Chapter II

Introduction
INTRODUCTION

Psychiatric research in the last decades greatly illuminated the role of genetics, epigenetics, hormones and brain processes in psychiatric disorders. At the same time a wealth of research on the phenotypic level has shown that co-occurrence of psychiatric symptoms from different domains is pervasive. For example, behavioral and emotional problems correlate with a correlation coefficient of around 0.5 and half of patients with a psychiatric diagnosis have a second diagnosis.\textsuperscript{1,2} However, the biology of the co-occurrence is less well understood and will be the theme of this thesis.

Perhaps the lack of study of co-occurrence in biological psychiatry is the result of biases, distorting our understanding of biology and impact the way we conduct research, arguably more than that of environmental processes. In the case of genetics Dar-Nimrod and Heine\textsuperscript{3} discussed the following biases (adapted here to a psychiatric perspective): 1. psychiatric traits are the results of single genes, 2. genes deterministically impact the occurrence of a psychiatric disorder i.e. carriers of risk variants are guaranteed to have the disorder, 3. if a disorder is genetic, there are no other causes 4. heritability of a psychiatric disorder implies, that those at genetic risk form a homogeneous and distinct group. 5. heritability of a trait implies that it is naturally occurring and not an artificial construct.

Many of these biases are being addressed successfully in current psychiatric genetic research. For example, psychiatric genetics is not dismissing the role of other causes, as twin research shows that all psychiatric disorders have some proportion of non-genetic causes, for many disorders constituting the majority of effects.\textsuperscript{4} Furthermore, the increasing use of polygenic scores, that predict levels of psychopathology based on hundreds to millions of SNPs, is reflecting the observation that psychiatric disorders are complex genetic disorders, which are influenced by many genetic variants.\textsuperscript{5} Researchers also acknowledge that the environment can reduce the risk of developing a disorder either by compensating the genetic risk, or by interacting with risk effects as proposed by a diathesis-stress or differential susceptibility models: the degree to which a genetic variant affects a person is dependent on the presence of environmental circumstances.\textsuperscript{6}

However, psychiatric genetics is still biased towards classification of distinct homogeneous groups. Most GWASs follow a case-control design in which the question is: does the frequenc of a genetic variant change the odds of having a disorder or not, thus implying that a genetic variant would contribute to separation of people into two distinct groups, for example, those with and without ADHD.\textsuperscript{7} While oversampling participants with diagnoses may make analyses more powerful by increasing contrasts, the lack of accounting for degree of symptom number or severity fails to capture the nature of psychopathology\textsuperscript{8} and has undesired statistical consequences\textsuperscript{9}. While there is an increase in GWAS studies of dimensional assessments, e.g. also of ADHD\textsuperscript{10}, thus acknowledging that genetic risk may gradually increase or decrease the number and in-
tensity of symptoms, another classification bias is still at play. GWAS of single disorders or single domains assume that genetic variants increase the risk of a specific disorder/domain only. However, the possibility also exists that many genetic variants increase the risk of developing any psychiatric symptom, i.e. these variants would increase levels of general psychopathology. General psychopathology here, however, does not imply that people with the same levels of general psychopathology will necessarily have the same set of symptoms. Thus, carriers of genetic risk for general psychopathology may not form a homogeneous group with the same symptoms and thus do not follow the implicit expectation of a genetic disorder. In this scenario, research method would require adjustment to measure and jointly analyze a broad set of symptoms.

This bias of attempting to find etiological factors which cause distinct diagnoses or narrow sets of symptoms instead of general psychopathology is not exclusive to genetic studies. Most biological studies focus on the analysis of single disorders or psychopathology domains at a time, whether it be neuroimaging or psychoendocrinological studies, despite evidence that neural and endocrine features are associated with multiple psychopathology domains and psychological variables in general. For instance, global white matter integrity is associated with cognitive abilities, depression, attention and internalizing problems; cortisol levels were associated with post-traumatic stress disorder, schizophrenia, bipolar disorder and treatment response to depression. Yet, systematic investigations of general psychopathology are lacking in biological psychiatry.

The main question of this dissertation is: which biological factors are associated with child psychopathology in general and which biological factors are specific to certain psychopathology domains? Before discussing how to separate general from specific effects, it is necessary to first introduce the psychopathology domains will be studied in this thesis. The most commonly studied domains in children are the internalizing, externalizing and attention disorders. Internalizing disorders include anxiety and depressive symptoms, whereas externalizing disorders consist of aggression and rule-breaking behaviors. Attention problems, especially at young age, are sometimes defined as externalizing, but there is evidence that they should be regarded as a separate domain in later school age.

General psychopathology can be investigated in several ways. One is the use of traditionally defined domain scores, such as internalizing and externalizing scores, followed by comparisons whether effects on these psychopathology scores are similar between the domains. However, if truly general effects are at play, then the associations with single domains may be downward biased compared to measures of general psychopathology, as each domain score would be an incomplete measure of general psychopathology. The simplest alternative is the use of a total sum of psychiatric symptoms scores. The advantage of this approach is the easy computation and interpretability of the score. However, it may not be the best representation of general psychopathology, as it assumes that all symptoms are equally affected by general psychopathology and it
does not take into account correlation between the symptoms nor between the general and specific factors. A more sophisticated approach has therefore been the use of latent variables models to specify both general and specific psychopathology factors simultaneously. In these bifactor models symptoms are hypothesized to be caused by a general psychopathology factor, as well as domain specific factors. These models can be extended to include multiple informants, reducing the chance that rater bias would inflate levels of general psychopathology. Relating the factors derived from a bifactor model to predictors or outcomes allows the testing of general and specific effects on/ of psychopathology.

All three approaches will be used in this thesis, with the individuals studies described in Chapter III-V. Chapter III attempts to differentiate which (mostly) biological factors associate with psychopathology in general and which factors with specific domains. Chapter IV focuses on one particular disorder: attention-deficit and hyperactivity disorder. Chapter V concludes with investigations into the stress hormone cortisol, which is believed to be causally involved in the development of psychiatric symptoms.

Chapter III consists of five studies investigating various potential predictors, causes and outcomes of general and specific psychopathology. The first study “Parental age and offspring childhood mental health: a multi-cohort, population-based Investigation” focuses on the beginning of life and discusses the age of parents at delivery and the risk of the child to develop psychiatric symptoms. It is well established that higher maternal age is associated with heightened risk of pregnancy complications and health problems in the offspring, with some evidence for also adverse effects of higher paternal age. This raises the question, whether the same is true for mental health, and if so, whether the effects are stronger for internalizing or externalizing problems, or the same.

As mentioned above, using only scores of individual domains may not be the best approach for disentangling general and specific effects. In the second study “The general psychopathology factor: An examination of the structure of child psychopathology across multiple cohorts” we therefore introduce a bifactor model of general and specific psychopathology. In this study we attempt to find a common structure of psychopathology in school-aged children among three different cohorts. Furthermore, we compare unifactor and bifactor structures in their ability to predict adult performance and mental health outcomes.

In the next paper “Single nucleotide polymorphism heritability of a general psychopathology factor in children”, we continue using latent factor models to determine the single nucleotide polymorphism (SNP) heritability of general psychopathology. SNP heritability refers to the variance explained by the additive effects of common genetic variants across the genome. Knowing the magnitude of the SNP heritability is interesting as individual SNPs typically have very small effect sizes. Thus the joint effect of all variants
across the genome, typically represented by a half million markers or more, is more informative of the overall heritability of a trait than the top associated SNPs.

While the total SNP heritability gives an important perspective on the overall contributions of SNPs, it is also important to detect the specific genetic loci associated with general psychopathology to improve understanding of etiology and for the detection of treatment targets. An approach to detect specific loci is to associate each SNP separately with an outcome in a genome-wide association study (GWAS). As a follow up to the SNP heritability study we therefore perform a GWAS of a total psychiatric sum score, as proxy for general psychopathology.

The last study in the first chapter revisits the bifactor models introduced in the previous studies, however, this time the general and specific psychopathology factors are related to white matter integrity. White matter is essential for efficient communication between brain regions and variations in microstructure may be associated with the presence and severity of psychiatric symptoms. Specifically, Zald et al. hypothesized that global white matter microstructure differences across the whole brain are related to variability in general psychopathology, whereas variation in specific region causes specific symptoms. We test this hypothesis in school-aged children.

Chapter IV presents an epigenetic approach to further our biological psychiatric understanding. A growing number of research investigates variations in DNA methylation in relation to psychopathology. DNA methylation is influenced by genetic and environmental factors and has the potential to impact gene expression. It is therefore an interesting potential mediator of genetic and environmental risks or biomarker for adverse exposures. Similar to a GWAS it is possible to associate DNA methylation at hundreds of thousands of CpG sites with psychiatric symptoms. The first EWASs of psychiatric symptoms are being performed, however, large multi-center consortia efforts are lacking. We present a prospective meta-analytic EWAS on ADHD, a common childhood disorder. Unlike the genome, the epigenome varies over time and thus assessment time becomes important. We therefore associate DNA methylation both at birth and at school-age with ADHD symptoms and compare results.

The final chapter revolves around the stress hormone cortisol. Cortisol is a hormone, that is released in reaction to both physical and psychological stress. Cortisol may also be involved in the etiology of psychopathology, as cortisol injections increase depressive behavior in animal models and alterations in baseline levels are associated with some disorders in humans. However, as cortisol is a highly dynamic hormone, not only responding to external stimuli, but also showing a diurnal rhythm, and an excretion as pulse pattern, finding the optimal cortisol assessment method has been challenging in psychiatric research.

The first study in this chapter investigates the utility of measuring cortisol in hair samples. Cortisol accumulates in hair and provides a more long-term profile of cortisol exposure. However, some research suggested that cortisol levels are related to hair color, though, it is difficult to distinguish to which degree this effect is due to hair col-
or or ethnicity/race. We attempted to disentangle the association by investigating the independent contributions of genetically determined hair color and genetic ancestry.

In the last study, we examine the genetics of acute cortisol levels in blood and saliva. Several studies investigated the heritability of cortisol using known family relationships to infer genetic effects, however, molecular studies are lacking. We therefore estimate and compare the SNP heritability of various acute cortisol measures.

**RESEARCH SETTING**

The primary focus of this dissertation is the identification of determinants and consequences of general psychopathology in children. As it would be unethical to randomize potential risk factors of psychopathology, we employ various epidemiological methods in large observational studies to study the causes of general and specific psychopathology. General psychopathology as defined here is a dimensional construct and the general population therefore displays varying degrees of it with no clear threshold for a disordered status. Therefore all the presented studies describe the general population and the whole range of general psychopathology.

The majority of the studies in this dissertation were conducted within consortia of many institutions and present the combined results of several cohorts. The study of parental age was embedded in the consortium of individual development (https://individualdevelopment.nl/) and included four Dutch cohorts. The study about the structure of psychopathology is the first DREAM BIG collaboration (http://dreambigresearch.com/) and comprises Canadian, British and Dutch cohorts. The GWAS on a total child psychiatric problem score is based on the results of 16 cohorts from North America, Europe and Australia from the EArly Genetics and Lifecourse Epidemiology (EAGLE) consortium. Finally, the CORNET\textsuperscript{36} consortium consisting of cohorts from Europe and the US contributed substantially to most analyses in the SNP heritability of cortisol paper.

Except for the latter, all studies involved the Generation R cohort. Generation R is a population-based birth cohort based in Rotterdam, the Netherlands.\textsuperscript{37} Expecting mothers with a delivery date from 2002 to 2006 were invited to participate in this study. The parents and later their children’s characteristics and development were assessed from birth. At the time of writing, the most recent assessment wave is at the age of 13 years. However, this thesis largely focuses on the early school-ages (6 to 10 years). This is an interesting period to study general psychopathology. Several disorders do not reach substantial incidence levels until puberty, but varying levels of general psychopathology may be already present and manifest in various disorders in childhood and later life. The study of general psychopathology in childhood is therefore likely of high relevance and I hope that the following chapters will contribute to our understanding of the etiology and biological correlates of general psychopathology.
REFERENCES


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