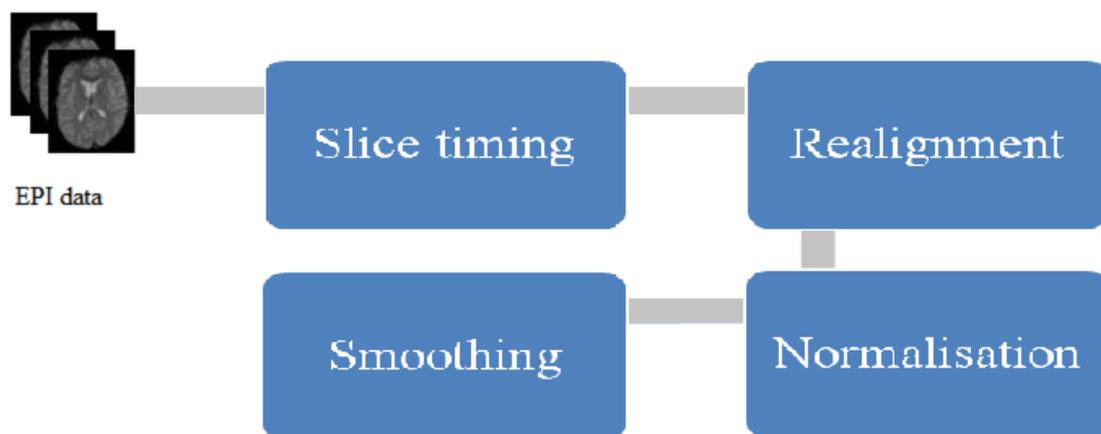


Figure 15 - Steps in spatial pre-processing of Echo Planar Imaging (EPI) data.

1.4.4.1. Slice time correction

A volume of the brain is acquired as a series of slices (see e.g. EPI data in Figure 15). Given this acquisition, there will be a temporal difference between the first and the last slice that is acquired. In case of an interleaved slice acquisition, for instance, all odd or even numbered slices are acquired first, followed by the even or odd numbered ones in order to account for the temporal difference. In that case, pre-processing should start with slice time correction (e.g. Sladky et al., 2011). Slice time correction temporally interpolates the slices and allows making certain assumptions about the images such as that a volume occurred at a particular point in time. The correction is usually done in reference to particular slice, e.g. the middle slice. Scanning with an inter-slice gap is thought to reduce intra-voxel de-phasing effects (Robinson, Windischberger, Rauscher, & Moser, 2004), which are due to an inhomogeneity in the static magnetic field and might cause signal extinction.

1.4.4.2. Realignment

Realignment aims to bring images into alignment and corrects for movement that might have occurred during scanning. Movement is thereby defined as translation (that is on an axis) or rotation (that is around an axis, see Figure 16 for illustration). Each image is realigned to the next in time series (see Figure 16), using previously estimated movement parameters (3 describing translation on x , y , and z axis, and 3 describing rotations around the x , y , and z axis which are labelled as pitch, roll and yaw). The original images are then rewritten, this time corrected for movement using rigid body transformation (rigid body is one type of transformation and referred to as such because the shape of the head is not changing, it remains a rigid body). The data in the current studies applied a 5 mm threshold for movement thus participants who moved more than 5 mm were excluded from subsequent analyses.

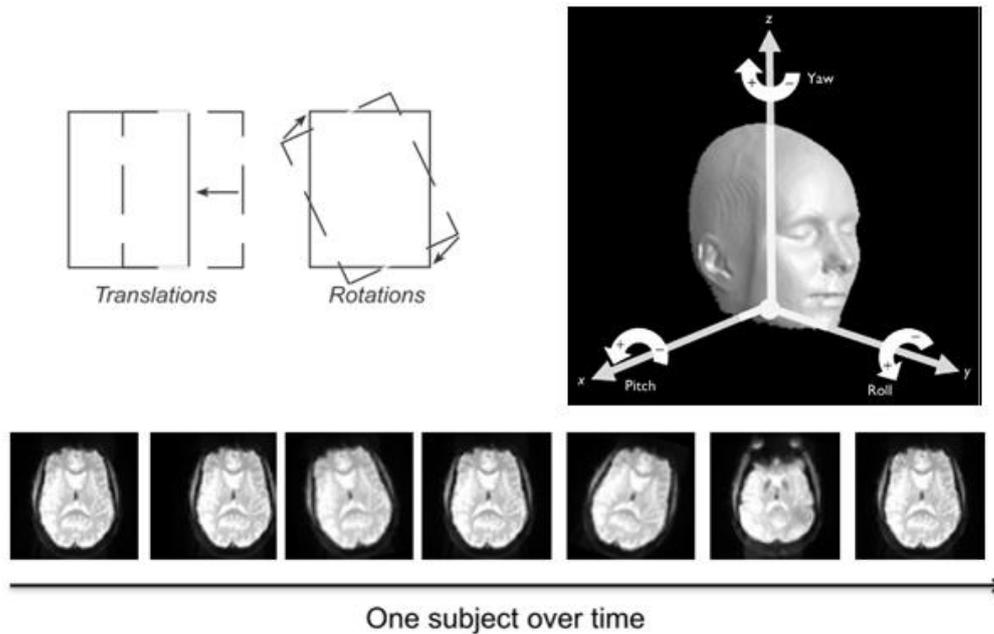


Figure 16 - Illustration of translation and rotation (upper left panel), rotation in detail (upper right panel) and movement in one participant across time series (lower panel).

Adapted from Heim et al. (2006)

1.4.4.3. Normalisation

In order to compare the brain's anatomy across participants and to assign observed activity to a particular anatomical structure, data has to be mapped onto a common anatomical space. This is the aim of normalisation. The simplest way of transformation model for normalisation uses the general linear transformation or affine transformation. A feature of affine transformations is that any set of points that fell on a line prior to the transform will continue to fall onto that line after the transform (Poldrack, Mumford, & Nichols, 2011). Thus, it is not possible to make radical changes to the shape of an object (such as bending) using affine transforms. Participants, even MZ twins, however differ in brain structure (Toga & Thompson, 2005). One might for instance have a larger frontal lobe yet a smaller hippocampus, in order to account for these differences, non-linear transformations are applied additionally to shrink and stretch the brain

into a common anatomical space. Such anatomical spaces are referred to as standard or stereotaxic spaces. The most famous of these makes use of a 3D Cartesian space and was developed by Jean Talairach (Talairach, 1967; Talairach & Tournoux, 1988) based on one hemisphere of an elderly lady. Orientation in the stereotaxic space in fMRI is given by an imaginary line that goes through the upper part of the anterior commissure (AC) and the lower part of its posterior counterpart, the posterior commissure (PC). As shown in Figure 17, the crossing between the AC-PC line and the interhemisphere line (vertical line of anterior commissure, VCA, which is orthogonal to the AC-PC line) which defines the origin of the stereotaxic space. Another space is the Montreal Neurological Institute (MNI) space. The latter was more recently developed at the MNI on the basis of 152 high resolution structural scans of the general population, that form the MNI template implemented in fMRI analysis programs such as Statistical Parametric Mapping (SPM).

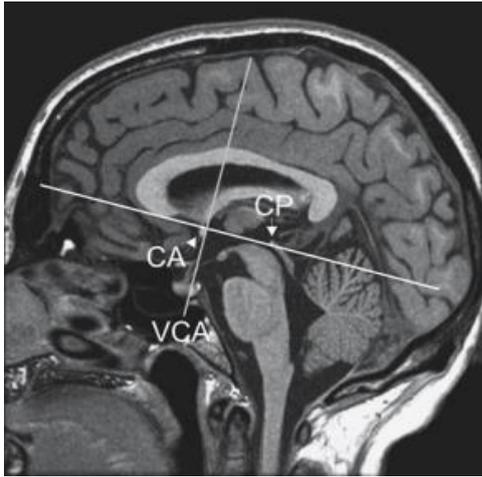
As soon as the locations of activation are identified, atlases can be used to identify the anatomical structure that underlies task-related activity. In order to achieve comparability between brain spaces, transformation of coordinates between, for instance, MNI and Talairach and Tournoux (1988), have been done. The fMRI coordinates can be transformed using linear transformations

see e.g.: <http://www.nil.wustl.edu/labs/kevin/man/answers/mnispace.html>) or non-linear ones,

see mni2tal.m or <http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>

(Brett, Johnsrude, & Owen, 2002).

In general, spaces in neuroimaging follow the convention of representing the left-right dimension by x , anterior-posterior by y and inferior-superior by z .



CA=anterior commissure,

CP=posterior commissure,

VCA=vertical line of anterior commissure.

From Schneider and Frank (2007).

Figure 17 - Illustration of the origin of the coordinate space.

1.4.4.4. Smoothing

Smoothing of the images is subsequently applied during pre-processing to reduce noise as well as the number of independent statistical tests that might have to be performed. Smoothing blurs the images by replacing the BOLD signal at each voxel with the weighted (by distance) average of the BOLD signal in the surrounding voxels. It also involves the application of a filter to the image, which removes high-frequency information. The current studies used a Gaussian filter or kernel of 8 mm at full width half-maximum (FWHM). In general, the larger the Gaussian filter, the higher the chance of finding large scale patterns of activation. A general recommendation is to smooth with a filter that is 1-3 times the voxel size (Ashby, 2011). There are a number of reasons to smooth data. First, smoothing increases the signal to noise ratio. BOLD activation patterns are generally expected to extend across a large number of voxels, therefore there is a net benefit in reducing the amount of small scale, and biologically most likely not plausible, activations. Second, as normalisation does not correct for all spatial location differences, blurring the data helps to increase the spatial matching between participants.

1.4.5. Experimental Designs

fMRI is particularly of use in collecting information on the neural correlates of task performance. Experimental task designs come in different flavours, i.e. block or event-related designs. The tasks used in the current studies during fMRI relied on a block design. In a block design, a session consists of series of blocks, alternating between the presentation of activation blocks and the presentation of control blocks. Within each block participants perform the same task over and over again for the duration of the block. The block design has the benefit that many images can be collected and that the BOLD signal collected over this block of trials is additive (see Figure 18). Also, the statistical power in such studies is considered to be greater than that obtained in event-related designs (Amaro & Barker, 2006).

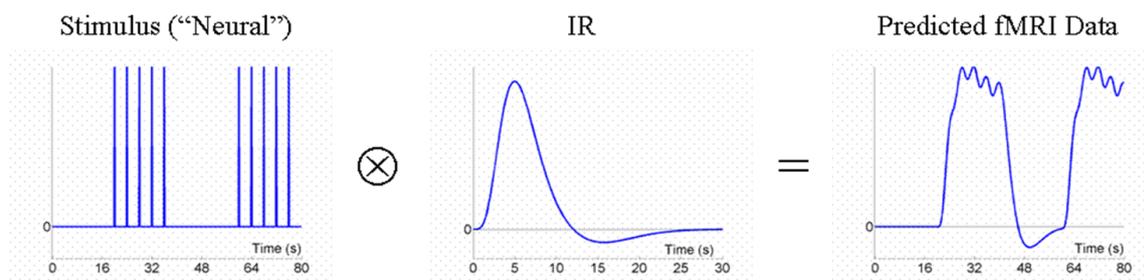


Figure 18 - Illustration of the additive blood oxygen level-dependent (BOLD) response in a block design.

IR=impulse response function, fMRI=functional Magnetic Resonance Imaging. From <http://imaging.mrc-cbu.cam.ac.uk/imaging/DesignEfficiency>.

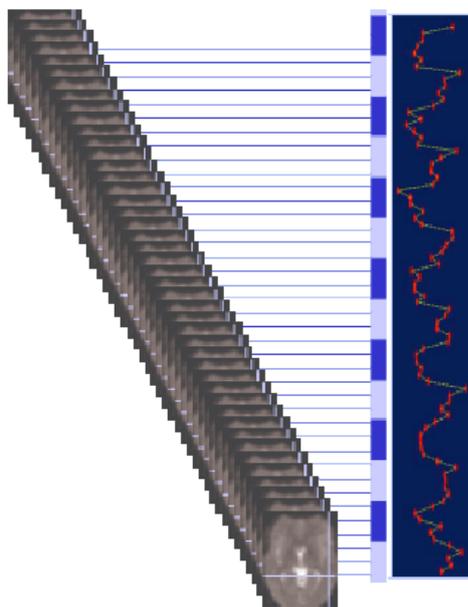
1.4.6. fMRI Data Analysis

Data “post-processing” is generally performed in two steps, first at the single-subject-level and second at the group-level. Both steps are necessary in order to prepare the fMRI data for subsequent statistical analyses and thereby allow inferences about the neural correlates of the task at hand. One of the most widely used programs to analyse fMRI data is SPM, obtained from: <http://www.fil.ion.ucl.ac.uk/spm/> (Friston, Ashburner, Kiebel, Nichols, & Penny, 2006).

At single-subject-level, a model is set up in order to specify the time course of the events/blocks that took place during the scanning (see Figure 19). This will result in a design matrix wherein the conditions, their onsets and durations are specified. The BOLD signal in block designs is modelled using a boxcar function taking into account the parameters specified in the design matrix. The general linear model (GLM) is then applied at every voxel in order to model the BOLD signal. The GLM relies on the following equation:

$$y = X\beta + \varepsilon$$

wherein X comprises the design matrix, β the treatment and ε the error term. The parameters in the β term are the ones that are to be estimated and tested for significance. The single-subject-level analysis results in an overview of the areas of activation in one subject.



Times series data is shown on the left, the alternating conditions are depicted in light and dark blue, the MR signal is shown on the right.

Figure 19 - Illustration of the blood oxygen level-dependent (BOLD) signal in one voxel throughout the scanning of one participant.

Subsequently, group-level analyses are preformed, wherein information across participants is integrated.

Similar to first-level analyses, β parameters are estimated and tested for significance but this

time on basis of the whole sample. Participants are hereby treated as random, which is why this is also referred to a random-effects model. One way to think about fixed and random factors is to imagine a replication of a certain study. This replication would use exactly the same task and design but in the fixed effect terms would recruit exactly the same participants again whereas in random effect terms would recruit at random different participants (Field, 2009). A random-effects analysis allows us to expand inferences to the level of the population. Significance of voxels is assessed by applying certain thresholds. For instance, family wide error (FWE) corrected at .05 indicates that active voxels have passed a .05 significance level that has additionally been corrected for multiple testing. Another way of setting a threshold on the results is given by setting a cluster size threshold, k_e , onto the results, meaning that only clusters that have a higher number of voxels than k_e will be presented. This is applied in order to obtain biologically meaningful activation, i.e. a cluster of three voxels might result as significant yet might not be biologically plausible and interpretable. Therefore, a k_e of 20-30 voxels, depending on the cluster size of the regions of main interest, might be chosen.

A variety of tools can be used to analyse the research questions one aims to answer in fMRI data analyses. The main interest generally lies in searching for neural correlates of a certain task contrast (wherein the BOLD signal during an activation condition is compared with the BOLD signal obtained during a control condition). One way to look for brain activity is to inspect the whole brain in order to reveal areas that are functionally relevant for a certain task, another is to focus on an a priori specified region, the former is generally known as a whole brain approach, the latter as region of interest analysis (ROI). There are some problems that can be encountered with whole brain analyses. One set of problems is that of multiple comparisons. A whole brain analysis focuses on the voxel as the unit of measurement and performs a statistical test at every voxel, which leads to a high amount of tests performed and to a potentially high amount of false positives, i.e. a test result that is not correct in reality

(Field, 2009). One way to circumvent this issue is given by using a region rather than a voxel as unit of measurement, and focussing on the activation obtained in that region. Difficulties however have also arisen with ROI approaches (Vul, Harris, Winkielman, & Pashler, 2009). Brain regions that are linked to behavioural outcomes should be selected in an independent fashion (e.g. from atlases) to avoid the non-independence error. The latter occurs, if, for instance the BOLD response in an area that appears to be significantly activated in response to a behavioural task, is used to test for a correlation with that task, this process has also been termed “double dipping” (Poldrack, 2007).

1.4.7. Summary Functional Magnetic Resonance Imaging

fMRI is a non-invasive technique used to reveal brain function in vivo. The main indicator of brain activity is given in by the BOLD signal. The studies presented in chapters three and four, investigated the BOLD signal underlying antisaccade task performance. In chapter three the activation obtained during the task was correlated with schizotypy features, thereby aiming to reveal the specific neural responses to positive, negative and disorganization-related schizotypy. In chapter four, the amount of genetic influences on the brain activity obtained during the antisaccade task was estimated, and thereby the quality of the antisaccade task as a valid imaging genetic endophenotype assessed.

1.5. Overview over the Current Studies

The current studies were necessitated by the following gaps in the previous literature:

- a lack of knowledge on the aetiological components that contribute to the link between schizotypy and other traits, most notably neuroticism,
- mixed evidence for the neural correlates of schizotypy, specifically sparse evidence on the dimension-specific brain dysfunctions and
- the use of brain measures as endophenotypes with a lack of conceptual proof of heritability of brain function measures, such as the BOLD response (de Geus, Goldberg, Boomsma, & Posthuma, 2008) with a specific application to the antisaccade task.

The current research line aims to fill these gaps and add more evidence to link schizotypy and schizophrenia spectrum disorders from a quantitative genetics and neurocognitive point of view. First, the aetiological nature of schizotypy was investigated, by means of a classical twin study and the frequently observed overlap between schizotypy and neuroticism explained. Second, the neural correlates of schizotypy, by means of a measure well-known as a neurocognitive deficit in schizophrenia spectrum disorders, i.e. antisaccade task performance, examined. Finally, building up on the neural correlates of the antisaccade task obtained from the previous work, the heritability of the neural correlates of antisaccade task performance estimated.

The study presented in the next chapter of the cumulative dissertation is based on data drawn from the Australian National Health and Medical Research Council Twin Register which received funding from the National Health and Medical Research Council (NHMRC) grants to Nicholas G. Martin and NIH grants to Andrew C. Heath.

Data analysis for this chapter was supported by the Deutsche Forschungsgemeinschaft (DFG) Emmy Noether program (ET 31/2-1) to Ulrich Ettinger; a project grant of the Förderprogramm für Forschung und Lehre (FöFoLe) of the Ludwig-Maximilians-University Munich to Ulrich Ettinger (Reg-Nr. 645); and a travel grant of the Graduate Center at the Ludwig-Maximilians-University Munich to me. The study presented here has been published as an original article:

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2. Substantial genetic overlap between Schizotypy and Neuroticism: A Twin Study

2.1. Introduction

Schizotypy is defined as schizophrenia-like traits expressed in an attenuated form (Chapman et al., 1978; Meehl, 1989; Rado, 1953; Venables & Bailes, 1994; Vollema & van den Bosch, 1995). Dimensions of schizotypy have been labelled according to their similarity to schizophrenic symptoms (Kwapil, et al., 2008; Vollema & van den Bosch, 1995). Cognitive and perceptual anomalies are summarized as positive (Chapman, et al., 1978; Eckblad & Chapman, 1983) while diminished interest in social interaction and pleasure deficits are regarded as negative schizotypy (Chapman et al., 1976). Other dimensions such as impulsivity and hypomania are also part of the multidimensional construct of schizotypy (Vollema & van den Bosch, 1995).

Previous studies indicate heritability estimates (h^2) of .33-.53 for positive, .27-.50 for negative features and .28-.58 for hypomania and impulsivity (Claridge & Hewitt, 1987; Hay et al., 2001; Linney et al., 2003; MacDonald et al., 2001). Several lines of evidence link schizotypy and the schizophrenia spectrum. Schizotypal personality disorder is more common in relatives of schizophrenia spectrum patients than in the general population (Kendler et al., 1993). Moreover, longitudinal studies indicate that schizotypal individuals are at higher risk for developing a psychosis-like pathology (Chapman et al., 1994), and twin and family studies reveal increased levels of schizotypal traits in first-degree relatives of schizophrenia patients (Kendler & Walsh, 1995). Adoption studies similarly report higher rates of schizotypal traits in offspring of schizophrenic patients strengthening evidence for a genetic association between

schizophrenia and schizotypal traits (Tienari, et al., 2003). In addition, gender differences in schizotypy are similar to those found in schizophrenia, with males presenting more frequently with negative and some evidence for a predominance of positive traits in females (Venables & Bailes, 1994).

Neuroticism is a heritable trait (Bouchard, 1994) characterized by high tension, irritability, dissatisfaction, shyness, low mood and reduced self-confidence (Eysenck & Eysenck, 1964). Females are known to score higher on neuroticism than males (Lynn & Martin, 1997). Neuroticism is associated with schizotypy in the general population, especially with the positive features of schizotypy (Barrantes-Vidal et al., 2009; Ettinger et al., 2005). Clinically, neuroticism also acts as both a risk- and as a maintenance-factor for full-blown psychosis (Freeman & Garety, 1999). High levels of neuroticism for instance increase odds for psychosis (Van Os & Jones, 2001) and are present in patients with schizophrenia (Horan, Blanchard, Clark, & Green, 2008). Additionally, both relatives of patients with schizophrenia and individuals high on schizotypy show enhanced emotional reactivity to daily stressors (Myin-Germeys, Krabbendam, & van Os, 2003), score high on neuroticism (Maier, Mingos, Lichtermann, Heun, & Franke, 1994) and frequently present with major depressive disorder (Baron & Gruen, 1991). Schizotypy increases risk for affective disorders (Verdoux et al., 1999), suggesting the existence of reciprocal associations between schizotypal and affective traits.

Given the oft-replicated association between schizotypy and neuroticism, and the relevance of these traits to the clinical domain, it is important to clarify the nature of this association. Behavioural genetic analyses using monozygotic (MZ) and dizygotic (DZ) twins may be of value. Classical twin designs use correlations between MZ and DZ twins and decompose these into genetic as well as environmental components. The same logic can be applied to the covariation between traits to assess the amount of common genetic aetiology

between variables. To our knowledge, no study to date has investigated the extent to which the association between schizotypy and neuroticism is of genetic origin. Therefore, based on the strong evidence of a correlation between neuroticism and positive schizotypy we aimed first to replicate the association of these traits. Subsequently, we examined potential gender differences in neuroticism and positive schizotypy. Then, we decomposed this covariance into genetic and environmental components finding significant evidence for shared genes. Driven by the results of the first analysis, a second, more comprehensive analysis was conducted to examine the extent of genetic overlap between positive schizotypy and anhedonic, hypomanic and impulsivity features of schizotypy in addition to neuroticism.

2.2. Methods

2.2.1. *Sample*

An unselected sample of 8,538 twins born 1964-1971 (4,087 males, 4,451 females; 3,378 MZ, 2,896 same-sex DZ (DZ_{ss}), 2,186 opposite-sex DZ (DZ_{os}) and 78 twins of unknown zygosity) drawn from the Australian National Health and Medical Research Council Twin Register was targeted in a mailed questionnaire survey conducted in 1989-1991. Despite extensive efforts to recontact all twins initially targeted, contact details could be generated for 6,122 twins. Those twins contacted were mailed a survey and were followed-up up to five times by phone if necessary. A total of 2,294 twin pairs and 474 individual twins (i.e. 5,062/6,122 contactable twins or 83%) provided any kind of questionnaire data. Of these 5,062 individuals, 3,349 individuals fulfilled our inclusion criteria which are outlined below.

2.2.2. *Schizotypy*

Schizotypy was assessed with a 12-item version of the Chapman Psychosis-Proneness Scales (PPS, Chapman & Chapman, 1985; Eckblad & Chapman, 1986). The PPS consists of four factors showing good reliability with Cronbach's alpha around the .80's for all four scales (Chapman et al., 1994).

The 12-item version consists of six scales with two items each. Of these, the Magical ideation (Mag) and Perceptual aberration (Per) scales assessed positive and the Social and Physical anhedonia scales (San and Pan, respectively) assessed negative schizotypy. Hypomania (Hyp) and impulsivity/non-conformity (Imp) scales targeted elevated mood and impulsive and unconventional behaviours.

The Mag scale (Eckblad & Chapman, 1983) taps beliefs about magical and unrealistic causes and effects. Sample items include items such as "I have wondered whether the spirits of the dead can influence the living". The Per scale (Chapman et al., 1978) covers body image and perceptual distortions, an example of an item from this scale is "Sometimes part of my body seems smaller than it really is". San (Eckblad et al., 1982) focuses on a lack of interest in experiencing pleasure from interpersonal relationships. Here, a sample item is "I prefer hobbies and leisure activities that do not involve other people". Pan pertains to a lack of experiencing physical pleasure (Chapman et al., 1976). Items such as "Trying new foods is something I have always enjoyed" are used here (please note that this item is scored reversed). Hyp captures features similar to but less severe than those of mania, such as grandiose ideas and elevated mood, the latter is captured by items such as "I often have moods where I feel so energetic and optimistic that I feel I could outperform almost anyone or anything". The Imp scale (Eckblad & Chapman, 1986) captures impulsivity, antisocial behaviour and insensitivity to others and is

assessed with items such as "I usually find myself doing things 'on impulse' ". All items were answered on a yes/no scale and scored in the direction of higher schizotypy.

2.2.3. *Neuroticism*

Neuroticism was assessed with the short form of the Eysenck Personality Questionnaire-Revised (Eysenck et al., 1985). All 12 items (e.g. "Does your mood often go up and down?") were answered on a yes/no scale. Higher scores indicated greater levels of neuroticism. Reliability for the neuroticism scale was good (Cronbach's alpha=.81).

2.2.4. *Zygoty*

Zygoty was determined by response to standard items and checked on a subset through genotyping micro-satellite markers across the genome (Cornes et al., 2005). Errors in zygoty assignment are estimated to be <1%.

2.2.5. *Data preparation*

After list-wise deletion of those who did not complete at least 75% of the neuroticism scale (nine or more items) and all of the schizotypy items 3,349 (1,449 MZ, 1,105 DZ_{ss} and 795 DZ_{os}) individual twins remained. The total sample size of 3,349 individual twins was composed of complete twin pairs (1,253 complete pairs) as well as of single twins (843 single twins). Excluded (5,062 - 3,349=1,713) individuals did not differ significantly from included ones in terms of zygoty status, gender distribution or educational level.

Given our exclusion criteria, we allowed for missing items on the neuroticism scale, therefore we used a percentage score. For every twin we calculated a sum score and a count score reflecting the item response and the number of items responded to respectively. Subsequently, we calculated a percentage score (sum score/count score) with higher percentage scores reflecting a higher level.

Item responses were subjected to principal component analysis (PCA) with varimax rotation using Predictive Analysis SoftWare (PASW Statistics, version 18; SPSS-Inc., 2009). Factors with eigenvalues greater than one were retained. Factor scores were extracted; missing factor scores were replaced by the mean and all corrected for age and gender (MacDonald, et al., 2001; McGue & Bouchard, 1984). Standardized residuals were used for further analyses.

2.2.6. *Preliminary analyses*

Participation bias was investigated by comparing factor scores of complete pairs with those of individual twins whose co-twin did not participate (3,349 twins; 1,253 complete pairs, 843 single twins). Effects of zygosity and twin order were examined by comparing MZ and DZ twins with each other and first- and second-born twins with each other, respectively. Pearson's r will be reported if not otherwise indicated.

2.2.7. *Quantitative genetic modelling*

The classical twin design decomposes phenotypic correlations between traits into components consistent with additive genetic (A), non-additive genetic (D; e.g. inter-actions between alleles), common environmental (C; e.g. any environmental factor that creates resemblance between family members) and unique environmental (E; e.g. individual friends but also

measurement error) influences. MZ share all while DZ twins share on average half of their genes. MZ twins correlate perfectly for A, D and C, but are uncorrelated for E. DZ twins correlate .5 for A, .25 for D, perfectly for C and are uncorrelated for E. Higher MZ than DZ twin correlations indicate genetic influences. Non-additive genetic and common environmental influences cannot be estimated simultaneously in twins reared-together. Therefore, either ADE or ACE models were fitted. Unique environmental influences are reflected in MZ twin correlations as MZ twins correlate perfectly for A and C (the remaining proportion of unexplained variance therefore must be due to unique environment). Model fitting was carried out using the extended structural equation modelling package OpenMx (Boker et al., 2011) and R (R-Development-Core-Team, 2010). Nested sub-models were fitted to test the contribution of each variance component (i.e. A, C or E). Comparison of model fit between nested sub-models (e.g. AE) and the full model (ACE) provides information on the importance of the respective component (here: C). Models were fitted using full information maximum likelihood and evaluated by Akaike's information criterion (AIC; Akaike, 1987). Thereby, a lower AIC was preferred. The difference in log-likelihood between the full and the nested sub-models is distributed as a χ^2 -statistic, which together with the difference in degrees of freedom between models is used to test for significance of model fit.

Modelling included three analyses. First, univariate sex-limitation modelling was done for neuroticism and positive schizotypy in data from 3,349 twins (1,253 complete pairs, 843 single twins). Given frequently reported sex differences between genders, quantitative and qualitative sex differences were examined. Quantitative sex differences are indicated if differences in the amount of A, C or E influences emerge between genders (if e.g. positive schizotypy is more heritable in males than in females), qualitative differences emerge if different as opposed to same A, C or E influences operate between genders (Neale & Maes, 2002).

Second, bivariate modelling was performed to estimate the amount of genetic and environmental overlap between positive schizotypy and neuroticism. Finally, multivariate modelling was applied to examine the interrelations between neuroticism and all facets of schizotypy. Both analyses made use of within-trait within-twin, within-trait cross-twin (e.g. neuroticism in twin one correlated with neuroticism in twin two and vice versa), cross-trait within-twin (e.g. positive schizotypy and neuroticism in twin one or two) and cross-trait cross-twin correlations (e.g. the correlation between positive schizotypy in twin one and neuroticism in twin two and vice versa). Both bi- and multivariate analyses used a Cholesky decomposition of the variance-covariance matrices, wherein the number of parameters estimated is equal to the observed parameters.

2.3. Results

2.3.1. *PCA of schizotypy*

PCA resulted in four factors, the first covering items of Per and Mag scales (Per-Mag). Hyp and Imp items were combined in a second factor entitled Hyp-Imp. Items representing San and Pan were extracted as third and fourth factors, respectively. Together, these factors explained 45.9% of the variance (15.8% for Per-Mag, 11.8% for Hyp-Imp, 9.5% for San, 8.8% for Pan).

2.3.2. *Preliminary analyses*

Complete pairs and single twins were compared to test for participation bias. No significant differences on measures of interest emerged (all $p < .05$), so single twins and complete pairs

were merged for further analyses. Effects of twin order (i.e. first-born compared to second-born) and zygosity (i.e. MZ compared to DZ twins) were also not significant (all $p < .05$).

2.3.3. *Sample description*

The final sample included 3,349 twins of Caucasian origin (2,506 twins from complete pairs, 843 single twins) consisting of 1,449 MZ, 923 female (372 complete pairs, 179 single twins), 526 male (209 complete pairs, 108 single twins), 1,105 DZ_{ss}, 684 female (259 complete pairs, 166 single twins), 421 male (140 complete pairs, 141 single twins) and 795 DZ_{os} (273 complete pairs, 249 single twins) twins. Mean age of the sample was 23.19 years ($SD=2.23$; range: 16-31 years). Age did not differ significantly between zygosity groups ($F(1, 3126)=1.9, p=.17$; see Table 1).

Educational level was examined between *MZ* and *DZ* twins and between first- and second-born twins. Results confirmed comparability of both zygosity groups ($F(4, 3275)=2.15, p=.07, \eta^2_p=.001$) and of first- and second-born twins ($F(1, 3278)=.02, p=.87$). Educational level for the sample was 14.9% high school up to 10 school years, 34.9% high school up to 12 school years, 13% achieved a diploma, 13.9% completed a technical college, 19.4% completed a University degree and 1.8% completed postgraduate education (2.1% did not provide data on educational level).

2.3.4. *Sex-limitation twin modelling*

Correlation patterns per gender and zygosity for neuroticism and schizotypy are illustrated in Table 2. As correlations of same- and opposite-sex twins differed in magnitude, and to test if

these differences were significant, we first tested quantitative and qualitative sex difference models for our two main variables of interest; neuroticism and Per-Mag. Given the twin correlations in Table 2, we applied models consistent of additive genetic, common and unique environmental influences whenever $r_{DZ} > \frac{r_{MZ}}{2}$ and models consistent of additive genetic, dominance-related and unique environmental influences whenever $r_{DZ} < \frac{r_{MZ}}{2}$. A test of quantitative differences suggested that models in which path estimates were constrained to be equal across sex fit the data well for both neuroticism ($\chi^2_3 = .42, p = .94$) and for Per-Mag ($\chi^2_3 = 3.15, p = .99$), indicating no significant quantitative sex differences. Qualitative sex differences allowing for specific genetic influences on males were examined subsequently. Results again indicated that setting qualitative differences to zero lead to a non-significant drop in fit as compared to an AE homogeneity model for neuroticism ($\chi^2_1 = 1.69, p \geq .99$) and for Per-Mag ($\chi^2_1 = .55, p \geq .99$). Given the absence of significant gender differences in the current sample, data from DZ_{os} and DZ_{ss} were pooled in subsequent analyses.

Table 1 - Number of twins, sex and age composition.

	<i>MZ</i>		<i>DZ_{SS}</i>		<i>DZ_{OS}</i>	
	<i>Pairs</i>	<i>Single</i>	<i>Pairs</i>	<i>Single</i>	<i>Pairs</i>	<i>Single</i>
<i>Male</i>	418	108	280	141	273	92
<i>Age</i>	23.0 (2.2)	23.1 (2.0)	23.0 (2.3)	23.5 (2.1)	23.1 (2.1)	23.5 (2.2)
<i>Female</i>	744	179	518	166	273	157
<i>Age</i>	23.3 (2.1)	23.0 (2.8)	23.3 (2.2)	23.2 (2.3)	23.1 (2.1)	23.5 (2.2)
<i>Total</i>	1162	287	798	307	546	249
<i>Age</i>	23.2 (2.2)	23.0 (2.6)	23.2 (2.2)	23.3 (2.3)	23.1 (2.1)	23.5 (2.2)

Notes: Number of twins is shown in bold. Mean age in years (standard deviations) are reported beneath the number of twins

MZ=monozygotic

DZ_{SS}=dizygotic same-sex

DZ_{OS}=dizygotic opposite-sex.

Table 2 - Correlations between twins for neuroticism and schizotypy.

<i>Twin zygosity</i>	<i>N</i>	<i>Neuroticism</i>	<i>Per-Mag</i>	<i>San</i>	<i>Pan</i>	<i>Hyp-Imp</i>
<i>Pairs/single twins</i>						
<i>MZMM</i>	209/108	.39**	.25**	.31**	.34**	.38**
<i>DZMM</i>	140/141	.15	.19*	.10	.23**	.08
<i>MZFF</i>	372/179	.37**	.27**	.37**	.31**	.21**
<i>DZFF</i>	259/166	.08	.15*	.04	.08	.03
<i>DZos</i>	273/249	.07	.07	.04	.05	.13*
<i>MZ</i>	1449	.38**	.26**	.36**	.32**	.27**
<i>DZ</i>	1900	.09*	.13	.05	.10	.08

Notes:

Per-Mag=perceptual aberration/magical ideation

San=social anhedonia

Pan=physical anhedonia

Pearson correlations are reported

Hyp-Imp=hypomania and impulsivity/non-conformity

MZMM=male monozygotic

MZFF=female monozygotic

* $p < .05$

DZMM=male dizygotic

DZFF=female dizygotic

DZos=opposite-sex dizygotic twins

** $p < .01$.

2.3.5. Phenotypic correlations between schizotypy factors and neuroticism

First, correlations between schizotypy and neuroticism were calculated based on the whole sample. Second, correlations between schizotypy factors and neuroticism were calculated separately for each zygosity. At the phenotypic level, neuroticism and Per-Mag correlated $r=.37$ ($p<.01$). Correlations of neuroticism with San, Pan and Hyp-Imp were low ($r_{San}=.11$, $p<.01$; $r_{Pan}=.11$, $p<.01$, $r_{Hyp-Imp}=.05$, $p<.01$). Table 3 shows the inter-correlations per zygosity group. Cross-twin within-trait correlations in MZ twins range from .26 to .38 (all $p<.01$). In DZ twins, these correlations were substantially lower suggesting a heritable basis for these traits. Cross-twin cross-trait correlations were significant for MZ twins and were substantially lower in DZ twins, suggesting shared genetic influences among these traits. We next formally modelled these effects.

2.3.6. Bivariate twin modelling on positive schizotypy and neuroticism

Results of bivariate modelling of positive schizotypy and neuroticism are illustrated in the most parsimonious model depicted in Figure 20. An AE model fit the data with no significant loss of fit as compared to the full ADE model ($\chi^2_3=.55$, $p>.99$). Genetic influences however could not be dropped from the model (see E-Model: $\chi^2_3=129.11$, $p<.01$). Likewise dropping the genetic covariance between neuroticism and Per-Mag resulted in a significant loss in model fit ($\chi^2_1=48.55$, $p<.01$), thereby highlighting the importance of a shared additive genetic influence for neuroticism and Per-Mag. Unique environmental covariance also could not be dropped without reducing model fitting significantly ($\chi^2_1=58.96$, $p<.01$), indicating that unique environmental influences also act to generate covariance between positive schizotypy and

neuroticism. Narrow sense heritability estimates (which can be obtained by squaring the path estimates) are indicated by path loadings on neuroticism ($h^2=.34$; 95% CI .28-.41) and Per-Mag ($h^2=.33^2 + .42^2=.29$; 95% CI .17-.41).

The genetic correlation, an estimate of the correlation between the genetic influences on neuroticism and those on positive schizotypy based on the correlated factor solution, was .62, indicating a large amount of genetic overlap. The proportion of the phenotypic correlation explained by genetic influences was .51 (95% CI .38-.64), indicating that 51% of the phenotypic correlation between neuroticism and Per-Mag can be accounted for by shared genetic factors. The unique environmental correlation was estimated at .26. The proportion of phenotypic correlation explained by unique environmental influences was estimated at .49 (95% CI .36-.62).

Table 3 - Correlations between neuroticism and schizotypy factors per zygosity.

		<i>MZ</i>									
		<i>Twin 1</i>					<i>Twin 2</i>				
		<i>Neuroticism</i>	<i>Per-Mag</i>	<i>San</i>	<i>Pan</i>	<i>Hyp-Imp</i>	<i>Neuroticism</i>	<i>Per-Mag</i>	<i>San</i>	<i>Pan</i>	<i>Hyp-Imp</i>
<i>Twin 1</i>	<i>Neuroticism</i>		.333**	-.142**	-.114**	<u>.019</u>	.377**	<u>.199**</u>	-.084*	-.077	<u>.042</u>
	<i>Per-Mag</i>	.397**		-.065	<u>.022</u>	-.008	.184**	.264**	-.014	<u>.072</u>	<u>.028</u>
	<i>San</i>	-.100**	<u>.014</u>		-.047	-.049	-.031	-.065	.358*	<u>.038</u>	-.038
	<i>Pan</i>	-.096**	<u>.022</u>	-.035		<u>.037</u>	-.016	<u>.027</u>	-.030	.323**	<u>.007</u>
	<i>Hyp-Imp</i>	<u>.039</u>	<u>.026</u>	<u>.046</u>	-.031		<u>.064</u>	<u>.067</u>	<u>.029</u>	<u>.057</u>	.274**
<i>Twin 2</i>	<i>Neuroticism</i>	<u>.094*</u>	<u>.076*</u>	<u>.004</u>	<u>.028</u>	<u>.045</u>		.342**	-.098**	-.125**	<u>.063</u>
	<i>Per-Mag</i>	<u>.040</u>	.125**	-.012	-.006	<u>.058</u>	.390**		<u>.008</u>	-.083*	<u>.052</u>
	<i>San</i>	-.029	<u>.059</u>	<u>.050</u>	<u>.029</u>	-.008	-.092**	<u>.025</u>		-.003	<u>.060</u>
	<i>Pan</i>	-.005	<u>.012</u>	<u>.019</u>	.104*	-.005	-.096**	<u>.004</u>	<u>.014</u>		<u>.016</u>
	<i>Hyp-Imp</i>	<u>.032</u>	<u>.055</u>	-.032	-.014	<u>.079</u>	<u>.062</u>	-.018	-.038	<u>.017</u>	
		<i>Neuroticism</i>	<i>Per-Mag</i>	<i>San</i>	<i>Pan</i>	<i>Hyp-Imp</i>	<i>Neuroticism</i>	<i>Per-Mag</i>	<i>San</i>	<i>Pan</i>	<i>Hyp-Imp</i>
		<i>Twin 1</i>					<i>Twin 2</i>				
		<i>DZ</i>									

Notes: Cross-twin within-trait correlations are given in bold, cross-twin cross-trait correlations are underlined

Per-Mag=perceptual aberration/magical ideation

San=social anhedonia

Pan=physical anhedonia

MZ=monozygotic twins

DZ=dizygotic twins (with grey background)

Hyp-Imp=hypomania and impulsivity/non-conformity

* $p < .05$

** $p < .01$.

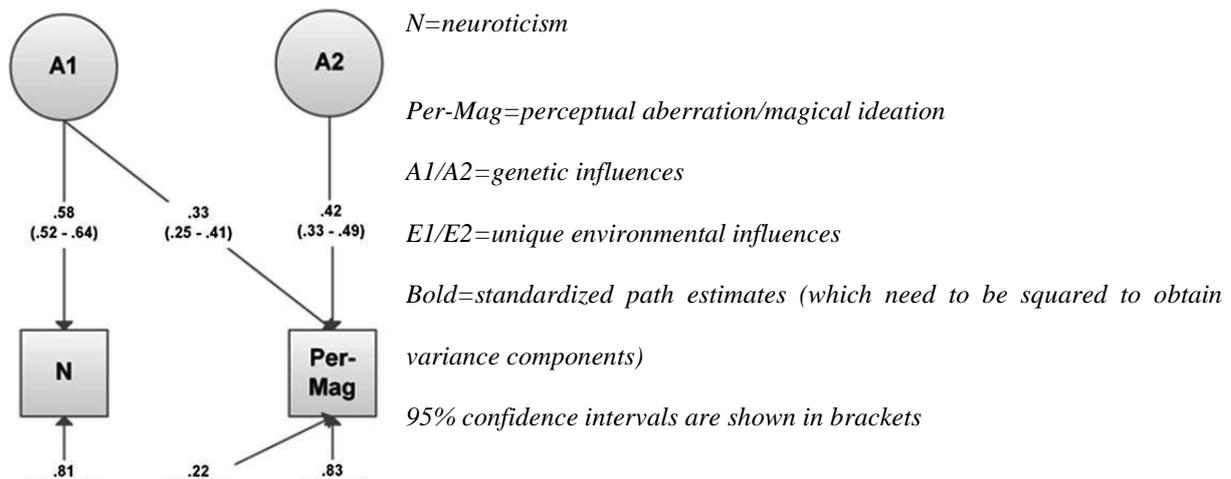


Figure 20 - Path diagram of the most parsimonious model for neuroticism and positive schizotypy.

2.3.7. Multivariate twin modelling of schizotypy and neuroticism

Moving to multivariate modelling, a five-factor Cholesky decomposition was constructed with neuroticism, San, Pan, Hyp-Imp, and Per-Mag entered in that order. To test whether Per-Mag had any significant shared genetic or shared environmental effects independent of neuroticism and the other components of schizotypy we attempted to drop the specific genetic and common environmental influences on Per-Mag, then both together. In all cases, this could be done with no significant loss of fit ($\chi^2_2=.16, p=.92$). Common environmental influences across the traits could be reduced to a single general factor ($\Delta\chi^2_{11}<.16, p>.99$) which could not itself be dropped ($\Delta\chi^2_5=11.37, p<.05$). The most parsimonious multivariate model is shown in Figure 21 and consisted of specific genetic influences on neuroticism, San, Pan and Hyp-Imp, shared genetic influences from neuroticism to positive schizotypy, a single common environmental component influencing neuroticism and schizotypy, and specific as well as shared unique environmental components. Genetic influences on Per-Mag were entirely accounted for by genetic influences shared with neuroticism, San, Pan and Hyp-Imp.

Consistent with the bivariate analysis, the multivariate analysis thus confirmed a strong (.81) genetic correlation between neuroticism and positive schizotypy, indicating large shared genetic influences. The increase in genetic correlation from bivariate (.62) to multivariate (.81) is a reflection of the increase in power (for instance to detect shared environmental effects) gained in the multivariate model. These shared genetic influences between neuroticism and positive schizotypy accounted for 46% of the phenotypic association (95% CI 23-67%). The unique environmental correlation between neuroticism and Per-Mag was significant, but more moderate at .26, accounting for a further 36% of the shared variance between the two traits. The remaining proportion of phenotypic correlation to be explained (i.e. 18%) was attributable to common environmental influences.

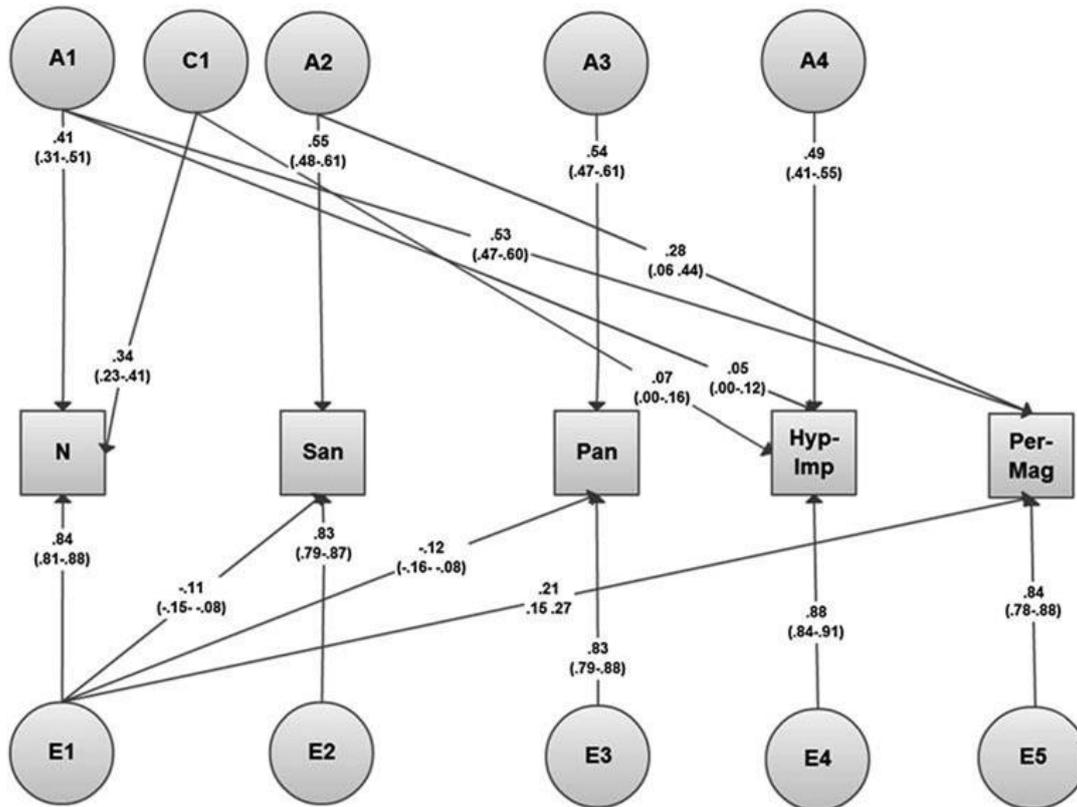


Figure 21 - Path diagram of the most parsimonious model for neuroticism and schizotypy.

A1 - A4=additive genetic influences, C1=common environmental influences, E1-E5=unique environmental influences, N=neuroticism, San=social anhedonia, Pan=physical anhedonia, Hyp-Imp=hypomania and impulsivity/non-conformity, Per-Mag=perceptual aberration/magical ideation, bold standardized path estimates, 95% confidence intervals are given below the estimate in brackets.

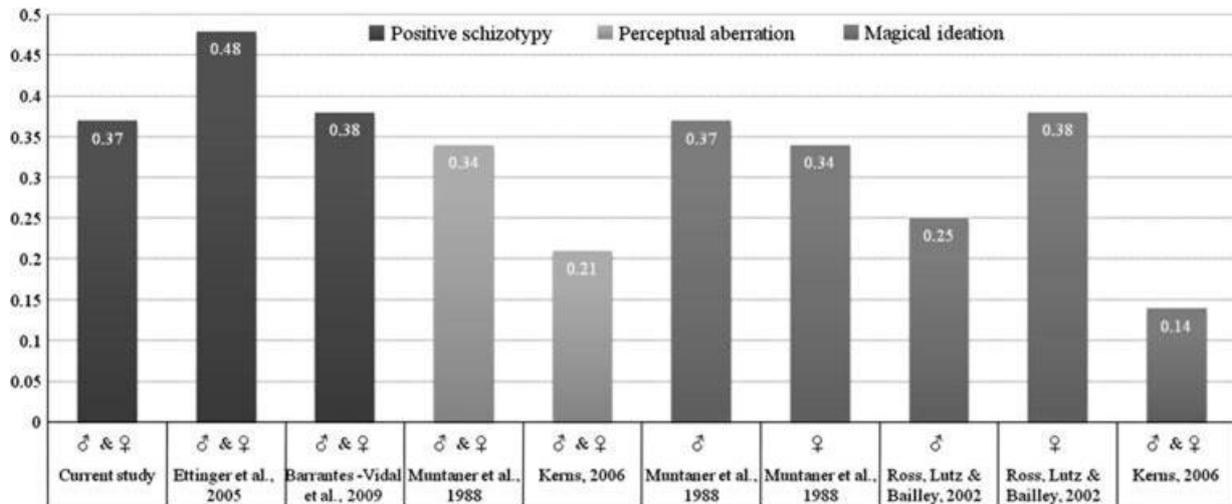


Figure 22 - Phenotypic correlations between neuroticism and positive schizotypy.

The y axis depicts Pearson's r correlations. Previous studies are listed along the x axis. The exact correlation coefficients are given in white in each column. Please note the correlations obtained by Muntaner et al. (1988) for perceptual aberration was .34 in males and females. ♂=males, ♀=females, ♂ and ♀=males and females pooled.

2.4. Discussion

The current study examined the nature of the association between neuroticism and schizotypy. First, the well-established phenotypic correlation between neuroticism and positive schizotypy was replicated and partitioned into genetic and environmental components. Second, anhedonic, hypomanic and impulsivity components of schizotypy were added to capture the full construct of schizotypy and examine the covariance of these components with neuroticism, and their net effect on the genetic influence on positive schizotypy.

The phenotypic correlation we have obtained (.37) fits nicely with previous findings. Figure 22 illustrates the association between neuroticism and positive schizotypy from various studies. Correlations of moderate size (.38 and .48) were found by Barrantes-Vidal et al. (2009) and Ettinger et al. (2005), both of these studies reported phenotypic correlation for both gender

types pooled. The studies by Muntaner et al. (1988), Kerns (2006) and Ross et al. (2002) focused on Per and Mag separately. Aside from Kerns (2006), who used a different measure to assess neuroticism (that is items from the International Personality Item Pool), all found correlations of moderate size between positive schizotypy and neuroticism similar to our finding.

Bivariate model fitting indicated that the association between positive schizotypy and neuroticism was best described by additive genetic and unique environmental influences. A substantial proportion (51%) of the association between positive schizotypy and neuroticism was accounted for by shared genetic influences, signifying a large genetic basis shared between neuroticism and positive schizotypy. Aside from the proportion of phenotypic association that was explained by shared genetic factors findings from the bivariate analysis also point to genetic influences on positive schizotypy which act independently from those on neuroticism. Previous studies examined the nature of individual differences in positive schizotypy and found evidence for significant genetic influences common with other schizotypy factors as well as independent of these (Hay, et al., 2001; Kendler & Hewitt, 1992; Linney, et al., 2003; MacDonald, et al., 2001). Despite that half of the genetic influences on positive schizotypy are independent of neuroticism, our study extends previous work by showing that a large proportion of genetic influences on positive schizotypy are shared with neuroticism. This finding from the bivariate analysis combined with previous work on the nature of individual differences in positive schizotypy motivated us to extend our work by a multivariate analysis.

Multivariate analyses included anhedonic, hypomanic and impulsivity components of schizotypy and focused on the genetic and environmental influences on positive schizotypy that could be explained by other schizotypy factors in addition to those captured by neuroticism. Common environmental influences were restricted to a single common factor exerting a modest

but significant influence on all traits, including a link between neuroticism and positive schizotypy.

No significant support was found for genetic influences specific to positive schizotypy. Instead, genetic influences on positive schizotypy were shared with neuroticism, and with the anhedonia, hypomania and impulsivity facets of schizotypy, indicating a complex genetic aetiology of positive schizotypy involving neuroticism and the other schizotypy dimensions. As has been mentioned by Loehlin (1996) the use of the Cholesky decomposition requires caution in the interpretation of the results as the order of variables entered into the Cholesky impacts on the outcome. Given the overall aim of decomposing the nature of the overlap between neuroticism and positive schizotypy as well as taking into account previous findings on the nature of positive schizotypy, we entered neuroticism first into the multivariate Cholesky decomposition, followed by the other schizotypy components in order to ensure that all the genetic and environmental influences that can be attributed to these manifest variables are covered first. This allowed us to examine the genetic and environmental influences on positive schizotypy over and above those that are shared with neuroticism, anhedonic, hypomanic and impulsivity components of schizotypy. In contrast with positive schizotypy, the anhedonic, hypomanic and impulsivity features of schizotypy showed evidence for significant additional specific genetic influences not shared with neuroticism, thereby also providing evidence for a specific genetic etiology of each of these dimensions. The multi-factorial nature of schizotypy at the genetic level has been suggested before (Linney, et al., 2003), and evidence at the psychometric level has long established a multi-factorial nature with up to five schizotypy factors (Vollema & van den Bosch, 1995). Together with the present data, this suggests that positive schizotypy, while it forms a reliably identifiable part of the schizotypy construct at a psychometric level, may at a genetic level be accounted for by anhedonic, hypomanic and

impulsivity components of schizotypy and neuroticism. Supporting this view, studies of the healthy siblings of schizophrenia patients indicate that they have higher levels of negative schizotypy but do not differ on positive schizotypy signs (Clementz, Grove, Katsanis, & Iacono, 1991; Franke, Maier, Hardt, & Hain, 1993). This might be explained methodologically by different patterns of responding to negative or positive features of schizotypy. Yet, it could be that positive schizotypy emerges over time as a result of environmental triggers, building on a biological substrate involving neuroticism, and negative schizotypy.

Given that psychometric questionnaire measures of neuroticism and schizotypy are thought to reflect subclinical variation in risk for affective disorder and schizophrenia, respectively, the current findings also imply an overlapping genetic aetiology for these two clinical conditions (Fanous & Kendler, 2004). Our data thus provide a possible explanation for the frequently observed comorbidity of affective and psychotic disorders. Affective symptoms are seen in up to 75% of schizophrenic patients (Siris, 2000). Depressive symptoms are also present prior to the onset of psychosis and have been postulated as an early risk factor of developing schizophrenia (Yung, Phillips, Yuen, & McGorry, 2004). Our findings suggest that, just as neuroticism and depression largely share a single underlying genetic architecture (Kendler & Myers, 2010), the clinical comorbidity of affective and schizophrenic disorder may be substantially genetic in origin, a view in line with findings in the largest current genome-wide association study (GWAS, Bergen et al., 2011).

Consistent with our speculations on the genetic overlap between schizophrenia and affective disorders, some molecular genetic variants that increase risk for both disorders have already been discovered. Some of the most promising candidate genes for schizophrenia, such as Disrupted-In-Schizophrenia 1, Neuregulin-1 and G72 have also been shown to be associated with mood disorder phenotypes (Harrison & Weinberger, 2005). These findings provide initial

support for the assumed molecular genetic overlap between schizophrenia and affective disorders that may be expected on the basis of our findings. Our findings provide help in the search for susceptibility loci for schizophrenia and affective disorders by referencing to their overlap. Focusing on the overlap might shed light on the molecular genetic basis of either clinical phenotype by making use of the susceptibility loci found for the other phenotype, that is looking at susceptibility loci for schizophrenia in affective disorders and vice versa.

Common environmental influences in our study were weak and accumulated in one component that had to be retained indicating a significant effect of one environmental factor shared between schizotypy and neuroticism. Extending these findings to the clinical domain might similarly indicate common environmental factors underlying schizophrenia and affective disorders. A number of environmental risk factors have been described for both schizophrenia and affective disorders (e.g. early environmental stressors, Agid et al., 1999). These factors might be of relevance in explaining the common environmental component of neuroticism and schizotypy observed in our study.

2.4.1. Limitations

The current findings have to be interpreted in light of their limitations. First, schizotypy was assessed through a small number of items with two to four items per factor. This might have resulted in a higher error of measurement, explaining the rather inflated specific unique environmental estimates and similarly the small overlap in unique environmental components between Per-Mag and neuroticism ($r_e=.26$) in the bivariate model. However, this short version of the Chapman scales has been validated and its equivalence to the full PPS shown by Hay et al. (2001). Also, heritability estimates of positive schizotypy are in line with previous studies

(that made use of the full PPS or other schizotypy measures) thereby providing additional support for the construct validity of the short schizotypy scale. Second, the current study used a twin sample and might therefore not generalize to the general population. However, the magnitude of the phenotypic correlation between neuroticism and schizotypy in our study is comparable to findings from previous studies in non-twin populations (Barrantes-Vidal, et al., 2009; Ettinger, et al., 2005), supporting the generalizability of our findings.

2.4.2. Conclusions

The current study highlights the genetic and environmental structures underlying the observed phenotypic association of schizotypy and neuroticism. Despite specific aetiological components to perceptual and ideational features of schizotypy, a substantial shared genetic influence was found between perceptual and ideational features of schizotypy and neuroticism, accounting for over half the phenotypic correlation. Moreover, the genetic components to positive schizotypy could be fully explained by genetic variance in anhedonia, hypomania and impulsivity facets of schizotypy and neuroticism by means of a Cholesky decomposition. These findings suggest that personality traits resembling the positive schizophrenia spectrum symptoms may be shared to a large amount with genetic factors underlying neuroticism and other schizophrenia spectrum features. The added importance of these findings lies in the possibility that similar genetic overlap could exist between affective disorders and full-blown psychosis.

The study presented in the next chapter of the cumulative dissertation is based on data collected at Ludwig-Maximilians-University Munich. Data collection for this chapter was supported by the Deutsche Forschungsgemeinschaft (DFG) Emmy Noether program (ET 31/2-1) to Ulrich

Ettinger; a project grant of the Förderprogramm für Forschung und Lehre (FöFoLe) of the Ludwig-Maximilians-University Munich to Ulrich Ettinger (Reg-Nr. 645). Please note that data from studies two and three overlap.

3. The Schizotypal Brain - An fMRI Antisaccade Task Study

3.1. Introduction

A growing body of evidence links schizophrenia with schizotypy, the latter which characterizes individuals who show traits similar to but less severe than schizophrenia symptoms (Meehl, 1962, 1989; Rado, 1953). The notion that psychotic-like features are expressed at levels below the clinical manifestation is referred to as psychosis proneness, psychotic experiences or schizotypy (Chapman, Chapman, & Kwapil, 1994; Meehl, 1962; Stefanis et al., 2002; van Os, Hanssen, Bijl, & Ravelli, 2000; Verdoux, van Os, et al., 1998; Yung et al., 2003). Consistent with the model that schizophrenia and schizotypy lie on a spectrum, both schizophrenia and schizotypy exhibit a similar factor structure consisting of positive, negative and disorganization-related features (Liddle, 1987; Venables & Bailes, 1994; Vollema & Van den Bosch, 1995).

Further support for an overlap between schizophrenia and schizotypy is given by common deficits at (neuro-) cognitive levels. One promising neurocognitive measure impaired in schizophrenia and schizotypy is antisaccade task performance (Ettinger, et al., 2005; Turetsky et al., 2007). Task performance requires the suppression of a reflex-like saccade (or prosaccade) towards a peripheral stimulus, combined with the concurrent initiation of a volitional saccade to the mirror image location of the stimulus (Hallett, 1978). Performance is usually assessed by the antisaccade error rate, that is the proportion of reflex-like saccades towards the target divided by the number of valid trials (see e.g.: Ettinger, et al., 2005; Hutton & Ettinger, 2006). Impairments in antisaccade task performance are found across the spectrum,

in schizophrenia (see e.g.: Fukushima, et al., 1988; Sereno & Holzman, 1995), schizotypal personality disorder (Brenner, et al., 2001) and schizotypy (Aichert, Williams, et al., 2012; Ettinger, et al., 2005; Holahan & O'Driscoll, 2005; Larrison, et al., 2000; O'Driscoll, Lenzenweger, & Holzman, 1998) which further strengthens the link between schizotypy and the schizophrenia spectrum.

These performance-based findings extend to fMRI findings of oculomotor task performance. In schizophrenia dysfunctional activations are found within the oculomotor circuit e.g. in FEF, SEF, DLPFC, VLPFC, ACC, posterior parietal cortex, thalamus and striatum (Brown, et al., 2006; DeSouza et al., 2003; Ford, et al., 2005; Matsuda, et al., 2004; McDowell, et al., 2008; O'Driscoll, et al., 1995; Raemaekers, et al., 2006; Sweeney, et al., 2007). In particular, impairments in FEF and SEF (Camchong, et al., 2008) and DLPFC activation (Fukumoto-Motoshita et al., 2009; McDowell & Clementz, 2001) have been found in schizophrenia. Goghari, Sponheim and MacDonald (2010) reviewed the neurocognitive deficit in schizophrenia revealed associations between medial temporal lobe and medial prefrontal cortex (PFC) dysfunction and positive, abnormalities in ventral striatum and ventrolateral PFC activity and negative, and DLPFC activation and disorganization-related symptoms, did however not include oculomotor tasks in their review.

Similarly scarce are findings from antisaccade fMRI research in schizotypy. The antisaccade task is a measure of cognitive control, specifically prepotent response inhibition, see e.g.: Friedman & Miyake, 2004. Other areas of executive functioning have been targeted in schizotypy. For instance, Mohanty et al. (2005) demonstrated that positive schizotypy was negatively associated with activity in left DLPFC and positively with activity in right DLPFC as elicited by an emotional Stroop task. These authors assessed 16 positive schizotypes and 16 healthy controls and found deviant activations in limbic structures such as the striatum, the

hippocampus and the amygdala indicating that emotion-cognition processing is similarly distorted in schizophrenia and schizotypy. Findings from Corlett and Flechter (2012) further strengthen the link between schizophrenia and schizotypy at neural levels. These authors reported dysfunctional frontal and striatal activation in response to a prediction error signal in an associative learning task being associated with positive schizotypy (the logic underlying this task being as follows: if $A \rightarrow B$, and A and $C \rightarrow B$, then B should be linked to the presence of A not C , if however $C \rightarrow B$, the latter should result in a prediction error). Their sample consisted of 18 subjects, who completed measures of positive and negative schizotypy. Similar associations between prediction errors and positive symptoms had been noted in schizophrenia before (Corlett et al., 2007). Aichert et al. (2012) investigated the neural correlates of the antisaccade task in positive schizotypy ($N=54$) and showed negative associations between positive schizotypy and activity in left IPS, left SEF and bilateral visual cortex during prosaccades. In addition, these authors found negative associations between positive schizotypy levels and activity in the right putamen, left cerebellum, right thalamus and bilateral visual cortex during antisaccades, yet no correlations between positive schizotypy levels and brain activity for the contrast comparing activity during antisaccades with that during prosaccades (this contrast is supposed to reflect oculomotor response inhibition). Similar findings as Aichert et al. report emerged before in schizophrenia. Raemaekers et al. (2002) for instance detected abnormal activation of the striatum and Camchong et al. (2008) showed dysfunctional activation at occipital sites during oculomotor tasks in schizophrenia.

Overall, evidence for dimension-specific patterns of brain activation in schizotypy is scarce, which is surprising given that studying schizotypal populations offers advantages such as identifying pathways of neurocognitive impairments in the schizophrenia spectrum in the absence of any effects of antipsychotic treatment, comorbid disorders, hospitalization or

motivational confounders as usually found with schizophrenia patient samples (Lenzenweger, 1994). Previous work in schizotypy so far has predominantly relied on assessing positive schizotypy and used small sample sizes. The current study therefore aimed to:

- (a) elucidate on the neural correlates underlying positive, negative and disorganisation-related features of schizotypy, by means of an antisaccade task during fMRI,
- (b) investigate the contrast comparing activation during antisaccades with that during prosaccades, which failed to show significant associations with schizotypy in Aichert et al.'s work,
- (c) rely on a large sample of 142 participants (previous studies used sample sizes of N=14-54) and
- (d) control for important confounding influences such as IQ and neuroticism, as both have been shown to be associated with enhanced schizotypy and schizophrenia. IQ was previously negatively linked to schizotypy and schizophrenia (Matheson & Langdon, 2008; Nieman, Bour, Linszen, Goede, Koelman, Gersons, & Ongerboer de Visser, 2000). Neuroticism was positively associated with schizotypy (Ettinger, et al., 2005; Macare, Bates, Heath, Martin, & Ettinger, 2012) and schizophrenia (Van Os & Jones, 2001). We therefore ensured to target variation of schizotypy controlled for the influence of IQ or neuroticism.

3.2. Methods

3.2.1. *Participants*

One-hundred forty-two healthy participants (70 males, 72 females) were recruited through advertisements placed in the local community, in regional newspapers, on websites and via circular emails (distributed at local schools and Universities in Munich) and took part in the study. Participants were screened prior to participation during a telephone interview. Exclusion criteria were past and current medical or neurological conditions, including head trauma, a personal history of head injury with loss of consciousness, current use of prescribed or over-the-counter medication and current *DSM-IV* axis I disorder (a past episode of *DSM-IV* axis I disorder was allowed). Diagnosis of a current *DSM-IV* axis I disorder was established using the German version of the Mini International Neuropsychiatric Interview (Ackenheil, Stotz-Ingenlath, Dietz-Bauer, & Vossen, 1999). Participants with first-degree relatives suffering from any psychotic disorder or ADHD were excluded to allow for an unconfounded assessment of schizotypy effects on antisaccades and brain function, as schizotypy and a family history of schizophrenia have interactive effects on antisaccade performance (Thaker et al., 2000). All participants were of Caucasian ethnicity. To reduce the effects of lateralization we focused on right-handed individuals. Handedness was assessed by the German version of the Edinburgh Handedness Inventory (Oldfield, 1971). Due to precise vision requested for the antisaccade task, participants with visual impairments except the use of corrective lenses were excluded.

3.2.2. Procedure

The testing procedure consisted of two sessions: a laboratory session in which participants provided data on demographical variables (e.g. age, gender, education, handedness and ethnicity) and personality and an fMRI session that took place after the laboratory session and required participants to perform the antisaccade task during fMRI. Participants received training on the antisaccade task prior to scanning to ensure that they understood task instructions. The study was approved by the ethics committee of the Faculty of Medicine of the University of Munich. Each participant provided written informed consent and received monetary compensation.

3.2.3. Measures

3.2.3.1. IQ

IQ has been shown to be impaired in non-clinical schizotypy (Nieman, et al., 2000). Here, we used the MWT-B (Mehrfachwahl-Wortschatz-Intelligenztest, Form B; Lehrl, 2005; Lehrl, Triebig, & Fischer, 1995) to assess IQ and controlled for its mediating effect on the link between schizotypy and antisaccade task performance. Participants were presented with four words (one real and three distractor words) and had to identify and mark the real word amongst the non-word distractors in each of 37 items. Test items increased in difficulty. Correct answers received one point, incorrect ones zero, giving a maximum of 37 points.

3.2.3.2. Schizotypy

We used the German adaptation (Klein, Andresen, & Jahn, 1997) of the SPQ (Raine, 1991; Raine, et al., 1994) to assess schizotypy. This 74-item questionnaire provides full assessment of all nine schizotypal personality disorder features as outlined in the *DSM-III* (American Psychiatric Association, 2000). Scales are summarized by three factors, usually cognitive-perceptual, interpersonal and disorganization (Raine, et al., 1994). The cognitive-perceptual factor reflects positive schizotypy and is covered by: ideas of reference (IR, 9 items), magical thinking (MT, 7 items), unusual perceptual experiences (UPE, 9 items) and suspiciousness (S, 8 items) scales. The interpersonal factor reveals negative schizotypy and included scales such as social anxiety (SA, 8 items), no close friends (NCF, 9 items) and constricted affect (CA, 8 items). Finally, disorganized schizotypy was represented by scales such as odd speech (OS, 9 items) and eccentric behaviour (EB, 7 items). Items are answered in a dichotomous response format (“yes” or “no”). Higher scores indicate higher levels of schizotypy. The German version has good internal validity (Cronbach’s alpha) and test-retest reliability (Total SPQ: $r=.88$, $\alpha=.88$, S: $r=.69$, $\alpha=.62$, OS: $r=.80$, $\alpha=.79$, EB: $r=.89$, $\alpha=.81$, IR: $r=.74$, $\alpha=.67$, NCL: $r=.93$, $\alpha=.64$, CA: $r=.87$, $\alpha=.62$, SA: $r=.76$, $\alpha=.73$, UPE: $r=.78$, $\alpha=.65$, MT: $r=.88$, $\alpha=.77$, Klein, et al., 1997).¹ Additionally, the SPQ shows the highest test-retest values amongst various schizotypy scales (Vollema & van den Bosch, 1995).

3.2.3.3. Neuroticism

Previous evidence showed significant correlations between neuroticism and schizotypy (see e.g.: Macare, et al., 2012), schizotypal personality disorder (Gurrera et al., 2005) and

¹ Internal consistency for each feature of schizotypy was: for positive schizotypy: Cronbach’s $\alpha=.78$, for negative schizotypy: Cronbach’s $\alpha=.83$ and for disorganized schizotypy: Cronbach’s $\alpha=.84$.

schizophrenia (Berenbaum & Fujita, 1994). We therefore examined neuroticism as a covariate in order to reveal pure effects of schizotypy on brain activity irrespective of neuroticism. Neuroticism was assessed using the German version of the NEO-Five Factor Inventory (Borkenau & Ostendorf, 1993). Each of the 12 items uses a five-point response format (“strongly disagree”= 0 to “strongly agree”= 4). Neuroticism showed high internal consistency (Cronbach’s $\alpha=.78$) in the current sample and good test-retest reliability (Berth, Goldschmidt, Ostendorf, & Angleitner, 2006).

3.2.4. Eye Movements

3.2.4.1. Data Acquisition

Eye movement acquisition during fMRI used a block design with five blocks in each of three conditions (antisaccades, prosaccades and fixation). Each block consisted of ten trials and lasted 30 seconds. All participants received the same quasi-random order of blocks.

Horizontal eye movements of the left eye were recorded using an MRI-compatible infrared oculographic tracker (MR-Eyetracker, CRS Ltd., Rochester, UK). Data were recorded using an infrared light emitter and detector array fixed to the headcoil. The eyetracker has a minimum spatial resolution of 0.2° and a horizontal range of $\pm 20^\circ$. Signals were digitized using a 12-bit analogue-to-digital converter (Data Translation DT9802) and sampled at 500Hz. A 3-point ($\pm 8^\circ$ and 0°) calibration was performed prior to scanning. In each block, the stimulus was a filled circle of $.5^\circ$ amplitude presented on a grey background. The colour of the stimulus varied between conditions, as described below.

Antisaccade: Blocks started by instructing participants to “Look in the opposite direction” (2 s), upon which a red central fixation stimulus (0° , duration 1000-2000 ms) followed by a black peripheral stimulus (1000-2000 ms) were shown. The peripheral stimulus was presented equally often at right ($+8^\circ$) and left (-8°) positions in each block. Overall, each trial lasted for 3000 ms.

Prosaccade: Task parameters were the same between anti- and prosaccade tasks. However, the central fixation stimulus was of green colour. The instruction for prosaccade blocks was “Follow the dot”.

Fixation: Each block began with the instruction “Centre”, reminding participants to focus on the stimulus in centre of the screen (i.e. 0°). In each block, the stimulus was presented in black in the central position (0°) for 30 s.

3.2.4.2. Data Preparation

Saccades were processed using Eyemap Version 2.1 (AMTech GmbH, Weinheim, Germany). Inclusion of saccades required a minimum latency of 80 ms and a minimum amplitude of 1° . For each participant, the main measures of cognitive control, that is the mean antisaccade error rate (in %), antisaccade latency (in ms) and antisaccade corrections (in %), were extracted.

3.2.5. fMRI – Data Acquisition

Participants were scanned in a supine position in a Siemens Verio scanner at 3-Tesla field strength using a 12-Channel Siemens headcoil (Siemens, Erlangen). Head movement was

limited by foam padding the head coil. Scanner noise was reduced through headphones. Stimuli were projected on a screen viewed by participants through a mirror attached to the head coil.

T₂*-weighted whole brain MR echo planar images (EPI) of the BOLD response were collected. A total of 240 functional images were acquired (TR=2 s). Four preceding volumes were discarded to ensure establishment of longitudinal magnetization. Each image volume consisted of 28 axial slices, each 4 mm thick with an inter-slice gap of 0.8 mm and in-plane resolution of 3 x 3 mm. The flip angle was 80° and TE was 30 ms. Slices were acquired in ascending sequence (inferior to superior) parallel to the anterior commissure-posterior commissure line.

3.2.6. Data Analysis

3.2.6.1. Demographical, Psychometric and Behavioural Data

Descriptive statistics on demographical data, psychometric assessment of schizotypy and neuroticism and behavioural data of antisaccade performance were analysed using the Statistical Package for the Social Sciences (SPSS, version 20; IBM Corp., Armonk, NY, 2011). A significance level of .05 (two-tailed) was applied if not otherwise specified. Correction for multiple testing due to testing for the effect of schizotypy levels was performed using the less stringent version of the Bonferroni correction, known as Bonferroni-Holm correction (Holm, 1979). The Bonferroni-Holm correction imposes the most conservative correction threshold for the most significant p-value. For example, when running nine tests using a significance level of .05, a Bonferroni correction would impose a threshold of .05/9 for each test, whereas the Bonferroni-Holm correction would impose a threshold of .05/9 for the most significant result,

a threshold of .05/8 for the second most significant results and a threshold of .05/7 for the third most significant result and so on. Thus, when testing for the effect of all schizotypy subscales a threshold of .05/9 was applied to the most significant result. Scores on the SPQ subscales were positively skewed, as previously reported in healthy samples. Therefore, SPQ scores were square root transformed. Given the oft-replicated positive correlation between the antisaccade error rate and schizotypy, we tested for this link one-tailed (Lenzenweger & O'Driscoll, 2006). Pearson's r will be reported if not otherwise indicated. Behavioural oculomotor data from 15 participants could not be recorded due to technical difficulties, resulting in behavioural oculomotor data from 127 participants.²

3.2.6.2. fMRI Data

Imaging data were pre-processed and analysed using a general linear model in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) running in MATLAB R2008a (The MathWorks Inc., 2000). Images were realigned to the first image in time series, normalized to the Montreal Neurological Institute (MNI) template and smoothed using an 8 mm full-width half-maximum (FWHM) Gaussian filter and a high-pass filter (128 s).

Data analysis involved two steps. First, task blocks of (1) antisaccades, (2) prosaccades, (3) fixations and (4) instructions were modelled using a synthetic canonical haemodynamic response function. Six realignment parameters were included in the model as multiple regressors in order to account for head movement. Head movement for all participants was less than 5 mm on x-, y- or z-axis. We focussed on the BOLD signal of the following contrasts: antisaccades vs. prosaccades. Prosaccades acted as controls for the contrasts comparing

² Participants providing behavioural data did not differ significantly from those with missing oculomotor data on demographical or schizotypy measures (all $p > .05$).

antisaccades and prosaccades. Both antisaccades and prosaccades require basic saccade processes, but antisaccades additionally place demands on complex cognitive processes. Comparison of the BOLD signal during anti- and prosaccades is supposed to reveal brain activity associated with inhibitory control, complex sensorimotor, volitional response selection and response conflict resolution (Ettinger et al., 2009; McDowell, et al., 2002; McNamee et al., 2008). Second, contrast images from the single-subject level were used for group-level analyses. The BOLD signal during each contrast independent of schizotypy has been reported extensively in previous research; we have therefore provided results of one-sample t-tests for the contrasts only in the supplementary materials. To reveal associations between brain areas in response to eye movement tasks and schizotypy, mean BOLD activation in significant clusters from the one-sample t-tests were extracted as regions of interest (ROIs), using MarsBaR release 0.43 (<http://marsbar.sourceforge.net>) and subsequently correlated with schizotypy scores. In order to correct for multiple testing due to the schizotypy subscales, Bonferroni-Holm correction was applied. Conversion from MNI to Talairach co-ordinates was performed using non-linear transformations (Brett, et al., 2002) and anatomical areas identified by drawing on previous findings (for the labels frontal and supplementary eye fields, see e.g.: Grosbras, Laird, & Paus, 2005) and the Talairach and Tournoux (1988) atlas.

3.3. Results

3.3.1. Demographical Data

One hundred forty-two participants (70 males, 72 females) aged 26.46 years on average ($SD=7.55$) participated. Mean verbal intelligence (MWT-B) of the sample was 30.4 points ($SD=3.03$). Participants spent an average of 15.78 years in education ($SD=2.48$). Professional status was distributed as follows: 59.2% were studying, 20.4% were working full-time, 8.5% were completing professional or job training, 5.6% were working part-time, 2.8% were unemployed, 2.8% went to school and professional status was unknown in .7%.

Age, gender and education: There were no significant differences in age between genders (males: $M=27.04$, $SD=7.59$, females: $M=25.90$, $SD=7.51$; $F(1, 140)=.83$, $p=.364$). Years spent in education was trend-level significant between genders (males: $M=16.18$, $SD=2.64$, females: $M=15.37$, $SD=2.25$; $F(1, 139^3)=3.81$, $p=.053$, $\eta^2_p=.006$). Overall, males and females were comparable on demographical measures.

Effects of age and gender on schizotypy: Age correlated negatively with odd speech (OS: $r=-.26$, $p=.002$), indicating a significant decrease of schizotypy levels with increasing age. Other measures of schizotypy did not show significant correlations with age. There were significant differences between genders on social anxiety ($F(1, 140)=11.09$, $p=.001$, $\eta^2_p=.073$); females scored on average higher than males (1.44 and .71, respectively). These gender differences remained when adding neuroticism scores as covariate ($F(1, 139)=4.03$, $p=.046$, $\eta^2_p=.028$). Other SPQ scales did not show significant differences between genders.

³ Information on years spent in education was missing in one participant.

Effects of age and gender on antisaccades: Task performance was not significantly correlated with age (all $p > .05$). There were differences between genders for the antisaccade error rate ($F(1, 125) = 4.46, p = .037, \eta^2_p = .034$), with a lower error rate in males ($M = 18.79, SD = 12.06$) than females ($M = 24.45, SD = 17.61$), which however did not survive corrections for multiple testing. Other behavioural antisaccade measures (i.e. latency and correction rate) did not show significant differences between genders (all $p > .05$).

3.3.2. Schizotypy and Antisaccade Task Performance

Schizotypy: Descriptive statistics are displayed in Table 4; correlations amongst variables are presented in Table 5. IQ did not correlate with any of the schizotypy features. We found significant correlations between schizotypy and neuroticism. As expected, features of positive schizotypy, specifically ideas of reference, magical thinking and suspiciousness correlated significantly with neuroticism: IR ($r = .24, p = .004$), MT ($r = .20, p = .019$) and S ($r = .28, p = .001$). Negative features of schizotypy also correlated significantly with neuroticism (no close friends: $r = .26, p = .002$, constricted affect: $r = .27, p = .001$ and social anxiety: $r = .43, p < .001$). Disorganized features of schizotypy also correlated significantly with neuroticism (odd speech: $r = .25, p = .002$ and eccentric behaviour: $r = .23, p = .007$ after Bonferroni-Holm correction).

Antisaccades: Task performance results are displayed in Table 4. Performance in the current sample is similar to previously reported findings in healthy samples (antisaccade error rate in %: $M = 21.60, SD = 15.28$; antisaccade correction rate in %: $M = 93.73, SD = 15.81$ and antisaccade latency in ms: $M = 255.01, SD = 38.83$; see e.g.: Hutton & Ettinger, 2006). Prosaccade data is reported as prosaccades were used as controls for antisaccades.

Correlations: Antisaccade error rate correlated with positive schizotypy, specifically scores on the magical thinking scale, did however not survive (one-tailed) Bonferroni-Holm corrections for multiple testing ($r=.19$, $p=.029$). Neither antisaccade latency nor correction rate correlated significantly with features of schizotypy (all $p>.05$).

Table 4 - Schizotypy and eye movement task performance.

	<i>Mean</i>	<i>Standard deviation</i>
<i>Positive Schizotypy</i>		
<i>SPQ ideas of reference</i>	1.14	1.49
<i>SPQ magical thinking</i>	.48	1.04
<i>SPQ unusual perceptual experiences</i>	.57	.91
<i>SPQ suspiciousness</i>	.92	1.01
<i>Negative Schizotypy</i>		
<i>SPQ social anxiety</i>	1.08	1.56
<i>SPQ constricted affect</i>	.80	1.14
<i>SPQ no close friends</i>	.76	1.30
<i>Disorganized Schizotypy</i>		
<i>SPQ odd speech</i>	1.69	1.96
<i>SPQ eccentric behaviour</i>	.56	1.31
<i>Eye movement task performance</i>		
<i>Antisaccade latency in ms</i>	255.06	38.83
<i>Antisaccade error rate in %</i>	21.60	15.28
<i>Antisaccade correction rate in %</i>	93.73	15.81
<i>Prosaccade latency in ms</i>	183.12	26.82

Notes: SPQ=Schizotypy Personality Questionnaire, raw scores are reported.

Table 5 - Correlations amongst demographical, personality and antisaccade measures.

	<i>MT</i>	<i>UPE</i>	<i>S</i>	<i>SA</i>	<i>NCF</i>	<i>CA</i>	<i>EB</i>	<i>OS</i>	<i>Age</i>	<i>IQ</i>	<i>Neuroticism</i>	<i>AS latency</i>	<i>AS error rate</i>	<i>AS correction rate</i>
<i>Ideas of reference</i>	.372*	.312*	.365*	.318*	.050	.166*	.325*	.282*	.055	-.124	.238*	-.033	.080	-.048
<i>Magical thinking</i>	-	.429*	.286*	.247*	.116	.089	.271*	.110	.144	-.099	.197*	-.112	.194	-.150
<i>Unusual perceptual experiences</i>		-	.388*	.195**	.080	.256*	.327*	.305*	-.061	-.160	.151	-.015	-.013	-.046
<i>Suspiciousness</i>			-	.288*	.276*	.285*	.343*	.386*	.002	-.110	.275*	-.064	.126	.034
<i>Social anxiety</i>				-	.352*	.358*	.240*	.263*	-.200	-.052	.427*	-.035	.152	.011
<i>No close friends</i>					-	.499*	.212*	.180*	.054	-.131	.262*	-.132	.051	-.106
<i>Constricted affect</i>						-	.246*	.302*	-.143	-.135	.265*	-.125	-.029	-.037
<i>Eccentric behaviour</i>							-	.427*	-.133	-.012	.225*	-.046	-.097	-.069
<i>Odd speech</i>								-	-.259*	-.112	.252*	-.102	-.177	-.064
<i>Age</i>									-	.112	-.083	.152	.144	-.106
<i>IQ</i>										-	-.084	.011	.015	.071
<i>Neuroticism</i>											-	.029	.041	-.059
<i>AS latency</i>												-	.093	-.135
<i>AS error rate</i>													-	.170

Notes:

IR=Ideas of reference
CA=Constricted affect
AS=Antisaccade

SA=Social anxiety
UPE=Unusual perceptual experiences
 ***p*<.01

EB=Eccentric behaviour
 **p*<.05.

MT=Magical thinking
S=Suspiciousness

NCF=No close friends
OS=Odd speech

3.3.3. Schizotypy and fMRI

3.3.4. Antisaccades vs. Prosaccades

Antisaccades > Prosaccades: No features of schizotypy showed significant links with brain activation in this contrast after Bonferroni-Holm correction.

Prosaccades > Antisaccades: BOLD deactivation showed significant links with schizotypy. BOLD in the inferior occipital gyrus correlated with constricted affect (see

Figure 23, left illustration, and Table 6, $r=-.25$, $p=.001$, corrected for neuroticism; $r=-.25$, $p=.003$). Constricted affect also showed correlations with BOLD deactivation in middle occipital gyrus (

Figure 23, right illustration, and Table 6, $r=-.30$, $p<.001$, corrected for neuroticism: $r=-.27$, $p=.001$). No other features of schizotypy showed significant links with brain activation in this contrast after Bonferroni-Holm correction.

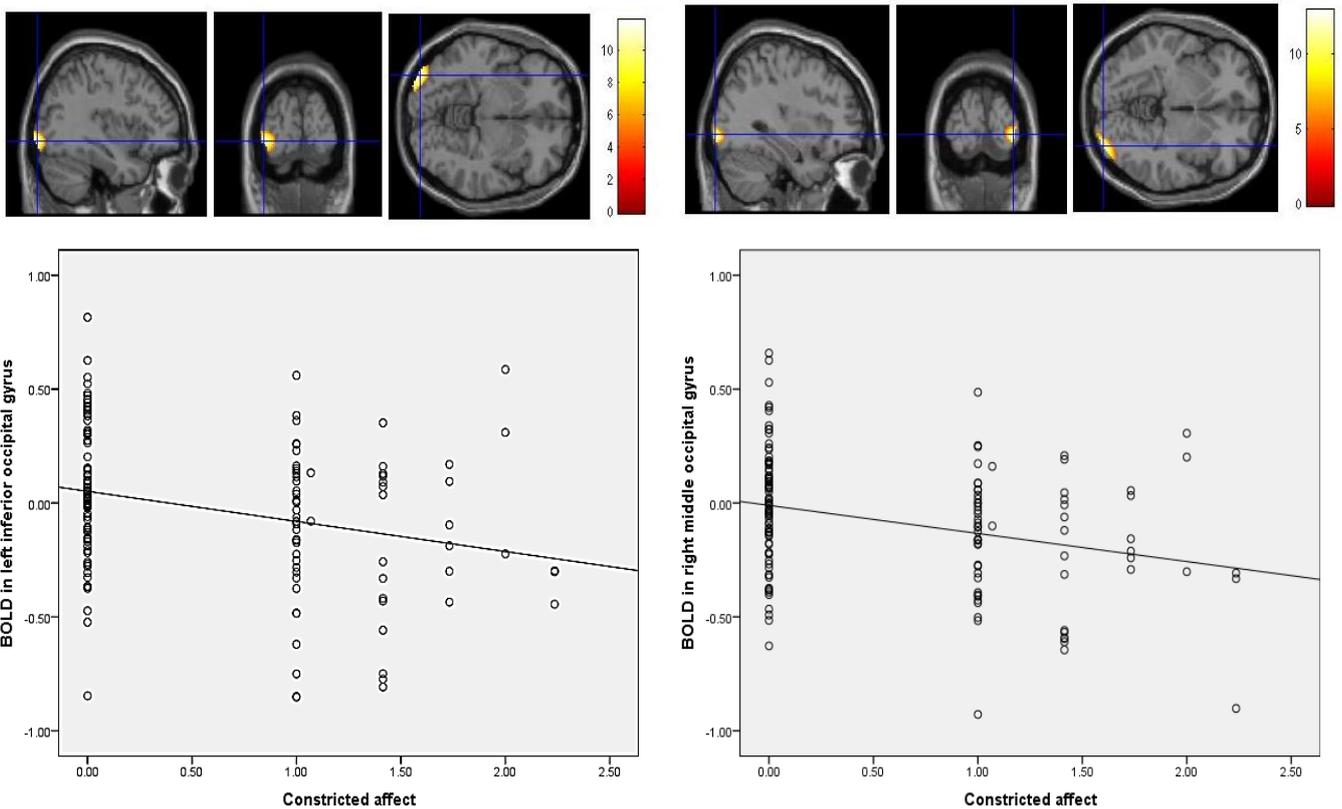


Figure 23 - BOLD deactivation for the contrast antisaccades vs. prosaccades and schizotypy.

Notes: First row: Anatomical views refer to sagittal, coronal and axial planes shown on upper left, middle and right panes, respectively. Coordinates of peak voxels in the left inferior occipital gyrus and the right middle occipital gyrus are given in Talairach space (for left inferior occipital gyrus: $x=-36$, $y=-89$, $z=-1$ and for right middle occipital gyrus: $x=34$, $y=-91$, $z=1$ as shown in the left and right illustrations, respectively and indicated by crosshairs). Colour bars indicate strength of the BOLD response, with light colour indicating higher BOLD responses expressed as T-values. Second row: Scatterplots illustrating associations between (transformed) schizotypy scores (on x-axis) and mean BOLD response (on y-axis) in the left inferior occipital and right middle occipital gyrus, respectively.

Table 6 - BOLD signal for the deactivation during eye movements and associated schizotypy scales.

<i>Contrast</i>	<i>Schizotypy scale</i>	<i>Cluster size</i>	<i>Macroanatomical label</i>	<i>Hemisphere</i>	<i>Brod-mann area</i>	<i>Coordinates in Talairach space</i>			
						<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>
<i>AS<PS</i>									
	CA	320	Inferior occipital gyrus	left	18	-36	-89	-1	11.48
	CA	246	Middle occipital gyrus	right	18	34	-91	1	12.91

Notes:

AS=Antisaccades

PS=Prosaccades

CA=Constricted affect.

3.4. Discussion

The aim of the current study was to investigate the neural correlates underlying psychometric schizotypy. We therefore conducted an eye movement fMRI study in a large sample of healthy individuals (N=142) and correlated brain activity during eye movement tasks with schizotypy levels. We thereby focussed on covering negative and disorganization-related features of schizotypy in addition to positive ones. Our main findings are as follows: We replicated the well-established fronto-parietal-occipital subcortical network underlying antisaccade task performance and found evidence for a pattern of associations between brain activity during the antisaccade task and schizotypy dimensions, in particular negative schizotypy. Our findings give tentative support for the link between schizotypy and the schizophrenia spectrum and might provide insights into the (neural) pathways to schizophrenia spectrum disorders via studying schizotypy.

3.4.1. Schizotypy

Schizotypy in the current sample was assessed with the SPQ, thereby allowing for a full assessment of all schizotypal features, that is positive, negative and disorganization-related. The current sample had an average SPQ total score of 8.00 ($SD=7.11$). This score underlines the healthy nature of our sample and is comparable to that of other samples from the general population (Kline et al., 2012; Rossi & Daneluzzo, 2002; Voelter et al., 2012).

We found age effects on schizotypy, specifically a negative association between age and disorganization-related schizotypy, which are in line with previous studies (e.g.: Bora & Baysan Arabaci, 2009; Ettinger, et al., 2005). In line with the current findings, gender differences for negative schizotypy, in specific higher levels of social anxiety in females than

males were reported before (Bora & Baysan Arabaci, 2009). In contrast to previous reports, we did not find links between IQ and schizotypy. IQ, specifically verbal IQ, as assessed with the MWT-B, was not linked to schizotypy. The majority of our sample (~60%) however was made up of University students and therefore not representative of the general population in terms of IQ.

Similar to previous studies across the schizophrenia spectrum, the current study found positive associations between schizotypy and neuroticism (for schizophrenia, schizotypal personality disorder and schizotypy see e.g.: Berenbaum & Fujita, 1994; Gurrera, et al., 2005; Macare, et al., 2012, respectively). Specifically, positive features such as ideas of reference and suspiciousness, negative features such as no close friends constricted affect and social anxiety and disorganization-related features of schizotypy, i.e. odd speech and eccentric behaviour, were associated with neuroticism, indicating a complex link between schizotypy and negative emotionality, i.e. neuroticism, which made it necessary to control for the influence of neuroticism when examining neural correlates underlying schizotypy.

3.4.2. Schizotypy and Behavioural Eye Movement Performance

Here, schizotypy levels were not significantly associated with antisaccade task performance. Associations emerged between antisaccade error rate and the positive schizotypy feature of magical thinking ($r=.19$) yet failed to surpass the significance threshold. Antisaccade errors are thought to indicate failures of response suppression and are considered reliable measures of antisaccade performance (Ettinger et al., 2003).

Correlations of small to moderate size (e.g. $r=.24$) have frequently been reported before between positive features of schizotypy and the antisaccade error rate (Aichert, Williams, et al.,

2012; Ettinger, et al., 2005; Holahan & O'Driscoll, 2005; O'Driscoll, et al., 1998). These studies used a range of questionnaires (symptom- and syndrome-based) to assess schizotypy. Explanations for our current finding include the small amount of variation that could be derived from the schizotypy measure. The SPQ has a dichotomous response format (yes/no) and as illustrated in Table 4, shows low dispersion of scores. One possible interpretation of this finding might be that deficits at the level of the brain have (not yet possibly) manifested as behavioural deficits. The discrepancy between the lack of association between behavioural antisaccade task performance measures and schizotypy and neural correlates of antisaccade task performance and schizotypy shows the need for assessing deficits at the level of the “neurome” in addition to at the level of the “phenome”.

Previous evidence links the schizophrenia spectrum and antisaccade task performance, specifically an increased antisaccade error rate in schizophrenia (Calkins, Iacono, & Ones, 2008; Fukushima, et al., 1988; Gooding & Basso, 2008; Mazhari et al., 2011; Nieman, et al., 2000) providing proof to showing consistent neurocognitive deficits across the schizophrenia spectrum. These deficits however do not consistently extend to schizotypy.

3.4.3. Neural Correlates of Schizotypy

In the current study, we were able to investigate the neural correlates of different features of schizotypy. The current findings showed significant negative associations between negative schizotypy (constricted affect) and deactivations during the contrast antisaccades<prosaccades in the left inferior occipital gyrus and in the right middle occipital gyrus. The inferior and middle occipital areas belong to the early sensory processing areas for visual input, these project to frontal and temporal cortical areas. Occipital areas such as the inferior and middle occipital

gyri harbour the cuneus. On structural levels, there is ample evidence for cuneus abnormalities in schizophrenia. In both first episode (Cocchi et al., 2009) and individuals at high risk for schizophrenia (Whitford et al., 2012) volume increases were documented. Decreases in cuneus gray matter volume in schizophrenia were reported over the course of the first four years of the illness (Mane et al., 2009). Next to consistent volume reductions (Bora et al., 2011), schizophrenia patients also show reduced gray matter density in the inferior occipital gyrus (Heuser, Thomann, Essig, Bachmann, & Schröder, 2011). In chronic schizophrenia volume decreases are found (Keshavan, Tandon, Boutros, & Nasrallah, 2008). Smaller volumes in cuneus have been found to be associated with suicidal attempts in schizophrenia (Giakoumatos et al., 2013), indicating altogether that cuneus volumes change over the course of the illness and that special relevance this area in schizophrenia spectrum disorders should be given. Similar to our finding in schizotypy, fMRI findings demonstrate reduced activation in schizophrenia in occipital areas (Schlösser et al., 2007) as well as lower functional coupling in early onset schizophrenia, specifically in the middle occipital gyrus (Kyriakopoulos, et al., 2012). Similar to the association with negative schizotypy we report here, reduced gray matter volume in the occipital lobes has been linked to the deficit syndrome in schizophrenia before (Cascella et al., 2010). Similarly, deficits during processing emotion (which relies on interpersonal functioning) were found and linked to reductions in white matter fractional anisotropy in the left occipital lobe in schizophrenia (Miyata et al., 2010), again strengthening the link between the negative symptom domain (to which negative features such as constricted affect count) and occipital lobe dysfunctions.

Positive schizotypy was assessed using features such as magical thinking, unusual perceptual experiences, suspiciousness and ideas of reference, of which neither showed

associations with the BOLD signal for the contrast antisaccades>prosaccades or for the contrast prosaccades>antisaccades in the current study.

Previous research on neural correlates of positive features links these features with activations in areas such as the precuneus. On structural levels, gray matter volume reductions in the precuneus were found in unaffected relatives of schizophrenia patients compared to healthy controls (Tanskanen et al., 2010), yet there is also evidence for significantly larger volumes in the precuneus with enhanced schizotypy levels (Modinos, et al., 2010). On functional levels, activity in the precuneus increases during self-consciousness, specifically self-attribution (Fukushima, Goto, Maeda, Kato, & Umeda, 2013). Positive features harbour by definition a faulty self-attribution process. Positive symptoms have been linked to a lack of insight in schizophrenia (Hwang, Chang, Lee, Ahn, & Kim, 2009). Bilateral precuneus perfusion has been found to be linked with preserved insight in schizophrenia and was suggested to act as compensation for other deficits in activity (Faget-Agius et al., 2012). The positive features in schizotypy are however less-severe than those found in schizophrenia, which might explain why in the current study we, similar to Aichert et al. (2012), did not find associations between positive schizotypy and brain activation underlying the activation during the contrast comparing antisaccades with prosaccades.

Disorganization and blood flow in left DLPFC, right temporo-occipital areas as well as in the medial prefrontal cortex has been linked before (Goghari, Sponheim, & MacDonald, 2010; Liddle et al., 1992). The evidence associating disorganization-related schizotypy with brain functioning is scarce. Here, we did not find significant links between neural correlates of oculomotor processing and disorganization-related schizotypy, possibly due to the low item endorsement on disorganization-related items in the current sample.

3.4.3. Conclusion

In order to facilitate the development of new agents in treating schizophrenia, a better understanding of the neuropathology underlying schizophrenia spectrum disorders is crucial. A useful strategy in this respect is the study of human brain functioning in the *schizophrenic phenotype* also called the *schizotype*, as the latter does not present with confounding influences such as medication, comorbid disorders, hospitalization or motivational confounders. The current study contributes to this study strategy. The pattern of associations between brain activity and schizotypy features obtained here stresses the need to look closely at the level of each feature rather than at single schizotypy dimensions. In addition, future studies might extend their investigations into examining activations as well as deactivations across schizophrenia spectrum disorders (MacDonald, Thermenos, Barch, & Seidman, 2009).

3.5. Supplementary Materials

One-sample t-tests were conducted for each contrast (i.e.: antisaccades > prosaccades, prosaccades > antisaccades). The threshold for statistical significance was set at $p < .05$, FWE-corrected at the voxel-level across the whole brain and a minimum cluster size of 20 voxels applied. These are illustrated in Supplementary Figure 24 and further details on these brain regions with information on hemisphere, cluster size, Brodmann area, Talairach coordinates and test statistics are shown in Supplementary Table 7.

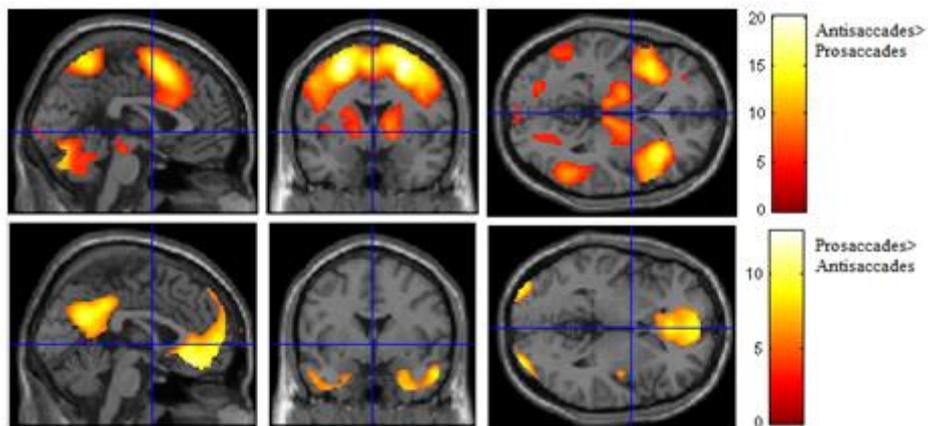


Figure 24 - Supplementary Figure of BOLD signal during eye movement tasks for each contrast.

Table 7 - Supplementary Table of significant clusters for antisaccades and prosaccades.

<i>Cluster size</i>	<i>Macroanatomical label</i>	<i>Hemisphere</i>	<i>BA</i>	<i>Talairach coordinates</i>			<i>T</i>
				<i>x</i>	<i>y</i>	<i>z</i>	
<i>AS > PS</i>							
30873	Superior Parietal Lobe	right	7	16	-55	58	20.13
29217	Middle Frontal Gyrus, FEF	right	6	26	3	53	20.06
133	Middle Frontal Gyrus	left	6	-32	46	-12	7.15
20	Cingulate Gyrus	right	31	14	-19	38	5.52
56	Middle Frontal Gyrus	right	47	48	44	-7	5.50
90	Cingulate Gyrus	right	23	4	-16	28	5.84
<i>PS > AS</i>							
246	Middle Occipital Gyrus	right	18	34	-91	1	12.91
320	Inferior Occipital Gyrus	left	18	-36	-89	-1	11.84
5982	Anterior Cingulate	left	32	-8	31	-10	10.95
512	Precuneus	left	19	-42	-72	44	10.89
3411	Posterior Cingulate	left	31	-4	-55	23	10.57
1487	Middle Temporal Gyrus	right	21	55	-5	-20	9.97
784	Insula	right	13	42	-9	15	9.91
212	Inferior Parietal Lobe	right	39	51	-64	40	8.99
100	Postcentral Gyrus	left	3	-42	-22	64	8.99
45	Precentral Gyrus	right	4	40	-16	65	7.94
302	Insula	left	13	-38	-17	17	7.54
75	Superior Frontal Gyrus	right	8	20	41	50	6.63

Notes: BA=Brodman area, AS=Antisaccades, PS=Prosaccades, FEF=Frontal eye fields.

The study presented in the next chapter of the cumulative dissertation is based on data collected at the Ludwig-Maximilians-University Munich. Ulrich Ettinger received funding for this study from the Deutsche Forschungsgemeinschaft (DFG) Emmy Noether program (ET 31/2-1) and from the Förderprogramm für Forschung und Lehre (FöFoLe) of the Ludwig-Maximilians-University Munich (Reg-Nr. 645). Please note that data from studies two and three overlap. The study presented in this chapter has been accepted as a brief report:

Macare, C., Meindl, T., Nenadic, I., Rujescu, D., & Ettinger, U. (2014). Preliminary findings on the heritability of the neural correlates of response inhibition. *Biological Psychology, 103*, 19-23.

4. Preliminary Findings of Heritability of the Neural Correlates of Antisaccade Performance

4.1. Introduction

Imaging genetics describes “the use of brain imaging in genetically informative designs” (de Geus, et al., 2008, p. 1). By placing the level of measurement closer to the level of gene function (i.e. brain activity instead of behaviour), larger genetic effects are expected with this approach. The validity of this approach is supported by a number of findings. First, 70% of the genes are expressed in the brain (Hariri & Weinberger, 2003). Second and more importantly, it is thought that the use of brain imaging phenotypes allows us to reveal pathways from gene action to increased risk for psychiatric conditions via alterations in brain structure, chemistry or functioning (e.g. Meyer-Lindenberg, 2010). A fundamental assumption of imaging genetics, however, is that inter-individual variation in brain activity as assessed by functional magnetic resonance imaging (fMRI) is significantly heritable. In fact, this has been demonstrated in only very few studies (de Geus, et al., 2008).

Twin designs are genetically informative and thus represent a crucial way of assessing genetic influences on brain activity. The classical twin design compares patterns of correlations between MZ, who share all, and DZ twins, who share on average 50% of their genetic makeup. This comparison allows revealing the proportion of variation attributable to genetic and environmental influences, the former being known as h^2 (see e.g.: Martin, et al., 1997).

One area of interest in previous twin fMRI studies is cognitive control. The construct harbours various processes that enable flexible guidance of behaviour and allocation of

cognitive resources. Previous twin fMRI studies have documented h^2 estimates for components of cognitive control in adults and have overall found mixed evidence for the heritability of the underlying BOLD signal (h^2 of 14 - 80% for working memory: Blokland et al., 2008; Blokland et al., 2011; Koten et al., 2009; and a non-significant h^2 of 38% (95% CI of 0-74%) for interference processing: Matthews et al., 2007). Mixed evidence for h^2 of the BOLD signal could have resulted from the broad range of sample sizes used across these studies (from N=319 to N=40 twins, Blokland, et al., 2011; Matthews, et al., 2007, respectively).

One fundamental component of cognitive control is inhibitory control, composed of inhibition-related processes such as prepotent response inhibition, resistance to distractor and resistance to proactive interference (Friedman & Miyake, 2004). The antisaccade task is a widely studied measure of prepotent response inhibition (Hutton & Ettinger, 2006; Sweeney, Levy, & Harris, 2002). Correct performance on this task involves the suppression of an automatic saccade (or prosaccade) towards a peripheral stimulus, combined with the concurrent initiation of a volitional saccade to the mirror image location of the stimulus (Hallett, 1978). Current models of antisaccade performance specify that the demands required to succeed on this task include working memory, goal or intention activation and attentional focus, which together support the inhibition of a prepotent response (see e.g.: Brown, et al., 2006; Hutton & Ettinger, 2006). The task also places heavy demands on spatially complex sensorimotor transformations (Medendorp, Buchholz, Van Der Werf, & Leoné, 2011). Failure to inhibit the automatic saccade results in an antisaccade direction error; that is a saccade towards the peripheral stimulus instead of an antisaccade.

Previous studies found substantial genetic influences on the antisaccade error rate at a behavioural level. Friedman and colleagues (2008) observed h^2 estimates of 56% in healthy adults whilst Malone and Iacono (2002) reported very similar findings in adolescence, i.e. 11

and 17 year old twins ($h^2=57\%$, 95% CI: 51-63). Greenwood and colleagues (2007) found h^2 estimates of 42% (95% CI: 27-57) in a family-based study (the Consortium on the Genetics of Schizophrenia (COGS) sample). In general, antisaccade performance is most parsimoniously explained by additive genetic and unique environmental influences (that is environmental influences that make twins differ from each other), leaving no space for common environmental (that is environmental effects that contribute to twins' similarity) or non-additive influences (e.g. dominance-related effects, i.e. those due to allelic interactions on the same gene).

To our knowledge, no study so far has examined the heritability of the neural correlates of antisaccade performance. Imaging studies contrasting brain activation during antisaccades to that during prosaccades, a saccadic control condition, reveal activations in FEF, SEF, posterior parietal cortex, DLPFC, VLPFC, ACC, thalamus, striatum and cerebellum (Aichert, Williams, et al., 2012; Brown, et al., 2006; DeSouza, et al., 2003; Ford, et al., 2005; Matsuda, et al., 2004; Raemaekers, et al., 2006; Sweeney, et al., 2007). A number of other inhibitory tasks such as the go/no-go and stop-signal tasks likewise show activations in DLPFC, ACC and striatum (Chambers, Garavan, & Bellgrove, 2009; Costa et al., 2012), providing support for the importance of these areas in inhibitory control and allowing for the possibility of generalising findings from fMRI tasks of antisaccades to the wider construct of inhibition.

An editorial on imaging genetics acknowledged the surprising lack of research on the h^2 of the BOLD signal (de Geus, et al., 2008). One way to fill this gap is to carry out twin fMRI studies. However, only a small number of twin fMRI studies have been published (Blokland, et al., 2008; Blokland, et al., 2011; Cote et al., 2007; Koten, et al., 2009; Matthews, et al., 2007). Here, we aim to fill this gap by first examining antisaccade performance in twins on a behavioural level and subsequently measuring the BOLD signal during antisaccade performance. In line with previous work on the heritability of antisaccade task performance,

we expected to find roughly equal additive genetic and unique environmental influences on the error rate (that is 50% of genetic and 50% of environmental influences). For the contrast comparing BOLD signal during antisaccades with that during prosaccades, we expected to find significant genetic influences for brain areas within the fronto-parietal and subcortical network, which was previously implicated in inhibition and antisaccade generation.

4.2. Methods

4.2.1. *Participants*

Twins were recruited through advertisements placed in the local community, in regional newspapers and on websites, from birth registers in Munich and via circular emails (distributed at schools and universities). One-hundred thirty-two same-sex reared-together healthy twins participated in the laboratory session. The sample consisted of 90 monozygotic (MZ; 32 male, 58 female) and 42 dizygotic (DZ; 24 male, 18 female) twins. Ninety-six of these (60 MZ; 28 male, 32 female and 36 DZ; 22 male, 14 female) were eligible for fMRI and agreed to participate. Ethical approval was obtained from the Faculty of Medicine of the University of Munich. Each participant provided written informed consent and received monetary compensation.

DNA was collected with DNAgenotek self-collection kits (DNA Genotek Inc, Ontario, Canada) for zygosity determination and then extracted from 3 ml saliva using QIAamp DNA-Blood-Midi-Kit (Qiagen, Hilden, Germany) based on silica membrane technology. Zygosity was determined using the Identifiler™-Kits of Applied Biosystems containing 15 highly

polymorphic short tandem repeats (STR). Fifteen STRs were used for zygosity determination; all offering a polymorphism information content of .70 to .85 (Jacewicz, Berent, Prośniak, Kadlubek, & Szram, 2004). Twins showing different DNA profiles were categorized as dizygotic. Monozygosity was determined with a probability of >99.99%.

4.2.2. Procedure

Twins were first screened during a telephone interview. Exclusion criteria for laboratory and fMRI session were past or current medical or neurological conditions, including head trauma, head injury with loss of consciousness, current use of prescribed or over-the-counter medication and current *DSM-IV* Axis I disorder (a past episode of *DSM-IV* axis I disorder was allowed). Diagnosis of a current *DSM-IV* Axis I disorder was established using the Mini International Neuropsychiatric Interview (Ackenheil, et al., 1999). Twins with first-degree relatives with a diagnosis of psychosis or ADHD were excluded. All individuals were of Caucasian ethnicity. Participants in the fMRI session were additionally required to be right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), and to have no visual impairment except the use of corrective lenses.

Testing involved two sessions. First, a laboratory session wherein the antisaccade task was assessed and second, a subsequent fMRI session that required participants to perform the antisaccade task during fMRI. Each session began with training on the task to ensure that participants understood task instructions.

In order to minimize intra-pair differences, each session (that is laboratory or fMRI) took place either on the same day or within a 2-day period for both twins (e.g. twin one and two

would either be tested on the same day or twin one or two would be tested with a maximum delay of two days to the co-twin).

4.2.3. Psychometric Assessment

Verbal intelligence was assessed with the MWT-B (Mehrfachwahl-Wortschatz-Intelligenztest, Form B; Lehrl, 2005; Lehrl, et al., 1995). Participants had to identify and mark a real word amongst three non-word distractors that increased in difficulty (37 items in total). Correct answers received one point; incorrect answers were assigned zero points, leading to a maximum of 37 points.

4.2.4. Laboratory Assessment

4.2.4.1. Eye Movement Data Acquisition

Eye movements were recorded using an Eyelink 1000 video-based eye-tracker (SR Research Ltd., Mississauga, Ontario, Canada, 2010). The right eye was tracked at a sampling rate of 1000 Hz. The stimulus (a black dot, $\sim 0.3^\circ$ visual angle in diameter) was shown on a grey background of a 17-inch monitor. Participants sat on a chair in a quiet, darkened room with their heads stabilised using a chin and forehead support. The distance between the participant's eyes and the monitor was 57 cm. A 9-point calibration was carried out before testing.

The horizontal step antisaccade task consisted of 60 trials. Each trial showed the stimulus in the centre of the screen (0°) for random durations of 1000-2000 ms. Subsequently, the stimulus was presented randomly in the periphery ($\pm 7.25^\circ$ or $\pm 14.5^\circ$ from 0°). Each

peripheral location was used 15 times. Participants were asked to perform a horizontal saccade to the mirror location of the peripheral target.

4.2.4.2. Eye Movement Data Analysis

Identification of saccades was performed with the software package Data Viewer (SR Research Ltd., Mississauga, Ontario, Canada, 2010) and additionally inspected by two raters (inter-rater reliability=.94). The first saccade following the peripheral target with a minimum amplitude of 1° and latency of 80 ms was included. The saccade was classified as either a correct antisaccade, if it was made to the opposite direction of the peripheral stimulus, or as an error, if it was made in the same direction as the peripheral stimulus. A corrective saccade was observed when an antisaccade error was followed by a saccade in the opposite direction, away from the peripheral stimulus.

The dependent variables were antisaccade direction error rate (=the number of direction errors/the number of valid antisaccade trials, in %, hereafter referred to as antisaccade error), antisaccade latency (=the reaction time of directionally correct antisaccades in ms) and antisaccade correction rate (=the number of corrected direction errors/the number of antisaccade errors made in the antisaccade task, in %) as defined before (Klein, et al., 2000).

4.2.5. *fMRI Assessment*

4.2.5.1. **Eye Movement Data Acquisition**

Eye movement acquisition during fMRI used a block design with five blocks in each condition (antisaccades, prosaccades and fixation). Each block consisted of 10 trials. Participants received the same quasi-random order of blocks.

Horizontal movements of the left eye were recorded using an MRI-compatible infrared oculographic tracker (MR-Eyetracker, CRS Ltd., Rochester, UK), using an infrared light emitter and detector array fixed to the headcoil. The system had a minimum spatial resolution of 0.2° and a horizontal range of $\pm 20^\circ$. Signals were digitized using a 12-bit analogue-to-digital converter (Data Translation DT9802) and sampled at 500Hz. A 3-point ($\pm 8^\circ$ and 0°) calibration was carried out prior to scanning. In each block, the stimulus (filled circle of $.5^\circ$ amplitude) was presented on grey background. The colour of the stimulus varied between conditions, see below.

Antisaccade: Blocks started with a 2 s-long instruction (i.e. “Look in the opposite direction”). Each trial consisted of a red central (0°) fixation stimulus (duration 1000-2000 ms) followed by a black peripheral stimulus (1000-2000 ms). Stimulus durations were such that each trial lasted for 3000 ms. The peripheral stimulus was presented equally often at right ($+ 8^\circ$) and left ($- 8^\circ$) positions in each block.

Prosaccade: Task parameters were identical to the antisaccade blocks. However, here the central fixation stimulus was of green colour. The instruction for prosaccade blocks was “Follow the dot”.

Fixation: Each block began with the instruction “Centre”, reminding participants to focus on the stimulus in centre of the screen (i.e. 0°). In each block, the stimulus was presented in black in the centre for 30 s.

4.2.5.2. fMRI Data Acquisition

Participants were scanned in a supine position using a Siemens Verio scanner at 3-Tesla field strength and a 12-channel Siemens head coil (Siemens, Erlangen). Foam padding in the head coil restricted head movement. Scanner noise was reduced through headphones. Stimuli were projected on a screen viewed by participants through a mirror attached to the head coil.

T₂*-weighted whole brain EPI images of the BOLD response were collected. A total of 240 functional images were acquired with a TR of 2 s. Four preceding volumes were discarded to ensure the establishment of longitudinal magnetization. Each image volume consisted of 28 axial slices, each 4 mm thick with an inter-slice gap of 0.8 mm and in-plane resolution of 3 x 3 mm. The flip angle was 80° and TE was 30 ms. Slices were acquired in ascending sequence (inferior to superior) parallel to the anterior commissure-posterior commissure (AC-PC) line.

4.2.5.3. Eye Movement Data Analysis

Saccades were analysed using Eyemap Version 2.1 (AMTech GmbH, Weinheim, Germany). Inclusion of saccades required a minimum latency of 80 ms and a minimum amplitude of 1°. For each participant, the mean antisaccade error rate, antisaccade and prosaccade latency and antisaccade correction rate were extracted as defined above. The prosaccade task acted as a

control condition for the antisaccade task, therefore we report prosaccade latency as a measure of accuracy; however the current study focussed on antisaccade performance.

4.2.6. Statistical Analysis

4.2.6.1. Demographical and Behavioural Data

Demographical, verbal intelligence data and behavioural data of oculomotor performance were analysed using Predictive Analysis SoftWare (PASW Statistics, version 18; SPSS-Inc., 2009). A significance level of .05 was applied to all analyses comparing demographical data between zygosity groups. Pearson's r will be reported if not otherwise indicated.

4.2.6.2. fMRI Data

Imaging data were preprocessed and analysed using a general linear model in SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/>) running in MATLAB R2008a (The MathWorks Inc., 2000). Pre-processing included realignment of images to the first image in time series, normalization to the MNI template and spatial smoothing using an 8 mm FWHM Gaussian filter and a high-pass filter (128 s).

Data analysis included two steps. First, task blocks of (1) antisaccades, (2) prosaccades, (3) fixations and (4) instructions were modelled using a synthetic canonical haemodynamic response function. Six realignment parameters were included in the model as multiple regressors to account for head movement. Overall, head movement was less than 5 mm on x-, y- or z-axis. We focussed on the BOLD signal contrasting activity during antisaccades with that

during prosaccades (antisaccades > prosaccades). Both antisaccades and prosaccades require basic saccade processes, but the antisaccade task additionally demands complex cognitive processes. By comparison of brain activity during antisaccades with that during prosaccades, brain activity related to the complex processes taking place during antisaccades, including inhibitory control, complex sensorimotor transformations, volitional response selection and response conflict resolution is expected to be revealed (Ettinger, et al., 2009; McDowell, et al., 2002; McNamee, et al., 2008).

Second, contrast images of interest (i.e. antisaccades > prosaccades) were subjected to group-level analyses. A one-sample t-test on the entire sample irrespective of zygosity was conducted yielding areas of significant activation by using the contrast images from the single-subject-level. The threshold for statistical significance was set at $p < .05$, FWE-corrected at the voxel-level across the whole brain and a minimum cluster size of 20 voxels applied.

Conversion from MNI to Talairach co-ordinates of peak voxels within a cluster was carried out using a non-linear transformation (Brett, et al., 2002) and identification of anatomic areas was achieved by consulting previous literature and the atlas of Talairach and Tournoux (1988).

MarsBaR release 0.43 (<http://marsbar.sourceforge.net>) was used to extract ROIs. In order to avoid biasing these data towards the group effect, selection of ROIs was based on data from an independent sample of 94 non-twin participants who were scanned under the same protocol as the twins in the current study. We analysed fMRI data from the non-twin participants according to the analysis steps outlined above and used the significant clusters from the second level one-sample t-test of the contrast antisaccades > prosaccades of the non-twin

data as ROIs for the current study (see Supplementary Materials). Mean activation in each extracted ROI was normally distributed and used for quantitative genetic modelling.

4.2.6.3. Quantitative Genetic Modelling

The classical twin design decomposes the phenotypic correlations between traits into components consistent with additive genetic (A), non-additive genetic (D; e.g. interactions between alleles at the same locus), common environmental (C; e.g. environmental factors that help to increase twin similarity) and unique environmental (E; e.g. individual environmental events but also measurement error) influences. MZ share all while DZ twins share on average half of their genes. MZ twins correlate perfectly for A, D and C, but are uncorrelated for E. DZ twins correlate .5 for A, .25 for D, perfectly for C and are uncorrelated for E. Higher MZ than DZ twin correlations indicate genetic influences. Non-additive genetic and C influences cannot be estimated simultaneously in twins reared-together. Therefore, either ADE or ACE models were fitted. Unique environmental influences are reflected in MZ twin correlations as MZ twins correlate perfectly for A and C (the remaining unexplained variance therefore must be due to E).

Model fitting was performed using the structural equation modelling package OpenMx (Boker, et al., 2011) and R (R-Development-Core-Team, 2010). Nested sub-models were fitted to test the contribution of each variance component (i.e. A, C or E). Comparison of model fit between sub-models (e.g. AE) and the full model (ACE) provides information on the importance of the respective component (in this case C). Models were fitted using full information maximum likelihood and evaluated by Akaike's Information Criterion (AIC; Akaike, 1987). Thereby, a lower AIC was preferred. The difference in log-likelihood between

the full and the nested sub-models is distributed as a χ^2 -statistic, which together with the difference in degrees of freedom (df) between the full and the nested model is used to test for significance of model fit (Neale & Maes, 2002). Univariate analyses were conducted for antisaccade task performance measures of the laboratory and fMRI session and for the BOLD signal of each ROI for the contrast antisaccades > prosaccades (twin correlations of <0 were not subjected to twin modelling).

4.3. Results

4.3.1. Sample Description

The laboratory sample consisted of 66 twin pairs (45 MZ: 16 male, 29 female, and 21 DZ: 12 male, 9 female), aged on average 23.64 years ($SD=6.10$). Age differed significantly between zygosity groups ($F(1, 64)=4.94, p=.03, \eta^2_p=.07$) and was therefore included in further analyses as covariate. MZ twins were on average older than DZ twins ($M=24.76, SD=6.96; M=21.26, SD=2.35$, respectively). Gender and zygosity in the laboratory sample were significantly associated ($\chi^2=5.46, p=.02$) with more MZ than DZ females. Female MZ twins tend to volunteer more frequently for participation in research than DZ twins (Kendler & Prescott, 2006). Verbal intelligence (MWT-B) did not differ between zygosity groups ($F(1, 64)=.89, p=.35, \eta^2_p=.01$, MZ: $M=29.92, SD=3.07$, DZ: $M=29.19, SD=3.75$) or between order at birth (i.e.: between first- and second-born twins: $F(1, 64)=.45, p=.51, \eta^2_p=.01$).

The fMRI sample consisted of a subsample of 48 twin pairs (30 MZ: 14 male, 16 female, and 18 DZ: 11 male, 7 female). MZ twins were trend-level significant older than DZ twins (MZ: $M=24.83, SD=6.83$; DZ: $M=21.53, SD=2.38$; $F(1, 46)=3.83, p=.056, \eta^2_p=.08$). Gender was

distributed evenly across zygosity groups ($\chi^2=1.88, p=.17$). Both zygosity groups and first and second-born twins were comparable on verbal intelligence ($F(1, 46)=.30, p=.59, \eta^2_p=.02$ and $F(1, 46)=.01, p=.93, \eta^2_p=.02$, respectively).

Twins who participated in both the laboratory and fMRI session did not differ from those who only participated in the laboratory session in age or years in education (all $p>.05$). Gender distribution was significantly different between the laboratory and fMRI sample; resulting from the frequent use of orthodontic retainers in females, which left these females unsuitable for imaging.

Employment status in the laboratory and fMRI samples was as follows: 48.5% and 54.2% were studying, 22% and 20.8% were working full-time, 9.8% and 6.3% were going to school, 9.1% and 8.3% were in professional training, 6.1% and 7.3% were working part-time, 2.3% and 1% were unemployed and employment status was unknown in 2.3% and 2.1%, respectively.

4.3.2. Antisaccade Performance

Antisaccade task performance in the entire laboratory sample was: antisaccade error rate $M=35.07$, $SD=22.91$, antisaccade latency $M=284.81$, $SD=40.85$ and antisaccade correction rate $M=99.00$, $SD=3.11$. There were no significant differences between zygosity groups on any of these measures: error rate ($F(1, 63)=.17$, $p=.68$, $\eta^2_p<.01$), latency ($F(1, 63)=.09$, $p=.77$, $\eta^2_p<.01$) or correction rate ($F(1, 63)<.01$, $p=.99$, $\eta^2_p<.01$; Table 8).

Antisaccade task performance in the entire fMRI sample was: antisaccade error rate: $M=18.89$, $SD=13.89$, antisaccade latency: $M=252.75$, $SD=38.84$ and antisaccade correction rate: $M=88.35$, $SD=21.79$. Zygosity groups did not differ significantly on any of these measures: error rate ($F(1, 45)=.20$, $p=.66$, $\eta^2_p=.01$), latency ($F(1, 45)=2.00$, $p=.16$, $\eta^2_p=.02$) or correction rate ($F(1, 45)=.14$, $p=.71$, $\eta^2_p<.01$). Measures of prosaccade performance were as follows in the entire fMRI sample: prosaccade latency: $M=187.00$, $SD=30.29$; see also Table 8.

Correlations between laboratory and fMRI task performance were significant for antisaccade error rate ($r_{MZ}=.36$, $p<.01$; $r_{DZ}=.77$, $p<.01$) and latency ($r_{MZ}=.60$, $p<.01$; $r_{DZ}=.62$, $p<.01$) but not for the correction rate ($r_{MZ}=-.21$, $p=.11$; $r_{DZ}=-.07$, $p=.68$).

Table 8 - Saccade task performance by zygosity.

	<i>MZ</i>		<i>DZ</i>	
	<i>Mean</i>	<i>Standard deviation</i>	<i>Mean</i>	<i>Standard deviation</i>
<i>Laboratory sample</i>				
<i>Antisaccade error rate (in %)</i>	35.34	23.00	34.02	22.95
<i>Antisaccade latency (in ms)</i>	285.79	41.49	287.22	43.00
<i>Antisaccade correction rate (in %)</i>	98.91	3.36	98.95	2.89
<i>fMRI sample</i>				
<i>Antisaccade error rate (in %)</i>	17.22	12.36	21.67	15.93
<i>Antisaccade latency (in ms)</i>	251.84	41.62	254.27	34.21
<i>Antisaccade correction rate (in %)</i>	85.78	24.70	92.63	15.18
<i>Prosaccade latency (in ms)</i>	189.37	30.15	183.05	30.52

Notes: *MZ*=monozygotic, *DZ*=dizygotic.

4.3.3. *fMRI Task Activation*

Figure 25-A illustrates the BOLD signal during the contrast antisaccades > prosaccades in the entire fMRI twin sample. Table 9 provides a detailed overview of these brain regions with information on hemisphere, cluster size, Brodmann area, Talairach coordinates and test statistics. Overall, activation was found in frontal, parietal, temporal and subcortical regions such as the superior and middle frontal gyrus, anterior and posterior intraparietal sulcus, superior and middle occipital regions, cingulate gyrus, globus pallidus and cerebellum. Two clusters, frontal and parieto-occipital, were large and spanned several regions. Peak activation of the frontal cluster was located in the FEF; areas such as the insula and cingulate cortex were included in this cluster. Peak activation in the parieto-occipital cluster was located in the precuneus; sub-peaks were found in the inferior parietal, superior and middle occipital lobe and were included in this cluster. Activation of a similar fronto-parietal and subcortical network has been obtained before with the antisaccade task (Ettinger, et al., 2008; McDowell, et al., 2002).

A very similar network of activation was observed for the same contrast in the sample of N=94 non-twin participants (see 4.5 Supplementary Materials).

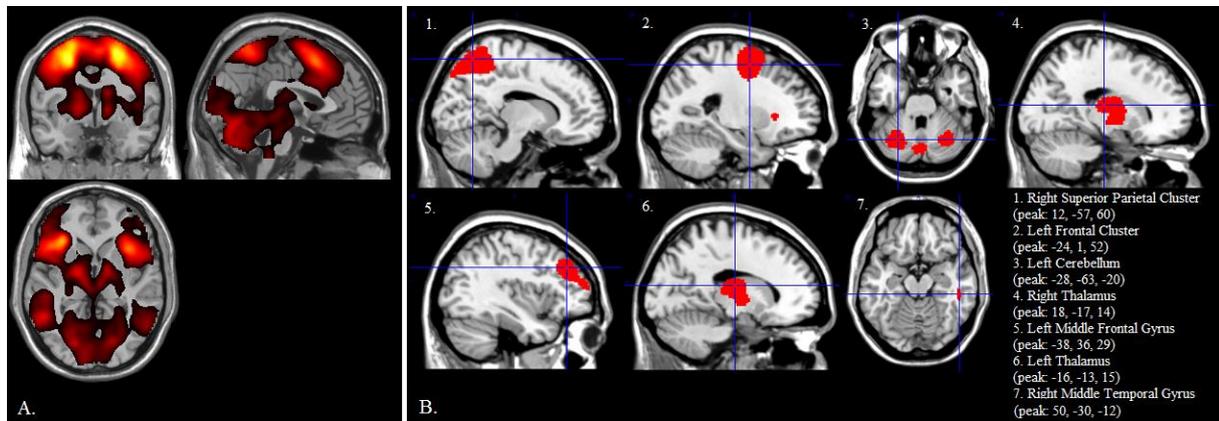


Figure 25 - BOLD signal for antisaccades > prosaccades (A) and ROIs (B) in the entire twin sample.

Notes: Brains are shown according to the neurological convention. Part A of the figure shows the activation during the contrast antisaccades > prosaccades in the entire twin sample (see Table 9). Part B shows the ROIs that were extracted on the basis of the analysis in the non-twin sample (see Supplementary Materials Table 13).

Table 9 - BOLD signal for the contrast antisaccades > prosaccades in the entire twin sample.

Cluster Size	Macroanatomical label	Hemisphere	Functional label	Brodmann area	Stereotaxic coordinates			T
					x	y	z	
12013	Middle Frontal Gyrus	r	FEF	6	26	2	50	17.20
	Middle Frontal Gyrus	l	FEF	6	-24	3	53	16.93
	Insula	r	-	-	34	25	-1	13.21
	Insula	l	-	-	-34	18	1	11.34
	Medial Frontal Gyrus	r	SEF	6	6	14	45	12.08
	Medial Frontal Gyrus	l	SEF	6	-6	3	57	11.02
	Inferior Frontal Gyrus	r	-	9	55	11	25	11.26
	Inferior Frontal Gyrus	l	-	9	-50	5	31	8.42
	Cingulate Gyrus	l	-	32	-8	23	28	6.88
13930	Precuneus	l	-	7	-10	-55	58	16.08
	Superior Parietal Lobe	r	-	7	16	-57	60	15.22
	Superior Parietal Lobe	r	-	7	26	-47	63	11.19
	Inferior Parietal Lobe	l	-	40	-32	-42	51	10.42
	Inferior Parietal Lobe	r	-	40	57	-35	35	10.14
	Inferior Parietal Lobe	l	-	40	-57	-25	34	8.84
	Superior Occipital Gyrus	r	Visual cortex	19	32	-80	28	7.42
	Middle Occipital Gyrus	l	Visual cortex	19	-32	-83	19	8.92
2528	Cerebellum	l	-	-	-34	-56	-27	10.76
	Cerebellum	r	-	-	40	-48	-30	7.53
871	Middle Frontal Gyrus	r	DLPFC	9	38	36	28	10.05
567	Middle Frontal Gyrus	l	DLPFC	9	-36	36	28	9.97
325	Globus Pallidus	r	-	-	16	-6	6	7.74
220	Temporo-parietal Junction	r	-	21	51	-50	3	6.93
	Middle Temporal Gyrus	r	-	21	51	-49	-1	5.18
45	Globus Pallidus	l	-	-	-14	4	0	5.60

Notes: Eight significant clusters emerged from the contrast antisaccades > prosaccades in the entire twin sample. Clusters are separated in the table by horizontal lines. Peak voxels in a cluster are given in bold; sub-peaks are given in regular letter format. Cluster size is given in number of voxels. FEF=Frontal eye field, SEF=Supplementary eye field, DLPFC=Dorso-lateral prefrontal cortex, r=right, l=left.

4.3.4. Quantitative Genetic Modelling

4.3.4.1. Laboratory Antisaccade Performance

Table 10 shows twin correlations and behaviour genetic modelling of antisaccade task performance. Cross-twin correlations for the antisaccade error rate were moderate ($r_{MZ}=.51$, $p<.01$; $r_{DZ}=.20$, $p=.41$). As hypothesized, twin correlations were larger in *MZ* than *DZ* twins indicating familial influences on the error rate. Antisaccade latency and correction rates did not show evidence for familial influences as indicated by larger *DZ* than *MZ* twin correlations (latency: $r_{MZ}=.34$, $p=.02$; $r_{DZ}=.44$, $p=.05$; correction rate: $r_{MZ}=.12$, $p=.43$; $r_{DZ}=.43$, $p=.06$).

Univariate twin modelling of the error rate revealed that additive genetic (A) and unique environmental (E) influences most parsimoniously described correlation patterns between twins (see comparison ADE vs. AE model: $\chi^2_1<.01$, $p>.99$). Genetic influences thereby could not be dropped (see comparison AE vs. E model: $\chi^2=12.24$, $p<.01$). Additive genetic influences accounted for 47% (95% CI: 22-65%), unique environmental influences accounted for the remaining 53% (95% CI: 35-78%) of variation in antisaccade error rate.

As twin correlations for measures such as antisaccade latency or correction rate did not show support for familial influences, no univariate twin modelling was conducted on these measures (see Table 10).

Table 10 - Univariate twin modelling of laboratory antisaccade task performance.

	r_{MZ}	r_{DZ}	Model	-2LL	AIC	$\Delta\chi^2$	Δdf	p	h^2	95% CI	d^2	95% CI	e^2	95% CI
<i>Antisaccade error rate</i>	.51**	.20	ADE	1178.92	924.92	5.99	6	.42	.47	.00-.65	.00	.00-.00	.53	.35-.78
			AE	1178.92	922.92	.00	1	>.99	.47	.22-.65			.53	.35-.78
			E	1191.16	933.16	12.24	1	<.01					1.00	1.00-1.00
<i>Antisaccade latency</i>	.34*	.44	-											
<i>Antisaccade correction rate</i>	.12	.43	-											

Notes: The table shows twin correlations and twin modelling results from the entire laboratory sample (N=132).

r_{MZ} =Pearson's correlations coefficient of monozygotic twins

-2LL=minus 2 * the log likelihood of each model (this follows a chi-square distribution)

$\Delta\chi^2$ =difference in chi-square statistic

h^2 =heritability estimate

e^2 =estimate of unique environmental influences

95% CI=95% confidence interval

r_{DZ} =Pearson's correlations coefficient of dizygotic twins

AIC=Akaike's Information Criterion

Δdf =difference in degrees of freedom

d^2 =estimate of dominance-related influences

* $p < .05$, ** $p < .01$

Model Variance components:

A=additive genetic

D=dominance-related

E=unique environmental variance components.

The most parsimonious model is shown in bold, nested sub-models were compared to the full ADE model. The first comparison quantifies the comparison between the saturated and ADE model.

4.3.4.2. fMRI Antisaccade Performance

Twin correlations for behavioural antisaccade performance during fMRI were larger in *DZ* than in *MZ* twins, indicating no evidence for genetic influences on antisaccade error rate ($r_{MZ}=.20$, $p=.30$; $r_{DZ}=.49$, $p=.04$), latency ($r_{MZ}=.63$, $p<.01$; $r_{DZ}=.67$, $p<.01$) or correction rate ($r_{MZ}=.05$, $p=.79$; $r_{DZ}=.72$, $p<.01$).

4.3.4.3. fMRI Regions of Interest

ROIs of the contrast antisaccades > prosaccades were extracted from the twin data on the basis of the clusters obtained in the non-twin sample (see Figure 25-B). Twin correlations for these ROIs are displayed in Table 11. Overall, cross-twin correlations were small to moderate in *MZ* (.10 to .43) and *DZ* twins (.02 to .36). Indication for familial influences as shown by higher *MZ* than *DZ* cross-twin correlations were found for left frontal lobe ($r_{MZ}=.22$, $p=.24$; $r_{DZ}=.02$, $p=.95$), left cerebellum ($r_{MZ}=.15$, $p=.44$; $r_{DZ}=.07$, $p=.78$), left middle frontal gyrus ($r_{MZ}=.30$, $p=.11$; $r_{DZ}=.03$, $p=.92$) and left thalamus ($r_{MZ}=.43$, $p=.02$; $r_{DZ}=.36$, $p=.15$). Other regions did not show evidence for familial influences. Univariate twin modelling to estimate the magnitude of significant genetic influences was conducted only for the former regions (see Table 12).

Univariate twin modelling showed that common environmental/dominance-related influences could be dropped from ACE/ADE models for all ROIs without significant loss of fit (see Table 12). The comparison between AE and E models allowed testing for the significance of the variance component pertaining to additive genetic influences (i.e. A). Significant additive genetic influences were retained only for left thalamus following model comparison (see comparison AE vs. E model: $\chi^2_I=8.50$, $p<.01$) indicating that the most parsimonious model to explain variation in BOLD signal for the contrast antisaccades > prosaccades includes additive

genetic influences ($h^2=50\%$, 95% CI: 18-72) and unique environmental influences ($h^2=50\%$, 95% CI: 28-82) in this ROI. Other ROIs were most parsimoniously explained by unique environmental influences only (see Table 12).

Table 11 - Twin correlations by region of interest.

<i>Coordinates in Talairach space</i>			<i>Macroanatomical label</i>	<i>Hemisphere</i>	<i>r_{MZ}</i>	<i>r_{DZ}</i>
<i>x</i>	<i>y</i>	<i>z</i>				
12	-57	60	Superior Parietal Lobe	r	.25	.32
-24	1	52	Frontal Lobe	l	.22	.02
-28	-63	-20	Cerebellum	l	.15	.07
18	-17	14	Thalamus	r	.10	.34
-38	36	29	Middle Frontal Gyrus	l	.30	.03
-16	-13	15	Thalamus	l	.43*	.36
50	-30	-12	Middle Temporal Gyrus	r	.20	.20

Notes: The clusters were extracted from the twin sample on the basis of the ROIs defined in the sample of non-twins (see Supplementary Table 14).

r_{MZ}=Pearson's correlations coefficient of monozygotic twins

r_{DZ}=Pearson's correlations coefficient of dizygotic twins

r=right

l=left

bold=used for twin modelling

**p*<.05.

Table 12 - Twin modelling of BOLD signal for the contrast antisaccades > prosaccades.

Macroanatomical label	Hemi-sphere	r_{MZ}	r_{DZ}	Model	-2LL	AIC	$\Delta\chi^2$	Δdf	p	h^2	95% CI	c^2/d^2	95% CI	e^2	95% CI
Frontal Lobe	left	.22	.02	ADE	-111.09	-295.09	12.37	6	.05	.22	(.00; .59)	.00	(.00; .34)	.78	(.41; 1)
				AE	-111.09	-297.09	.00	1	>.99	.22	(.00; .59)	.78	(.41; 1)		
				E	-110.17	-298.17	.92	1	.34	1					
Cerebellum	left	.15	.07	ADE	-67.89	-251.89	4.25	6	.64	.15	(.00; .48)	.00	(.00; .00)	.85	(.52; 1)
				AE	-67.89	-253.89	.00	1	>.99	.15	(.00; .48)	.85	(.52; 1)		
				E	-67.28	-255.28	.61	1	.44	1					
Middle Frontal Gyrus	left	.30	.03	ADE	-85.94	-269.94	17.96	6	.01	.31	(.00; .68)	.00	(.00; .00)	.69	(.32; 1)
				AE	-85.94	-271.94	.00	1	>.99	.31	(.00; .68)	.69	(.32; 1)		
				E	-84.51	-272.51	1.43	1	.23	1					
Thalamus	left	.43*	.36	ACE	-133.67	-317.67	3.43	6	.75	.39	(.00; .71)	.10	(.00; .58)	.51	(.29; .85)
				AE	-133.60	-319.60	.07	1	.79	.50	(.18; .72)	.50	(.28; .82)		
				E	-125.10	-313.10	8.50	1	<.01						

Notes:

r_{MZ}/r_{DZ} =Pearson's correlation coefficient for MZ (monozygotic) and DZ (dizygotic) twins

C=common environmental

-2LL=-2 * the log likelihood of each model (this follows a chi-square distribution)

AIC=Akaike's Information Criterion

Δdf =difference in degrees of freedom to previous model

c^2 =estimate of common environmental influences

e^2 =estimate of unique environmental influences

Bold=most parsimonious model

Note that this cluster contains more than one region, the peak in this cluster is indicated by the name of the cluster, i.e. Frontal Lobe.

A=additive genetic

D=dominance-related

E=unique environmental variance components

$\Delta\chi^2$ =difference in chi-square statistic

h^2 =heritability estimate

d^2 =estimate of dominance-related influences

95% CI=95% confidence interval

* $p < .05$

4.4. Discussion

Here, we investigated the heritability of the neural correlates of antisaccade task performance. To this purpose, we assessed task performance in a laboratory and an fMRI session and examined the heritability of task performance and its associated BOLD signal. The main findings are as follows. First, we successfully replicated heritability estimates of antisaccade task performance in the laboratory (see e.g.: Malone & Iacono, 2002). Second, we successfully replicated the pattern of BOLD signal in the fronto-parietal subcortical network pertaining to antisaccade task performance both in the twin sample and a sample of non-twin participants (see e.g.: McDowell, et al., 2008). Finally, we obtained tentative evidence for significant additive genetic influences on variability of the BOLD signal, specifically in the thalamus, but not for antisaccade task performance during fMRI or BOLD signal in any other ROI.

4.4.1. Heritability of Laboratory and fMRI Antisaccade Task Performance

We found evidence for substantial h^2 (47%, 95% CI: 22-65) on the antisaccade error rate in the laboratory. Despite the small sample in the laboratory, which might have influenced the large CI obtained, the current finding is consistent with previous results from healthy samples (56%, 42% and 57% in Friedman, et al., 2008; Greenwood, et al., 2007; and Malone & Iacono, 2002, respectively). Antisaccade latency or correction rate did not show evidence for significant genetic influences.

In terms of environmental influences, we replicated previous findings of zero to low common environmental influences and substantial evidence for unique environmental

influences (53%, 95% CI: 35-78) on the error rate (Friedman, et al., 2008; Malone & Iacono, 2002). Precise unique environmental influences on antisaccade task performance remain to be specified. Environmental influences for measures of early inhibition (e.g.: pre-pulse inhibition) in rodents for instance include isolation rearing (mainly post-weaning to adulthood), maternal deprivation and developmental stressors (e.g.: prenatal dexamethasone exposure, exposure of pregnant females to stressors, animals exposed to enriched or improvised conditions during development; Swerdlow, Weber, Qu, Light, & Braff, 2008). It remains to be shown whether these environmental influences impact on human performance on volitional measures of inhibition, too.

Antisaccade task performance during fMRI did not show evidence for significant familial influences whereas task performance in the laboratory, specifically the error rate, showed significant genetic influences. This could be due to a number of reasons. First, the sample used for fMRI was small (smaller than that used in the laboratory) and therefore made detection of h^2 more difficult. Second, the ratio between *MZ* and *DZ* twins was unbalanced; both factors impact on the amount of heritability that can be detected (Visscher, 2004). Third, mean performance scores in error rate and latency changed between sessions and reliability puts an upper limit to the heritability that can be detected.⁴ Overall, issues due to sample size and composition of the fMRI sample most likely account for the lack of finding genetic influences on the antisaccade task performance during fMRI.

⁴ However, it should be noted that the comparison of behavioural task mean performance levels between the fMRI and laboratory sessions is not straightforward. The data from the fMRI sample was obtained at a second assessment of the task, allowing for the possibility of effects of repeated exposure, and under different test settings (e.g. in a supine position during scanning vs. seated in front of a computer in the laboratory) and with slightly different task parameters (e.g. number of peripheral targets differed: laboratory: $\pm 7.25^\circ$ or $\pm 14.5^\circ$ and fMRI: $\pm 8^\circ$) than the data from the laboratory sample. Whilst stability of antisaccade task performance under identical conditions is reported to be good (Ettinger, et al., 2003; Klein & Fischer, 2005; Roy-Byrne, Radant, Wingerson, & Cowley, 1995; Smyrnis, 2008; Woestmann et al., 2013), these differences have to be taken into consideration in assessing mean performance differences between the two samples reported here.

Zygoty groups differed in terms of performance stability between laboratory and fMRI. MZ twin correlations between laboratory and fMRI sessions were lower than DZ twin correlations, so specifically MZ twins showed a less consistent pattern on the antisaccade error rate than DZ twins across sessions. Considering that it is the magnitude of the MZ cross-twin correlation that impacts greatly on the estimate of heritability (Neale & Cardon, 1992) and given that the MZ but not DZ cross-twin correlation dropped from laboratory to fMRI session, it is not surprising that a drop in heritability of the antisaccade error rate was found between the laboratory ($h^2=47\%$) and the fMRI session ($h^2=0\%$).

4.4.2. Neural Correlates Underlying Antisaccade Task Performance

McDowell and colleagues (2008) summarized the neural correlates for the contrast antisaccades > prosaccades and revealed brain activity in parietal regions, FEF, SEF, DLPFC, ACC, striatum and thalamus in non-twin samples. Our findings from a twin sample (see Figure 25) are broadly consistent with the pattern of activations previously reported from non-twin samples as well as the pattern of activations we observed in a non-twin sample (see Supplementary Materials), thus supporting the comparability of our twin sample to non-twin samples.

It has to be mentioned that the antisaccade and prosaccade conditions differ in various respects (e.g. demands placed on working memory, goal or intention activation and attentional focus, as outlined before); therefore, the BOLD signal that emerges from this contrast has to be interpreted with caution. However, in our choice of this contrast we were drawing on previous research wherein the contrast was commonly used (McDowell, et al., 2008).

4.4.3. Heritability of BOLD Signal Underlying Antisaccade Task Performance

We found evidence for additive genetic influences on the BOLD signal during the contrast antisaccades > prosaccades only in the left thalamus ($h^2=50\%$). BOLD signal in the other ROIs did not show evidence for significant heritability.

The thalamus forms part of a subcortical network that is involved in saccade generation and antisaccade inhibition (Dyckman, et al., 2007; Matsuda, et al., 2004; O'Driscoll, et al., 1995). Genetic influences on the volume of the thalamus have been shown before (Ettinger et al., 2007). Van 't Ent and colleagues (2009) previously found evidence for genetic risk on the BOLD in the left thalamus during an fMRI Stroop interference task using MZ twins, who were concordant for low or for high problems with attention and hyperactivity. Those findings are in line with the current ones indicating a role for the thalamus in inhibition and pointing to genetic influences on the inter-individual variability of the BOLD signal in the thalamus. The remaining variability in BOLD signal in the left thalamus in our sample was accounted for by unique environmental influences, a pattern that has also been documented before for thalamus volume in a pediatric sample (in a pediatric sample: Schmitt et al., 2007).

The fact that no other ROI showed evidence for significant genetic influences has to be interpreted with caution, as a number of limitations impact on the amount of heritability that can be detected.

First, the ratio between MZ and DZ twins to detect 50% heritability (previous studies of oculomotor measures suggest 40-60% heritability) should be 1:1 (Visscher, 2004). The ratio in the current sample however was 5:3 (30 MZ and 18 DZ pairs), which was possibly not balanced enough to detect significant h^2 for other ROIs. Due to stricter inclusion criteria for

fMRI than for the laboratory, a smaller number of twin pairs was recruited (i.e. 48 pairs for fMRI and 66 pairs for the laboratory). Even more important however is achieving a larger sample size.

Second, sample size alongside the actual dimension of cognitive control that is investigated is important to consider. Previous twin fMRI studies used wide ranges of sample sizes, e.g. from 40 to 319 twins with varying ratios between MZ and DZ twins, and found mixed evidence for significant h^2 of the BOLD signal. For working memory, only an increase in sample size led to finding significant h^2 of the underlying BOLD signal (Blokland, et al., 2008; Blokland, et al., 2011). The same might be true for the genetic influences underlying neural correlates of inhibition. In line with the latter, post-hoc power calculations (performed in OpenMx) on the current sample revealed low power for detecting h^2 of 60% and e^2 of 40% at $\alpha=.05$. A total of 655 twin pairs (MZ:DZ ratio=1:1) would have been required to detect h^2 of 60% and e^2 of 40% with 80% power. Thus, investigation of the h^2 of the BOLD signal underlying inhibition requires larger twin samples. Nevertheless, two points need to be made: first, a sample of 96 twins, though small to moderate for a twin study, is of considerable size for an fMRI study and second, obtaining small confidence intervals is more informative for interpretability of the results.

A final point that should be considered is the reliability of the BOLD signal. Test-retest reliability of the BOLD signal is diverse with Intra Class Correlations (ICC) ranging from .33 to .66 (Bennett & Miller, 2010) and appears to depend on the cognitive domain investigated. Aron and colleagues (2006) for instance obtained ICC of $>.80$ using a classification learning task. High reliability of the BOLD signal also emerged from domains such as working memory (Manoach et al., 2001; Wei et al., 2004). Evidence for reliability of the BOLD signal during inhibition, however, is sparse. Test-retest reliability of task-related activation for the contrast

antisaccades > prosaccades was generally found to be low (as indicated by an overlap ratio of .27; Raemaekers et al., 2007). Ettinger and colleagues (2009) found mixed evidence for reliability of the BOLD signal in areas relevant for the contrast antisaccades > prosaccades, ranging from negative and zero reliabilities to a maximum of .66. Thus, reliability of the BOLD signal differs between components of cognitive control with domains such as working memory showing high reliability (and substantial heritability for the BOLD signal underlying task performance). Further research on the reliability of the BOLD signal for measures of inhibitory control is awaited.

In line with the rationale underlying imaging genetics, larger heritability estimates were expected at the neural than at the behavioural level (*here*: the neural correlates underlying antisaccade task performance assessed during fMRI compared to behavioural task performance). Our findings suggest that caution needs to be exerted when estimating genetic effects on the BOLD signal. Twin correlations varied extensively between regions, favouring more nuanced interpretations that take into account the phenotype (e.g. inhibitory control) and the brain regions that are investigated. Specifically, our data suggest that for the neural correlates of inhibitory control genetic effects can be easier detected in some regions (*here*: thalamus) than in other regions (*here e.g.*: DLPFC or FEF). Overall, it is not sample size, the phenotype or a specific brain region per se, but rather a focus on the interaction of these factors that will most likely advance the study of the genetic influences on the BOLD signal.

4.4.4. Conclusion

One assumption underlying imaging genetics is the heritability of the BOLD signal. The current study is the first to examine this assumption for the antisaccade task, a measure of cognitive

control known to be impaired in various psychiatric disorders with compromised inhibitory control (Hutton & Ettinger, 2006). We estimated the heritability of antisaccade task performance on a behavioural level as well as for the BOLD signal associated with performance. Our findings showed a substantial amount of genetic influences on the error rate at a behavioural level in a first laboratory session and tentative evidence for region-specific significant genetic influences on individual variability of the BOLD signal. Future studies investigating the aetiological factors underpinning the BOLD signal in inhibitory control might benefit from the current findings and apply larger samples for estimating genetic influences at the level of the brain and most importantly a sufficiently reliable BOLD signal. Establishing heritability of the BOLD signal during inhibitory control remains a challenging undertaking.

4.5. Supplementary Materials

Regions of interest were extracted from a dataset of 94 participants who underwent the same procedure and whose data were preprocessed and analysed in the same way as in the twins. This sample was comparable in terms of gender distribution (47.9% males), age in years ($M=27.93$, $SD=7.92$), employment status (61.7% studying, 21.3% full time employment, 6.4% professional training, 5.3% part-time employment, 4.3% unemployed and 1.1% going to school) and task performance (see Supplementary Materials Table 13) to the twins.

Table 13 - Supplementary Table of saccade task performance in the non-twin sample.

	<i>Mean</i>	<i>SD</i>
<i>Laboratory session</i>		
<i>AS error rate in %</i>	28.43	21.23
<i>AS latency in ms</i>	285.89	47.53
<i>AS correction rate in %</i>	98.29	10.51
<i>fMRI session</i>		
<i>AS error rate in %</i>	22.57	16.79
<i>AS latency in ms</i>	258.73	40.60
<i>AS correction rate in %</i>	94.49	16.71
<i>PS latency in ms</i>	179.81	23.68

Notes: AS=antisaccade, PS=prosaccade.

Results of the one-sample t-test FWE-corrected, $p<.05$, cluster size threshold at 20 voxel) conducted in this sample on the contrast antisaccades > prosaccades revealed seven significant

clusters spanning frontal, parietal, temporal, cerebellar and subcortical areas (see Supplementary Table 14 and Supplementary Figure 26 for details).

Table 14 - Supplementary Table of BOLD signal for the contrast antisaccades > prosaccades in the non-twin sample.

<i>Cluster size</i>	<i>Macroanatomical label</i>	<i>Hemi- sphere</i>	<i>Brodmann area</i>	<i>Stereotaxic coordinates</i>			<i>T</i>
				<i>x</i>	<i>y</i>	<i>z</i>	
17656	Superior Parietal Lobe	r	7	12	-57	60	15.27
17917	Frontal Lobe	l		-24	1	52	14.97
3112	Cerebellum	l		-28	-63	-20	9.19
1336	Thalamus	r		18	-17	14	8.64
1070	Middle Frontal Gyrus	l		-38	36	29	8.13
969	Thalamus	l		-16	-13	15	8.01
70	Middle Temporal Gyrus	r		50	-30	-12	6.15

Notes: Coordinates are given in Talairach space. r=right, l=left.

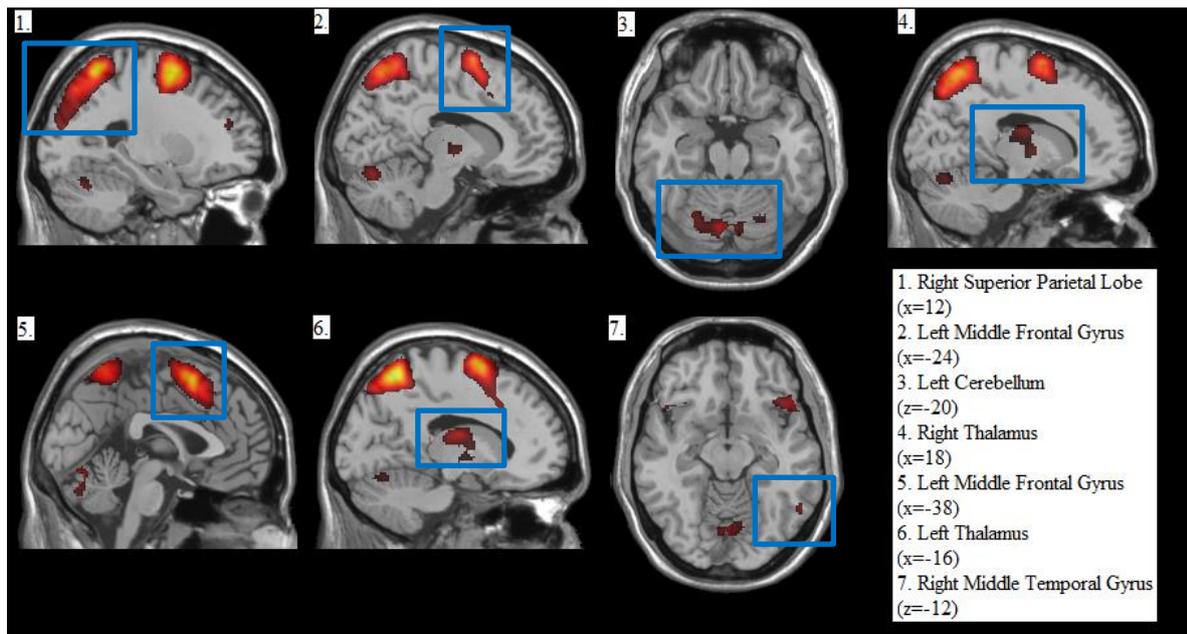


Figure 26 - Supplementary Figure of BOLD signal for the contrast antisaccades > prosaccades in the non-twin sample.

5. General Discussion

5.1. General Summary

The studies presented in the empirical chapters two, three and four examined the aetiology of schizotypy and antisaccades using behavioural genetic and neurocognitive methods. Each finding has been discussed separately in the Discussion section of each chapter. Here, an overall summary, limitations to the conceptual and methodological approaches used in the studies and an overall conclusion will be given.

The study in chapter two investigated the nature of schizotypy in relation to neuroticism. Schizotypy features and neuroticism are positively associated but it was unknown to what extent these constructs share a common aetiology. We replicated the often reported phenotypic correlation between neuroticism and positive schizotypy, specifically aberrant perceptual and magical ideational features (.37) and decomposed the covariation between positive schizotypy and neuroticism into its underlying genetic and environmental components. We found 51% of shared additive genetic influences between neuroticism and positive schizotypy. We extended this bivariate analysis by a multivariate analysis which allowed us to examine the relationship between the full construct of schizotypy and neuroticism. Results revealed that the genetic influences that impact on neuroticism and other non-positive features of schizotypy cover the additive genetic influences that impact on positive schizotypy, indicating that additive genetic influences of perceptual and magical ideational components of schizotypy completely overlap with those of neuroticism, negative and impulsivity and hypomania-related features of schizotypy.

Given the importance of non-positive features of schizotypy in its aetiology, we subsequently examined the neural correlates underlying the construct of schizotypy. In contrast

to previous studies, we made sure to assess all schizotypy features that is positive, negative and disorganization-related and did so in a substantially large fMRI sample of participants. To probe the neural correlates of schizotypy, we relied on a schizophrenia-related endophenotype, i.e. oculomotor inhibition as assessed with antisaccade task performance (Greenwood et al., 2012; Malone & Iacono, 2002). The study presented in chapter three therefore set out to investigate the neural correlates underlying the construct of schizotypy making use of eye movements. In the, so far, largest sample of healthy individuals (N=142), we investigated antisaccade and prosaccades tasks during fMRI and correlated brain activity during these tasks with positive, negative and disorganization-related dimensions of schizotypy. In line with previous studies, we found activation in a fronto-parietal-occipital subcortical network underlying eye movements. Brain activity pattern in this network were differentially associated with negative features of schizotypy, which similar to the findings presented in the first study confirm the importance of non-positive features in schizotypy.

Finally, in the last study, we targeted the main brain areas previously detected during antisaccades and assessed the validity of using the BOLD response as an endophenotype in a twin fMRI study. Consistent with previous research, that revealed additive genetic influences on the behavioural antisaccade error rate (see e.g.: Malone & Iacono, 2002), we found moderate estimates of heritability on antisaccade task performance in the laboratory $h^2=47\%$. We furthermore replicated the pattern of BOLD response in the fronto-parietal-occipital subcortical network pertaining to antisaccade task performance in our twin sample (see e.g.: McDowell, et al., 2008) and obtained the first, yet tentative, finding for additive genetic influences on variability of the BOLD response during antisaccades, specifically in the thalamus. Our findings tentatively indicate that the BOLD response obtained during eye movement tasks

might be used as an endophenotype. Further replication of this finding in a larger sample is however necessary to draw further conclusions.

5.2. Limitations

The current findings have to be placed within the conceptual and methodological limitations of the assumptions and methods that were applied throughout the studies.

5.2.1. Endophenotypes and Imaging Genetics

The importance of genetics in the aetiology of psychiatric disorders has been discussed before (Puls & Gallinat, 2008), yet, determining specific functional genetic variants remains challenging (Meyer-Lindenberg, 2010). Due to the health costs and the increased risk for mortality that are associated with psychiatric disorders (Uhl & Grow, 2004), it is crucial to reveal the aetiology underlying these disorders. One way to facilitate the search for specific genetic variants might be given by reducing the pathway from genes to phenotypes by the use of intermediate imaging phenotypes such as brain functioning deviations associated with the disorder. This is the core of the field of imaging genetics. Biological endophenotypes, such as the BOLD response, were suggested to lie closer to gene action (e.g. Glahn, Paus, & Thompson, 2007). In chapter four, we put one assumption of the imaging genetics approach to the test by assessing the heritability of the BOLD response during oculomotor inhibition. We used the BOLD response in a fronto-parietal-occipital subcortical network as endophenotypes and examined the amount of genetic influences on the BOLD response in each area individually. We found tentative support for additive genetic influences on the BOLD response in the thalamus. Examining the use of neuroimaging endophenotypes has been suggested before, for

the prediction of treatment responses for instance (Phillips, 2007). Latter has been examined for psychosis and cognitive behavioural therapy (Kumari et al., 2011). It was found that schizophrenia patients presenting with at least one symptom showed a reduced BOLD response in areas such as the left thalamus in the post-treatment assessment (the treatment included cognitive behavioural therapy for psychosis and treatment-as-usual, the control group received treatment-as-usual only); the alteration of the BOLD response also correlated with symptom improvement (Kumari, et al., 2011). In line with our tentative evidence for genetic influences on the BOLD signal in the thalamus in chapter four, this region seems to be a promising neuroimaging endophenotype. The study reported in chapter four can contribute to further establish brain measures as endophenotypes and provides tentative proof for the assumption of heritability of measures of brain functioning for the field of imaging genetics.

The study reported in chapter four estimated the amount of genetic influences; this finding needs to be undermined by close investigation of mechanisms of action. A few genetic candidates were suggested for schizophrenia endophenotypes such as antisaccade task performance, e.g. Nitric oxide synthase 1 adaptor protein (*NOS1AP*) on 1p23.3, alpha7 nicotinic acetylcholine receptor subunit gene (*CHRNA7*) on 15q13.3 or calcium channel, voltage-dependent, gamma subunit 2 (*CACNG2*) on 22q12.3 (Greenwood, et al., 2012). Specifying mechanisms of action from susceptibility genes to the liability to express the disorder via dysfunctional brain activity remain to be specified in detail.

5.2.2. Assumptions of the Classical Twin Design

A few limitations of the current twin studies are bound to the assumptions of the classical twin design. Random mating is assumed in order to draw valid conclusions from twin studies. There is evidence for little assortative mating (up to .20) for personality traits (Vandenberg, 1972). There is also evidence for assortative mating amongst patients with psychiatric disorders, including schizophrenia (Parnas, 1988). Non-random mating would have biased the estimation obtained from twin modelling towards lower h^2 estimates. One way to check whether this assumption is fulfilled is to obtain information from the parents. As we did not have obtained parental measures of schizotypy, personality or brain activity during eye movements in the current studies, we cannot rule out that our estimates might have been biased due to assortative mating. However, the h^2 estimates we have derived were in line with findings from previous studies indicating that non-random mating was unlikely to distort our results.

The classical twin design is limited to estimating additive genetic effects. A failure to take non-additive genetic effects into account may be one of the main reasons why studies of twins result in different heritability estimates compared to studies of adoptees and nuclear families (Plomin, et al., 2008). Studies in adoptees are rare. For instance, there is none for antisaccade task performance, its underlying BOLD signal or schizotypy. There is however evidence on personality measures from adoption studies. Findings from the latter show increased estimates for common environmental effects (as compared to twin studies); yet these effects were non-significantly different from those estimated by twin studies (Matteson, McGue, & Iacono, 2013). Due to the fact that twin samples are more closely matched for age, familial, and social influences than are half siblings or parents and offspring, the former represent a better choice of study design.

One drawback of twin samples used in most behaviour genetic research is that these are mainly drawn from certain socio-economic classes where, as Scarr (1992) points out, the variance in parental effectiveness is relatively small, which lowers the estimates of common environmental influences. The first and third studies reported here attempted to sample from the general population and avoid this sampling bias. The sample in the first study was drawn from the Australian National Health and Medical Research Council Twin Register and, as indicated by educational levels, covered the whole of the general population. The sample in the third study was recruited from the general population, yet the majority of the participants were drawn from student populations. Latter is due to the feasibility of recruiting healthy twin samples. One in eighty pregnancies is a twin pregnancy in Caucasians, 40% of these twins are MZ, 30% same-sex and 30% opposite-sex DZ twins (Buselmaier & Tariverdian, 2007). Given these frequencies and the inclusion criteria the twins had to fulfill to participate in fMRI, we decided to include all available twin pairs, irrelevant if they were drawn from student populations or not; we might therefore have underestimated the effects of common environmental influences. However, given the rarity of studies on the heritability of the BOLD response, we felt that this study deserved to be presented nevertheless.

Finally, findings from twin studies help in quantifying the amount of different aetiological influences yet do not specify their nature. Molecular genetic candidates for schizophrenia, which have been suggested relevant for mood phenotypes include Disrupted-In-Schizophrenia 1, Neuregulin-1 and G72 (Harrison & Weinberger, 2005). Similarly, several environmental factors such as cannabis use, minority group status, urbanicity or developmental trauma have been proposed for schizophrenia (van Os, Kennis & Rutten, 2010) and early environmental stressor were said to affect mood pathology as well (Agid et al., 1999).

Despite these limitations, the major contribution derived from classical twin designs is the quantification of heritability as well as guidance on where to “dig deeper” using molecular genetic approaches to reveal specific genetic variation.

5.2.3. The Assessment of Schizotypy

Proper assessment of the phenotype under study is crucial or as Green et al. put it: “rigorous psychometrics are essential” (Green, et al., 2008, p. 710).

The first study used a short version of the Chapman Psychosis-Proneness Scales to target psychosis-proneness, which can be seen as an umbrella term, that includes schizotypy as well as affective features generally found in psychotic patients (e.g.: Schultze-Lutter, Schimmelmann, Klosterkötter, & Ruhrmann, 2012). The short version has been evaluated before and found comparable to the original 265-item version (Hay, et al., 2001). This brief measure provided an assessment of schizotypy and associated affective features such as hypomania and impulsivity/non-conformity in a nation-wide twin sample.

The Schizotypal Personality Questionnaire was used in the second study. The SPQ has been criticised for its’ restricted coverage of cognitive disorganization-related features which are only assessed through features such as odd speech and eccentric behaviour (Gruzelier, 1996). Similarly, the measure has been said to have limited ability to capture anhedonic features of schizotypy properly, which was suggested to be at the core of negative schizotypy (Ruiz, Barrantes-Vidal, Guitart, & Fañanás, 2008). The SPQ however allows a full assessment of positive, negative and disorganization-related features in ‘just’ 74 items, which, as has been argued before reflects the multi-factorial nature of the schizotypy construct better than an abbreviated version (Compton, et al., 2009). In the third study however, we decided that the

benefits of having a complete, feasible assessment of all features outweigh the limitations of the SPQ. We were able to replicate associations between schizotypy levels and neuroticism in healthy participants from the general population found in previous studies with other measures (Barrantes-Vidal, et al., 2009; Ettinger, et al., 2005) thereby validating the use of the SPQ.

In sum, schizotypy has been addressed here using various measures which covered the whole construct. The added importance of studying schizotypy lies in the opportunity of extending findings to the schizophrenia spectrum. The current findings suggest that similar to the genetic overlap found for schizotypy and neuroticism, genetic overlap could exist between full-blown psychosis and affective disorders, which might guide the search for molecular genetic variation underlying these disorders. In addition, the current findings indicate that alterations at the level of brain functioning in schizotypy features might mimic those found in the schizophrenia spectrum; suggesting altogether that similarities between schizotypy and indices of schizophrenia spectrum disorders exist from the level of the phenotype to the level of the “neurome”.

5.2.4. Limitations of the Antisaccade Task

The second and third studies used eye movement tasks to investigate the neural correlates underlying schizotypy and examine the degree of genetic and environmental influences on the BOLD response in these brain regions. The neural correlates were derived from contrasting BOLD responses during antisaccades with the BOLD response during two control tasks, i.e. prosaccades and fixations. The BOLD response obtained during antisaccades however is the result of the combined effect of various processes required to complete the task, including inhibitory control, complex sensorimotor transformations, volitional response selection and

response conflict resolution (Ettinger, et al., 2009; McDowell, et al., 2002; McNamee, et al., 2008), therefore we acknowledged that antisaccades cannot be said to reflect inhibitory control only.

On behavioural levels, we relied on the antisaccade error rate as a measure of inhibitory control, this measure has previously been extensively used and we were therefore relying on a well-established tool here (Hutton & Ettinger, 2006). Using structural equation modelling approaches, Friedman and Miyake (2004) showed that the error rate can be subsumed as a measure prepotent response inhibition which is part of the inhibition construct. There is evidence of an increased antisaccade error rate in various conditions such as Obsessive Compulsive Disorder or ADHD (e.g. Hutton & Ettinger, 2006). These findings highlight that the error rate is non-specific and should therefore not be labelled as a ‘marker’ of any condition, but rather be approached as a general indicator of dysfunctional inhibitory control.

We used this task here due to its well-established associations with schizotypy (e.g.: Aichert, Williams, et al., 2012; Ettinger, et al., 2005; Holahan & O'Driscoll, 2005; O'Driscoll, et al., 1998). Overall, antisaccades challenge inhibitory control amongst other processes and, as demonstrated in the second and third study, activate associated brain circuits including frontal, parietal, occipital and subcortical regions (e.g. superior and middle frontal gyrus, anterior and posterior intraparietal sulcus, superior and middle occipital regions, cingulate gyrus and globus pallidus).

5.2.5. Limitations of the BOLD Signal

The studies reported in chapters three and four used fMRI to assess the BOLD response and used this measure as measure of brain activity. fMRI has been addressed as the new “phrenology” (Shermer, 2008) given that the BOLD response has a weak temporal resolution (1 - 3 s) and is considered an indirect measure of neural activity. The BOLD response however has a good spatial resolution, e.g. 25 - 30 cubic millimetres, which facilitates localisation of task-relevant areas in an accurate and non-invasive manner (Ashby, 2011). In the current studies two and three, we attempted to localize the neural correlates of oculomotor inhibition and capitalized predominantly on the spatial resolution of fMRI. Despite its limitations, the technique of fMRI allows for the assessment and localisation of brain activity in a non-invasive fashion, which suited our needs in challenging brain activation related to oculomotor inhibitory control.

5.3. Conclusions

Altogether the studies reported here provide evidence for the use of schizotypy as a model to approach the aetiology of the schizophrenia spectrum using behaviour genetic and imaging methods. The first study reported highlights the aetiological overlap between positive features of schizotypy and the personality trait underlying negative emotionality, i.e. neuroticism. As genetic components to positive schizotypy could be fully explained by genetic variation in anhedonia, hypomania and impulsivity features of schizotypy and neuroticism, the findings obtained here stress the need to focus on non-negative, deficit-centred features of schizotypy. Further work could focus on using these latter features, reveal their genetic underpinnings, compare these to the genetic variants found across the schizophrenia spectrum and thereby help in establishing schizotypy as a model for studying schizophrenia.

To fully demonstrate the path from “genome” to “phenome” (see also Figure 2) and thereby capture the nature of schizophrenia at different levels, a better understanding of the neuropathology underlying schizophrenia spectrum disorders is crucial. The study of brain function in the *schizophrenic phenotype* also called the *schizotype* allows for the assessment of brain pathology underlying spectrum features without confounding influences from medication, comorbid disorders or hospitalization. The second study contributes hereto by showing that brain functioning in response to an endophenotype in schizophrenia, namely antisaccade task performance, triggers a similar pattern of brain activity as found in schizophrenia spectrum disorders and by showing that non-positive features of schizotypy can be linked to the BOLD signal found during the antisaccade task. Finally in study three, brain activation underlying oculomotor inhibition during the antisaccade task was examined and its heritability estimated. This study tested for one assumption underlying imaging genetics, namely the heritability of the BOLD response. The findings provide first tentative evidence supporting genetic influences on the BOLD response in the thalamus during oculomotor inhibition. The finding of the last study in particular requires replication in larger samples to firmly establish the heritability of the BOLD response.

6. General References

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Eidesstattliche Versicherung/Affidavit

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that this dissertation is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

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