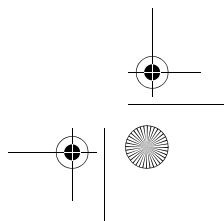
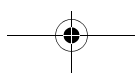
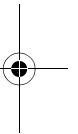
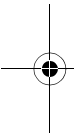
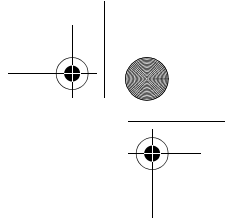


The role of genetic factors and life events in the development of anxiety and depression

Christel M. Middeldorp





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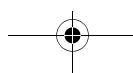
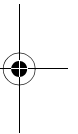
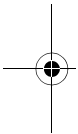
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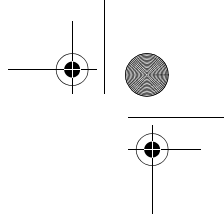
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THE ROLE OF GENETIC FACTORS AND LIFE EVENTS IN THE
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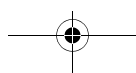
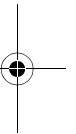
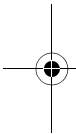
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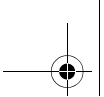
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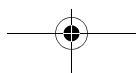
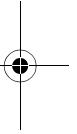
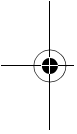
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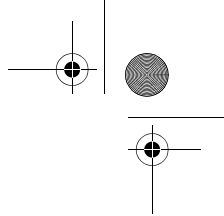
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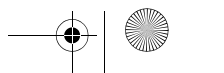
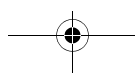
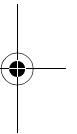
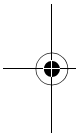
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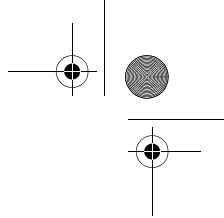




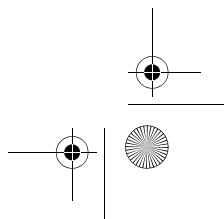
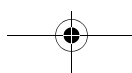
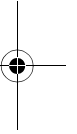
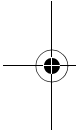
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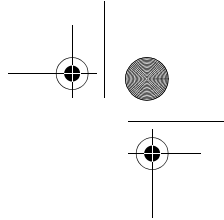
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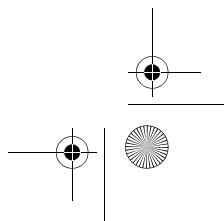
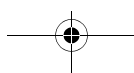
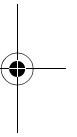
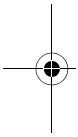
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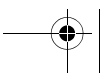
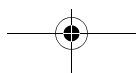
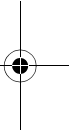
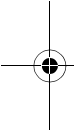
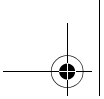


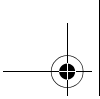


I have no patience with the hypothesis occasionally expressed, and often implied, especially in tales written to teach children to be good, that babies are born pretty much alike, and that the sole agencies in creating differences between boy and boy, and man and man, are steady application and moral effort. It is in the most unqualified manner that I object to pretensions of natural equality. The experiences of the nursery, the school, the University, and of professional careers, are a chain of proofs to the contrary.

Sir Francis Galton in "Hereditary Genius"



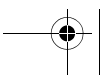
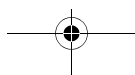
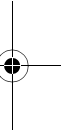
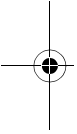




Chapter

1

Introduction



“First there were those wicked biological psychiatrists in the nineteenth century, then psychoanalysts and psychotherapists came along to defeat the biological zealots, establishing that mental illness resulted from unhappiness in childhood and stress in adult life. ... Today, it is clear that when people experience a major mental illness, genetics and brain biology have as much to do with their problems as do stress and their childhood experiences. ...If there is one central intellectual reality at the end of the twentieth century, it is that the biological approach to psychiatry – treating mental illness as a genetically influenced disorder of brain chemistry – has been a smashing success.”

Edward Shorter (1997), p vii.

This is the history of psychiatric theorizing in a nutshell, as it is applicable to all psychiatric disorders, including anxiety and depression, the subject of this thesis. Nowadays, it is a well-known fact that anxiety disorders and major depression are for at least 30%-40% heritable (Hettema et al., 2001; Sullivan et al., 2000). Studies that take measurement error into account find heritability estimates between 50%-66% (Foley et al., 1998; Kendler et al., 1999). The remaining part of the variance is explained by individual specific environmental factors, i.e. circumstances to which members of the same family are differently exposed, whereas environmental factors shared by family members do not seem to be of major importance (Hettema et al., 2001; Sullivan et al., 2000). Stress caused, for example, by unemployment, life events or lack of social support has also consistently been found to be associated with anxiety and depression (de Graaf et al., 2002a; de Graaf et al., 2002b; Meertens et al., 2003; Paykel et al., 2005).

So far for the *smashing success*, also shaded by Shorter (1997) in his more extensive description of the history of psychiatry, later in his book. It is well known that precise descriptions of causal mechanisms leading to mental disease have not been unraveled yet. Several reasons can account for this apparent lack of success. Without trying to provide an exhaustive list, some of the complicating issues will be discussed below. Probably the most important problem is the complexity of the brain. It is more and more acknowledged that different areas of the brain interact with each other, forming circuits with complex feedback loops. This signifies, for example, that although antidepressants influence the amount of serotonin in the brain, the cause of depression could lie in another system, which is in contact with the serotonin system. This complicates hypothesis driven research such as association studies on candidate genes. Another problem is that the etiology of psychiatric disorders is multifactorial with a variety of genetic as well as environmental pathways, that can increase an individual's vulnerability to a certain disorder

(Stoltenberg & Burmeister, 2000). Probably, neither the presence of one genetic variant nor the occurrence of one environmental adversity in itself is sufficient to lead to symptoms. Instead, a combination of unfavorable factors, additive to or interacting with each other, is required to develop a psychiatric disease (Stoltenberg & Burmeister, 2000). Moreover, risk factors, which appear to be environmental, do not always occur randomly in a population. There is evidence that associations between genetic and environmental risks exist, so called gene-environment correlations (Rutter & Plomin, 1997). This association can arise when the environment of an offspring depends on the genotype of parents (Eaves, 1987). For example, children who inherit the risk for depression may also grow up in a sub-optimal environment because of a depressed parent. Gene-environment correlation can also arise because an individual's environment depends on his own genotype, for example, in creating adverse life events (Eaves, 1987). Another important issue in the search for etiological factors of psychiatric disorders is the frequent co-morbidity. This might be a side-effect of the classification systems, such as the Diagnostic and statistical manual of mental disorders, 4th edition (DSM IV) (American Psychiatric Association, 1994), in which clusters of symptoms, actually belonging to one syndrome, are categorized as two different syndromes (Klein & Riso, 1993; Neale & Kendler, 1995). Co-morbidity might also be due to etiological factors that are shared for both disorders (Klein & Riso, 1993; Neale & Kendler, 1995).

Facing these complex issues, Kendler (2005b) stated that "What we can best hope for is lots of small explanations, from a variety of explanatory perspectives, each addressing part of the complex etiological processes leading to disorders. It will be particularly challenging to understand how these many different small explanations all fit together." This thesis aims to add some "small explanations" to the current knowledge on anxiety and depression from a genetic perspective. There are several distinct paradigms to investigate the role of genetic factors in the etiology of psychiatric disorders (Kendler, 2005a). The paradigm of advanced genetic epidemiology will be applied in most chapters. This paradigm goes beyond the question of heritability and tries to explore the nature and mode of action of these genetic factors by examining questions like "Are the genetic risk factors specific to a given disorder or shared with other psychiatric disorders?", "Do the genetic risk factors affect disease risk similarly in males and females". In one chapter, the paradigm of gene finding is employed. The goal of gene finding methods is to establish which genes are associated with a disorder.

Outline of this thesis

The first part of this thesis, chapters two to five, focuses on the genetic risk factors for anxiety and depression. The first three chapters aim to provide more insight into the genetic background of these disorders in order to find out what the best strategy is for a gene finding study. Chapter two reviews twin- and family studies investigating different models to explain the co-morbidity between anxiety and depression. More specifically, is co-morbidity due to one disorder being an epiphenomenon of the other or can it be explained by overlapping etiological factors? In chapter three, the association between personality dimensions and anxious and depressive psychopathology is studied while taking co-morbidity into account. DSM IV categories are possibly not the most suitable phenotypes when trying to discover robust genetic markers (Charney et al., 2002). Dimensional traits correlated to these categories might be more appropriate phenotypes for linkage or association studies, especially since the power to detect an effect of a gene is much larger for a continuous scale than for a discrete trait (Williams & Blangero, 2004). Chapter four describes a twin-family study on MDD, panic disorder and/or agoraphobia, social phobia and generalized anxiety disorder (GAD) in a combined Australian and Dutch twin sample. In this study, sex differences in familial, probably genetic, factors influencing these disorders were also investigated. Chapter five describes the results of family based association analyses in a large sample of siblings and their parents between the serotonin transporter gene polymorphism (5-HTTLPR) and scores on self-report questionnaires of neuroticism, anxiety and depression, measured at five points in time. Since Lesch et al. (1996) reported an association between 5-HTTLPR and anxiety-related personality traits, such as neuroticism, numerous studies have tried to replicate this finding, but with conflicting results.

The second part, chapters six to nine, focuses on risk factors for anxiety and/or depression that are mostly considered to be environmental. Chapter six and seven focus on burnout, employment and the relationship with anxious depression. Chapter six investigates to what extent burnout might also be influenced by familial factors. In the following chapter, two bivariate genetic epidemiological analyses are performed in order to find out whether the association between employment and anxious depression and between burnout and anxious could be explained by overlapping etiological factors. Chapter eight and nine concentrate on the association between various life events and anxious depression. Chapter eight examines whether twins are more prone to certain life-events than singletons. If this is the case, twin studies on the effect of life events might not generalize to the general population. In the same chapter, the influences of genetic and common environmental effects on the occurrence of life events are assessed. The results of this chapter are taken into account in the analysis of the association between life-events and anxious

depression performed in chapter nine, which aims to provide more insight in the underlying mechanism of this association. The role of the personality measures neuroticism and extraversion, which are related to anxious depression, are also investigated as they might explain part of the relation between life events and anxious depression.

The last chapter consists of a summary and a general discussion, in which, considering the overall results, the few “small explanations” for the development of anxiety or depression deriving from this thesis will be discussed followed by recommendations for further research aiming to add other small bits of knowledge.

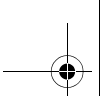
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Chapter
1

Introduction

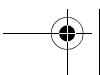
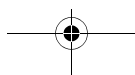
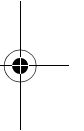
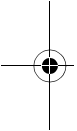
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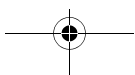
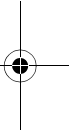
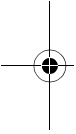
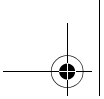


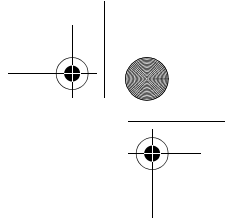
Part

1

Genetic Factors







Chapter

2

The co-morbidity of anxiety and depression in
the perspective of genetic epidemiology.
A review of twin and family studies.

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Abstract

Background: Co-morbidity within anxiety disorders, and between anxiety disorders and depression, is common. According to the theory of Gray & McNaughton (2000), this co-morbidity is caused by recursive interconnections linking the brain regions involved in fear, anxiety and panic and by heritable personality traits such as neuroticism. In other words, co-morbidity can be explained by one disorder being an epiphenomenon of the other and by a partly shared genetic etiology. The aim of this paper is to evaluate the theory of Gray & McNaughton using the results of genetic epidemiological studies.

Methods: Twenty-three twin studies and twelve family studies on co-morbidity are reviewed. To compare the outcomes systematically, genetic and environmental correlations between disorders are calculated for the twin studies and the results from the family studies are summarized according to the method of Klein & Riso (1993).

Results: Twin studies show that co-morbidity within anxiety disorders and between anxiety disorders and depression is explained by a shared genetic vulnerability for both disorders. Some family studies support this conclusion, but others suggest that co-morbidity is due to one disorder being an epiphenomenon of the other.

Conclusions: Discrepancies between the twin and family studies seem partly due to differences in used methodology. The theory of Gray and McNaughton that neuroticism is a shared risk factor for anxiety and depression is supported. Further research should reveal the role of recursive interconnections linking brain regions. A model is proposed to simultaneously investigate the influence of neuroticism and recursive interconnections on co-morbidity.

Introduction

In the etiology of anxiety and depression both genetic and environmental factors play a role. Two recent meta-analyses obtained heritability estimates between 30%-40% for the liability to major depression (MDD) and anxiety disorders, while the remaining variance in liability could be attributed entirely to unique environment (Sullivan et al., 2000; Hettema et al., 2001a). An important issue in the search for etiological factors of anxiety disorders and MDD is the frequent co-morbidity. The results of the Epidemiologic Catchment Area (ECA) Study and the National Co-morbidity Survey (NCS) have shown that the occurrence of one anxiety disorder increases the risk of having an additional anxiety disorder (odds ratio on average 6.7) (Kessler, 1995). The same holds for the combination of affective disorders (including dysthymia and mania) and anxiety disorders (odds ratio 7.0) (Kessler, 1995). These increased odds ratios indicate that co-morbidity between anxiety and depression is not only due to chance. Moreover, since the ECA and NCS studies are population based, sampling bias is highly unlikely to explain co-morbidity rates.

The issue of co-morbidity gives rise to questions at a nosological level (Neale & Kendler, 1995). Do anxiety disorders and MDD reflect an arbitrary division of a single syndrome? Are the different anxiety disorders and MDD distinct entities, possibly influenced by common genetic and environmental etiological factors? Are the co-morbid conditions independent of the separate anxiety disorders and MDD? Klein & Riso (1993) presented a comprehensive description of models explaining the causes of co-morbidity (referred to as models KR1-KR11). These models have been partly redefined and extended by Neale & Kendler (1995) (referred to as models NK1-NK12). All models are summarized in Table 2.1. The relationship between these models and the nosological questions regarding co-morbidity is introduced and discussed below. With respect to chance and sampling bias as possible explanations of co-morbidity, results from the ECA and NCS studies indicate that these factors are unlikely to explain co-morbidity in anxiety and depression. Therefore, these models (i.e. KR1-2/NK 1-2) will not be further addressed in this article.

Models KR4 (overlapping diagnostic criteria) and KR5-7/NK5-8 (multiformity) refer to the possibility that the different disorders are distinct entities. Multiformity signifies that co-morbidity is due to disorder B being an epiphenomenon of disorder A. In other words: having disorder A increases the risk that a subject develops disorder B without being vulnerable to disorder B itself. Neale & Kendler (1995) interpreted the description of heterogeneity (KR7) by Klein & Riso (1993) as multiformity in both directions. Thus, disorder B can be an epiphenomenon of disorder A and vice versa. In model KR8/NK9 the co-morbid condition is considered as a third, independent disorder. Model KR9/NK4 supposes that the disorders are all expressions of one disease. In models KR10-11/ NK10-12 the disorders are considered to be distinct entities with

overlapping etiological processes. In contrast with the multiformity models, in these models vulnerability to one disorder is correlated with vulnerability to the other disorder.

Table 2.1: Models of co-morbidity (from Klein & Riso (1993) (KR) and Neale & Kendler (1995) (NK)).

KR1 / NK1	Co-morbidity due to chance
KR2 / NK2	Co-morbidity due to sampling bias
KR3 / NK3	Co-morbidity due to population stratification
KR4	Co-morbidity due to overlapping diagnostic criteria
KR5-KR7 / NK5-NK8	Co-morbidity due to multiformity: one disorder is an epiphenomenon of another disorder.
KR8 / NK9	The co-morbid disorder is a third, independent disorder
KR9 / NK4	The pure and co-morbid conditions are different phases or alternative expressions of the same disorder
KR10 / NK11	One disorder is a risk factor for the other
KR11 / NK10	The two disorders arise from overlapping genetic and environmental etiological processes
NK12	Reciprocal causation

Co-morbidity research: twin and family studies

Cross-sectional data on unrelated individuals cannot discriminate between co-morbidity models. Twin and family data as well as longitudinal data are more suitable for this purpose (Klein & Riso, 1993; Neale & Kendler, 1995). Since the aim of this paper is to investigate the co-morbidity of anxiety disorders and MDD from a genetic epidemiological point of view, the focus will be on twin and family studies. In a twin or family design, two main statistical methods are used to study co-morbidity models, namely 1) biometrical model fitting using twin and/or family data and 2) comparing prevalence rates, odds ratios or relative risks ratios of disorders between relatives of different proband groups.

In twin studies, biometrical model fitting is mostly used to estimate the influences of genetic, common environmental and unique environmental factors on disease liability. Twin studies make use of the fact that monozygotic (MZ) twin pairs share all (or nearly all) their genes, whereas dizygotic (DZ) twin pairs share on average half of their segregating genes. Consequently, if MZ twin pairs are more similar for a trait than DZ twin pairs this suggests that genetic factors influence this trait. If, on the other hand, MZ and DZ twin pairs show the same amount of similarity, then common environmental factors, shared by family members, probably play a role. The differences between MZ twin pairs are explained by unique environmental factors (for an overview of the methodology of twin studies see Boomsma et al. (2002)). This univariate

design can be extended to a multivariate approach (Heath et al., 1993; Duffy & Martin, 1994) in which the correlation between disorders is decomposed in a part due to genetic factors shared by these disorders, a part due to shared common environmental factors and a part due to shared unique environmental factors. This approach provides the opportunity to test whether disorders are caused by overlapping genetic or environmental factors (model KR11 / NK10). Under certain conditions, this multivariate design can also be used to test models of causality, namely disorder A causes B or reciprocal causation (models KR10 / NK11 and NK12 respectively) (Heath et al., 1993; Duffy & Martin, 1994). Subsequently, Neale & Kendler (1995) have described how other co-morbidity models can be tested in a twin or family design as well.

Family studies mostly compare prevalence rates, odds ratios or relative risk ratios of disorders between relatives of different proband groups to test co-morbidity models. Klein & Riso (1993) emphasized that, to be able to discriminate properly between the different models, the relatives of four proband groups need to be studied: 1) probands with a pure form of disorder A, 2) probands with a pure form of disorder B, 3) probands with co-morbidity of A and B and 4) controls with neither A nor B. Table 2.2 shows which patterns of findings can be predicted for each model according to Klein & Riso (1993). The diagnosis in relatives is the dependent variable while the expected ordering of the proband groups is the independent variable (see also Wickramaratne & Weissman (1993)). For example, the predictions for KR4 (overlapping diagnostic criteria) should be read as follows. The chance of having a relative with disorder A is highest in probands with disorder A, followed by probands with disorders AB. This chance is not elevated in probands with disorder B when compared with controls. The chance of having a relative with disorder AB is equal in probands with disorder A, AB or B, but elevated when compared to controls. Finally, the chance of having a relative with disorder B is highest in probands with disorder B, followed by probands with disorders AB. This chance is not elevated in probands with disorder A when compared with controls.

Table 2.2: Predictions of co-morbidity models regarding familial transmission (from Klein & Riso (1993)).

Models	Diagnosis in relatives	Relations of proband groups
KR4: overlapping diagnostic criteria	A	A>AB>B=C
	AB	A=AB=B>C
	B	B>AB>A=C
KR5 and KR6: multiformity in one direction	A	A=AB>B=C
	AB	A=AB>B=C
	B	B>A=AB=C
KR7: multiformity in both directions	A	A>AB>B=C
	AB	A=AB=B=C / AB>A=B>C*
	B	B>AB>A=C
KR8: three disorders	A	A>AB=B=C
	AB	AB>A=B=C
	B	B>A=AB=C
KR9: alternative forms or phases of one disorder	A	A=AB=B>C
	AB	A=AB=B>C
	B	A=AB=B>C
KR10: one disorder is a risk factor for the other	A	A=AB=B>C
	AB	A=AB=B>C
	B	A=AB=B=C
KR11: overlapping etiological processes	A	A=AB>B>C
	AB	A=AB=B>C
	B	B=AB>A>C

* According to Wickramaratne & Weissman (1993)

Co-morbidity within the perspective of the theory of Gray and McNaughton

Gray & McNaughton (2000) developed a theoretical model about the co-morbidity within anxiety disorders and between anxiety disorders and MDD. In their theory they implement results from animal and psychopharmacological research, which suggest that the disorders are distinct entities, as well as results of genetic research, which suggest overlapping etiologies.

The basis of their theory is that different threat stimuli lead to diverse behavior patterns with emotions regulated by different brain areas. Figure 2.1 shows a summary of their theory. First, four different threat stimuli are distinguished: actual and potential threat stimuli which both can be avoidable or unavoidable. These different threat stimuli give rise to activation of particular brain areas resulting in six behavioral reaction patterns with emotions. For example, an avoidable actual threat can lead to activity in the amygdala followed by a flight reaction with fear, whereas an avoidable potential threat can lead to activity of the septo-hippocampal system followed by risk assessment with anxiety¹. This part of the theory, mostly based on animal research, provides an explanation of the adaptive reactions to realistic threats.

Gray and McNaughton (2000) argue that, at the level of symptoms, there is no fundamental difference between adaptive and pathological emotions, the latter being a consequence of hyperactivity of the same brain regions as the former. They admit that at the syndrome level, it seems a gross oversimplification to align a syndrome to one single brain area, since a syndrome consists of several symptoms. However, they stress that the various neural structures, which control defensive behavior, are strongly and recursively interconnected. This is necessary since in most real-life situations, the available stimuli will not be selective for just one of the four distinct functional categories. "The rabbit which sees a fox coming towards it does not necessarily know whether the fox has seen it. Thus, while the presence of the fox is definite and actual, the threat presented by the fox must be treated as having simultaneously the properties of both actual and potential threat. Thus both fear and anxiety goal-processing systems will be primed for intense action" (Gray and McNaughton, 2000, p. 296-297). According to Gray and McNaughton (2000), it follows from this example that pathology in a specific control center may give rise to a cluster of symptoms. Subsequently, to relate the symptoms of the DSM III-R anxiety disorders (American Psychiatric Association 1987) to activity in the brain, they reason that fear, panic and anxiety are the core symptoms of respectively simple phobia, panic disorder and generalized anxiety disorder. In addition, they consider anxiety, and not fear, as the core symptom of social phobia and agoraphobia, since the supposed threat is potential and not actual.

1. *In this way, Gray and McNaughton (2000) have redefined the terms fear, panic and anxiety as emotions specific to certain circumstances. This differs from the usual definitions.*

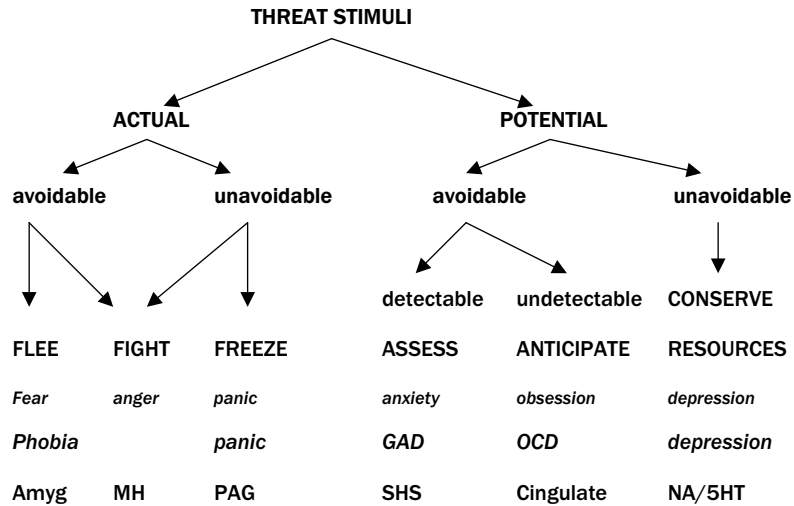


Figure 2.1: Nature of stimuli (top three rows) and their relation to function (fourth row), emotion (small italics), psychological disorder (large italics), and principal neural system involved (bottom row).

Amyg: amygdala,
AG: periaqueductal grey,
NA: noradrenaline,
 (Copied with permission from Gray & McNaughton (2000) p. 295).

MH: medial hypothalamus,
SHS: septohippocampal system,
5HT: 5-hydroxytryptamine.

In this part of the theory, the different disorders are treated as separate entities. The recursive interconnections linking brain regions are hypothesized to explain part of the co-morbidity within anxiety disorders. For example, high levels of anxiety / fear can precipitate panic. Therefore, subjects with agoraphobia or social phobia for whom the threat stimuli are difficult to avoid might develop a panic disorder. On the other hand, panic attacks can, through conditioning, give rise to agoraphobia.

Subsequently, the influence of neuroticism on the development of anxiety disorders is incorporated in the theory. Gray & McNaughton (2000) state that, since neuroticism is a personality trait that is about 50% heritable and related to most anxiety disorders ‘... there is heritable control over a single, quantitatively varying susceptibility towards suffering from any or all of the neurotic disorders, be they termed panic, anxiety or depression; and this is so irrespective of which particular brain mechanism proximately mediates the symptoms displayed’ (p. 342).

To summarize, this theory proposes two mechanisms to explain co-morbidity of anxiety and depression. Firstly, co-morbidity can be caused by recursive interconnections linking the brain regions. This can be interpreted as multiformity in both directions (model KR7/NK5). Secondly, co-morbidity can

be caused by the influence of the heritable personality trait neuroticism, which makes a subject vulnerable to anxiety disorders and MDD. This is equivalent to model KR11/NK10 (overlapping etiological factors). In this paper, the results of twin and families studies are discussed in the light of the theory of Gray and McNaughton.

Methods

The medline database was searched for all adult twin and family studies published between 1966 and 2003 containing combinations of the following keywords: 1) anxiety, panic disorder, agoraphobia, social phobia, specific phobia, generalized anxiety disorder, depression, mood disorders, neurosis, neuroticism, personality 2) genetics, family studies, twin studies.

Twin and family studies were included if causes of co-morbidity were a focus in the analyses. Therefore, it was required that bivariate or multivariate analyses had been carried out. In the family studies that compared prevalence rates, odds ratios or relative risk ratios, few studies included relatives of three proband groups and a control group as recommended by Klein & Riso (1993). Hence, it was decided to include studies with two proband groups plus a control group as well.

In family studies, different methods are used to establish a diagnosis in relatives: family history, direct interview and best estimate diagnosis based on direct interview, medical records, and family history data. The best estimate diagnosis is considered to be the most accurate method to collect data (Leckman et al., 1982). The overall accuracy of the family history method is relatively poor and subject to several biases (Roy et al., 1996). Consequently, studies were excluded that collected data only through the family history method.

Results of studies are summarized as follows. In those studies that have used biometrical model fitting, the correlations of the genetic and environmental factors between disorders are tabulated. In case these correlations were not described in the original article they were calculated from the (standardized) estimates of the variance explained by the common and specific genetic and environmental factors (For the exact formula see Neale & Cardon (1992) p.194). The results of the family studies that compared prevalence rates are described in the same way as Klein & Riso (1993) described the predictions of the different models, thus with the diagnosis in relatives as the dependent variable and the observed ordering of the proband groups as the independent variable (see Table 2.2). However, this was hampered by two problems. Firstly, in some studies one proband group did not differ significantly from the other proband groups but did differ from the control group, regarding the prevalence of a disorder in the relatives, whereas the other

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proband groups did not differ from the control group. This outcome is not taken into account by the predictions of Klein & Riso (1993). Secondly, in some studies proband groups were only compared with controls and not among themselves. Strictly speaking, in these two cases results cannot be described according to one KR pattern as is required to choose between the different models. To provide the reader with a complete description of the results without losing the opportunity to discriminate between the co-morbidity models, the results are described as follows. It is indicated whether prevalence rates of a disorder in the relatives differ between proband groups and controls and, if available, whether prevalence rates of a disorder in the relatives differ within proband groups. These results are summarized in one pattern and the KR models that are compatible with this pattern are shown.

Studies have used dimensional and/or categorical data. Dimensional data are measured on a quantitative scale (e.g. Beck Depression Inventory) and are continuous. Categorical data, on the other hand, are mostly based on the DSM categories (American Psychiatric Association, 1980; American Psychiatric Association, 1987; American Psychiatric Association, 1994), leading to dichotomous data, usually affected or unaffected. These results will be discussed separately.

Conclusions about similarities and differences between studies are not based on statistical measures of significance, since no formal meta-analysis was performed.

Results and conclusions from twin and family studies***Twin studies (Table 2.3)***

All twin studies, except Neale & Kendler (1995), tested model KR11 (Table 2.3). The fit of this model was reasonable in most studies. It should be kept in mind that a high correlation between factors does not imply a strong effect of these factors. For instance, a genetic correlation can be 1, while the variance explained by the shared genes is low, because the two traits have low heritabilities.

Table 2.3: Twin studies on categorical data (above bold line) and dimensional data (below bold line).

Study	N of twins and other relatives	Diagnoses	rG	rC**	rE
Sundet et al. (2003)*	282 twins, 239 spouses, 306 offspring of twins	Situational fears, illness-injury fears	.28	-	.27
		Situational fears, social fears	.12	-	.27
		Situational fears, fears of small animals	.32	-	.17
		Illness-injury fears, social fears	.11	-	.29
		Illness-injury fears, fear of small animals	.29	-	.18
		Social fears, fear of small animals	.13	-	.18
		GAD, PD	.71	-	.45
SChantarujikapong et al. (2001)*/ Scherrer et al. (2000)*	6654 twins				
Kendler et al. (2001c)*	2396 twins	AgP, SocP	.47	1.00	.46
		AgP, Animal P	.69	0	.30
		AgP, Situational P	.59	0	.26
		AgP, Blood/injury P	.80	1.00	.34
		SocP, Animal P	.40	0	.35
		SocP, Situational P	.34	0	.30
		SocP, Blood/injury P	.46	1.00	.41
		Animal P, Situational P	.50	0	.19
		Animal P, Blood/injury P	.67	0	.26
		Situational P, Blood/injury P	.57	0	.22
Nelson et al. (2000)*	1344 twins	SocP, MDD	1.0	-	0
SKendler (1996)/ Kendler et al. (1995)* / Kendler et al. (1992a)	1874 twins	P and GAD	.58	-	.36
		P and PD	.95	-	.26
		P and MDD	.31	-	.37
		GAD and PD	.77	-	.41
		GAD and MDD / last year MDD	.86-1.00	-	.51-.70
		PD and MDD	.59	-	.42
Neale & Kendler (1995)*	2060 twins	MDD, GAD	1	.41	.28
Roy et al. (1995)	1484 twins	GAD, MDD	1	-	.28

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Co-morbidity of anxiety and depression

Table 2.3: Twin studies on categorical data (above bold line) and dimensional data (below bold line). (Continued)

Study	N of twins and other relatives	Diagnoses	rG	rC**	rE
Kendler et al. (1993b)	2163 twins	MDD, any P	.07	-	.22
		MDD, AgP	.16	-	.32
		MDD, SocP	.11	-	.12
		MDD, animal P,	.12	-	0
		MDD, situational P	0	.09	.16
		AgP, SocP	.25	-	.69
Kendler et al. (1992b)*	2163 twins	AgP, Animal P	.43	-	.29
		AgP, Situational P	.24	-	.49
		SocP, Animal P	.57	-	.20
		SocP, Situational P	.32	-	.34
		Animal P, Situational P	.56	-	.14
		MDD, Neur	Females: .41 Males: .68	-	Females: .32 Males: .33
Ono et al. (2002)	402 twins	Dep, Harm avoidance	.71	-	.19
		Fear of Negative Evaluation, Subscales of Emotional Dysregulation factor	.49-.80	-	.20-.40
Boomsma et al. (2000)*	6426 twins	Anx, Neur	Males : .84 Females : .85	-	Males : .47 Females : .51
		Anx, Somatic Anx	Males : .76 Females : .77	-	Males : .26 Females : .20
		Anx, Dep	Males : .86 Females : .74	-	Males : .48 Females : .54
		Neur, Somatic Anx	Males : .71 Females : .75	-	Males : .40 Females : .33
		Neur, Dep	Males : .80 Females : .71	-	Males : .42 Females : .43
		Somatic Anx, Dep	Males : .73 Females : .65	-	Males : .29 Females : .18
Roberts & Kendler (1999)*	2163 twins	MDD, Neur	.68	-	0

Table 2.3: Twin studies on categorical data (above bold line) and dimensional data (below bold line). (Continued)

Study	N of twins and other relatives	Diagnoses	rG	rC**	rE
Gustavsson et al. (1996)*	1110 twins + 30 MZ reared apart	Psychasthenia, Somatic Anx	1	-	.29
		Psychasthenia, Psychic Anx	1	-	.40
		Somatic anxiety, Psychic Anx	1	-	.50
Kendler et al. (1993a)*	1414 twins	Neur time 1, Neur time 2, last year MDD time 2	.75	-	.17
Martin et al. (1988)*	2903 twins	Neur, heart pounding	Males: .93 Females: .65	-	Males: .21 Females: .30
		Neur, feelings of panic	Males: .92 Females: .48	-	Males: .28 Females: .48
		Heart pounding, feelings of panic	Males: .98 Females: .65	-	Males: .29 Females: .33
Kendler et al. (1987)*	5810 twins	6 symptoms of Dep and 7 symptoms of Anx.	Males: .37-.99 Females: .38-.95	-	Males: .11-.70 Females: .25-.86
Phillips et al. (1987)	500 twins, 182 siblings, 682 parents	7 Fear factors	.43-.89	-	.17-.76

AgP: agoraphobia, Anx: symptoms of anxiety, Dep: symptoms of depression,

GAD: generalized anxiety disorder, MDD: major depressive disorder,

Neur: Neuroticism, P: Phobia,

PD: panic disorder with or without agoraphobia, SocP: social phobia.

rG: Correlation between genetic factors, rC: Correlation between common environmental factors,

rE: Correlation between unique environmental factors.

Diagnoses are lifetime unless mentioned otherwise.

* Correlations are calculated based on the (standardized) estimates of the variance explained by the common and specific genetic and environmental factors reported in the articles.

** Dash (-) indicates that in the multivariate analyses common environmental factors were not found to have a significant effect on the disorders under study.

§ These studies used the same population. Therefore, their results are shown together.

Studies that have analyzed categorical data (upper part of Table 2.3) found that, in general, genetic factors overlap more than unique environmental factors, while common environmental factors generally do not overlap (Kendler et al., 1992a; Kendler et al., 1992b; Kendler et al., 1995; Neale & Kendler, 1995; Roy et al., 1995; Kendler 1996; Nelson et al., 2000; Scherrer et al., 2000; Chantarujikapong et al., 2001; Kendler et al., 2001c). MDD and generalized anxiety disorder (GAD) appear to be most closely genetically related with the correlation between the genetic factors (r_G) varying from .86-1.00 (Kendler et al., 1992a; Kendler et al., 1995; Kendler, 1996). However, there are a few exceptions to this general finding. Social Phobia (SocP) seems to share less genetic liability with the other phobic disorders than the other phobic disorders do among each other (Kendler et al., 1992b; Kendler et al., 2001c). Furthermore, in females the correlation between the unique environmental factors (r_E) is mostly larger than r_G for the combinations of MDD with phobic disorders (Kendler et al., 1993b; Kendler et al., 1995). As an exception, Nelson et al. (2000) did find SocP and early onset MDD to be completely influenced by the same genes. Differences in age between study populations could explain these divergent findings. Significant overlap in common environmental factors were only found for Agoraphobia (AgP) and SocP in males (Kendler et al., 2001c) but not in females (Kendler et al., 1992b). However, common environmental factors do explain very little variance in these disorders. Finally, results from Kendler et al. (1995) on the co-morbidity between MDD, GAD, panic disorder (PD) and any phobic disorder (P) suggest that there are two common genetic factors with MDD and GAD loading on one, any P loading on the other and PD loading on both.

Studies that have analyzed dimensional data report very comparable results (lower part of Table 2.3), i.e. in general, genetic factors overlap more than unique environmental factors (Jardine et al., 1984; Kendler et al., 1987; Phillips et al., 1987; Gustavsson et al., 1996; Boomsma et al., 2000; Sundet et al., 2003). Data on neuroticism reveal consistently that neuroticism is genetically related to both depression (measured categorically or dimensionally) and anxiety. Although to a lesser extent, there is overlap in unique environmental factors between neuroticism, depression and anxiety (Jardine et al., 1984; Martin et al., 1988; Kendler et al., 1993a; Gustavsson et al., 1996; Roberts & Kendler, 1999; Boomsma et al., 2000; Fanous et al., 2002; Ono et al., 2002; Stein et al., 2002). No study found an influence of common environment and thus no significant correlation between common environmental factors (r_C) either.

As mentioned at the beginning of this paragraph, Neale & Kendler (1995) tried to distinguish between several models of co-morbidity. With respect to the relationship between MDD and GAD, the models of multiformity (NK6),

overlapping etiologies (NK 10), MDD causing GAD (NK 11) and reciprocal causation (NK12) were all found to fit the data. MDD causing GAD seemed to be the best fitting model.

Family studies

Table 2.4 shows the results from the family studies that compared prevalence rates, odds ratios or relative risk ratios of different diagnoses in relatives per proband group. The structure of this table is as follows. The columns 'proband versus controls' show whether the three proband groups, consisting of one group of subjects with disorder A, one group of subjects with disorder B and one group of subjects with the co-morbid condition, are significantly different from controls. The columns 'proband versus each other' show whether proband groups are significantly different from each other. In other words, do probands with disorder A have more or the same amount of relatives with disorder A than probands with disorder B or than probands with the co-morbid condition. The column 'relations of proband groups' combines the results to subsequently decide which co-morbidity models are compatible with the results.

It becomes clear from the last column that the models 4-8 are most often compatible with the results (Weissman et al., 1993; Wickramaratne & Weissman, 1993; Goldstein et al., 1994; Mannuzza et al., 1994; Fyer et al., 1995; Maier et al., 1995; Fyer et al., 1996; Klein et al., 2003). Model KR8 (the co-morbid condition is a third disorder) does not seem to be an appropriate explanation, since all combinations of co-morbidity are seen among the anxiety disorders (Kessler 1995). From a clinical point of view, model KR4 (overlapping diagnostic criteria) is not very probable regarding the co-morbidity between PD and MDD since these disorders do not share most of their diagnostic criteria. With regard to the co-morbidity within the anxiety disorders, model KR4 cannot be excluded as an explanation, according to data from Fyer et al. (1995; 1996). However, these results should be interpreted cautiously since the analyses are not performed with the relatives subdivided in groups with mutual exclusive diagnoses. Instead, the group of relatives with disorder A+B is included in the group with disorder A as well as in the group with disorder B. Otherwise there was not enough power for statistical analyses due to the low number of relatives with the co-morbid disorder. This leaves models KR5-KR7 (multiformity) as most likely options to explain the co-morbidity between MDD and the anxiety disorders and possibly also within the anxiety disorders. Klein et al. (2003) have studied the co-morbidity between MDD and all anxiety disorders. Their results are incompatible with any of the KR models. They conclude that their results are compatible with an independent familial transmission of the disorders with co-morbidity caused by non-familial etiological factors.

Co-morbidity of anxiety and depression

Table 2.4: Family studies, using prevalence rates, odds ratios or relative risk ratios.

Study	N probands (P) / N relatives. / N Controls (C) / N relatives.	Diagnosis in relatives.	Probands versus controls	Probands versus each other	Relations of proband groups†	Compatible KR models
Klein et al. (2003)	P: 345 / 1432 C: 352 / 1176	MDD MDD + AnxD AnxD	MDD>C MDD=C MDD=C MDD+AnxD>C MDD+AnxD>C MDD+AnxD>C	AnxD=C MDD=AnxD MDD=AnxD AnxD>MDD MDD=MDD+AnxD MDD=MDD+AnxD MDD=MDD+AnxD	MDD=MDD+AnxD MDD+AnxD>AnxD=C MDD+AnxD>MDD=C AnxD=MDD+AnxD>MDD=C	5 and 6 8 none
Fyer et al. (1996)	P: 118 / 325 C: 77 / 231	SocP* PD+SocP PD*	SocP>C SocP=C SocP=C	SocP>SocP+PD SocP=SocP+PD SocP=SocP+PD	SocP>SocP+PD=PD=C SocP=SocP+PD=PD=C PD>SocP+PD=SocP=C	8 7 5 and 6, 8
Maler et al (1995)	P: 280 / 883 C: 109 / 409	PD MDD+PD MDD	PD>C PD=C PD>C	PD=MDD+PD PD=MDD+PD PD=MDD+PD	PD=MDD+PD>MDD=C MDD=MDD+PD>PD=C MDD=MDD+PD>PD>C	5 and 6 5 and 6 9
Fyer et al. (1995)	P: 103 / 285 C: 77 / 231	SP* SocP*	SP>C SP=C	SP>SocP SocP=SP	SP>SocP=C SocP>SP=C	4-8 4-8
		SP* PD*	SP>C SP=C	SP>PD PD>SP	SP>PD=C PD>SocP=C	4-8 4-8
		SocP* PD*	SocP>C SocP=C	SocP>PD PD>SocP	SocP>PD=C PD>SocP=C	4-8 4-8
Mannuzza et al. (1994)	P: 126 / 347 C: 77 / 231	MDD MDD+PD PD	MDD+PD>C MDD+PD>C MDD+PD=C	PD=MDD+PD MDD+PD>PD PD=MDD+PD	MDD+PD>PD=C MDD+PD>PD=C PD>PD+MDD=C	4-7 5 and 6, 8 5 and 6, 8

Table 2.4: Family studies, using prevalence rates, odds ratios or relative risk ratios. (Continued)

Study	N probands (P) / N relatives. / N Controls (C) / N relatives.	Diagnosis in relatives.	Probands versus controls	Probands versus each other	Relations of proband groups [¶]	Compatible KR models
§ Goldstein et al. (1994)/ Weisman et al. (1993)/ Wickramaratne & Weisman (1993)	P: 148 / 792 C: 45 / 255	PD PD+MDD MDD**	PD>C PD=C PD=C	MDD**=C MDD**>C MDD**>C	PDPD+MDD>MDD**=C PDPD+MDDMDD**>C MDD**PD+MDD>PD=C	4-7 4, 7, 9-11 4,7

Anx dis: anxiety disorders, GAD: generalized anxiety disorder,
MDD: major depressive disorder, P: Phobia,
PD: panic disorder with or without agoraphobia, SocP: social phobia,
SP: Specific Phobia.

¶ This column shows a summary of the results shown in the columns probands versus controls and probands versus each other and is comparable with the last column in Table 2.

* Diagnoses include the co-morbid condition.

** MDD with age of onset <30 years.

§ These studies used the same population. Therefore, their results are shown together.

Table 2.5 shows the outcomes of the family studies that, similar to the twin studies, have used biometrical model fitting and tested the hypothesis that different disorders or traits arise from overlapping etiological processes (KR11 / NK 10) (Leckman et al., 1983; Tambs, 1991; Merikangas et al., 1994; Sham et al., 2000). In contrast to the other family studies, they conclude that a single common familial factor accounts for a substantial proportion of the covariances between depression and anxiety and neuroticism.

Table 2.5: Family studies, using biometrical model fitting.

Study *	N of relatives	Diagnoses	rF	rE
Sham et al. (2000)*	5909 sibs	Neur, high positive affectivity	-.65	-.29
		Neur, anxious arousal	.70	.21
		High positive affectivity, anxious arousal	-.70	-.40
§Merikangas et al. (1994) / Leckman et al. (1983)	Probands: 133 / 810 Controls: 82 / 521	MDD, anxiety disorders	.99	0
Tambs (1991)*	814 fathers, 880 mothers, 564 siblings	Anx / Dep	.77	.27

Anx: symptoms of anxiety,

MDD: major depressive disorder,

rF: correlation between familial factors,

Dep: symptoms of depression,

Neur: Neuroticism,

rE: Correlation between unique environmental factors.

*Correlations are calculated based on the (standardized) estimates of the variance explained by the common and specific genetic and environmental factors reported in the articles.

§ These studies used the same population. Therefore, their results are shown together.

To summarize, the results of the family studies mostly indicate multiformity as possible explanation for the co-morbidity both within anxiety disorders and between anxiety disorders and MDD, but the model of overlapping etiology could also fit the data.

Discussion

The results of the twin and family studies indicate that the anxiety disorders and MDD are distinct entities and no alternative phases of one disease. The results also rule out that the co-morbid condition is a third disorder. According to the twin and family studies, which used biometrical model fitting, overlapping etiological factors explain the co-morbidity within anxiety disorders

and between anxiety disorders and MDD. This common background could, to some extent, be explained by neuroticism since both anxiety and depression do share etiological factors with neuroticism. In general, there is substantial overlap among the genetic factors. Shared unique environmental factors explain a smaller part of the co-morbidity. Common environment tends not to explain variance in anxiety, depression or neuroticism and cannot contribute to co-morbidity between these traits. However, according to most family studies that compared prevalence rates, co-morbidity between MDD and PD and within the anxiety disorders is best explained with the multiformity models.

Before considering these conclusions in the light of the theory of Gray and McNaughton (2000), possible causes of the discrepancy in the results will be discussed. The different approaches that are used by the twin and family studies investigating co-morbidity seem a first possible explanation, since the different results coincide with the different methods. Two simulation studies testing the validity of the Klein and Riso predictions and the Neale and Kendler model fitting approach revealed that the latter method was more valid to discriminate the correct co-morbidity model (Rhee et al., 2003; Rhee et al., 2004). The predictions of Klein & Riso (1993) did not seem to be valid under some circumstances (Rhee et al., 2003). In addition, another drawback of the family studies comparing prevalence rates is that the predictions of Klein and Riso (1993) do not consider that co-morbidity can be explained by non-familial etiological factors (Klein et al., 2003). Twin and family studies using biometrical model fitting do take this possibility into account.

However, a major limitation of the twin studies is that they only tested model NK11 and left the other models out of consideration. The simulation study has shown that using biometrical model fitting, it is difficult to discriminate within and between the classes of multiformity (KR5-7/NK5-8) and overlapping etiology models (KR10-11/NK10-12) (Rhee et al., 2004). This is supported by Neale & Kendler (1995), who tested all co-morbidity models on MDD and GAD and found that three overlapping etiology models as well as one multiformity model fitted their data. Therefore, when model KR11/NK10 fits the data, this does not exclude the possibility that another overlapping etiology model (KR11/NK10 and NK12) or multiformity model (KR5-7/NK5-8) fits as well.

Another reason for the discrepant findings between twin and family studies could be that different diagnoses are analyzed. With the exception of Klein et al., (2003), the family studies that assessed mutual exclusive diagnoses in the probands as well as the relatives focused on MDD and PD (Weissman et al., 1993; Wickramaratne & Weissman, 1993; Goldstein et al., 1994; Mannuzza et al., 1994; Maier et al., 1995), whereas just one twin study investigated these disorders (Kendler et al., 1995).

Finally, discrepancies in the findings between family and twin studies could be caused by differences in the study populations. Family studies mostly use clinical populations, while twin studies are most often population based. When family history influences help seeking behavior, this could bias the results. However, this does not seem to play an important role since the studies that used biometrical model fitting with a clinical population found equal results, i.e. that model KR11 fitted the data (Merikangas et al., 1994; Roy et al., 1995).

Regarding the theory of Gray & McNaughton (2000), this review agrees that the anxiety disorders and MDD are distinct entities. Given the methodological issues, the current results are not conclusive to whether co-morbidity is due to overlapping etiology, probably expressed as the personality trait neuroticism (KR11/NK12), multiformity because of neural recursive interconnections (KR5-7/NK5-8) or both. However, since model KR11/NK12 fits the data in 23 twin and three family studies, the hypothesis that overlapping genetic etiological factors are of importance seems to be supported. This would imply that future research aiming to find genes underlying the vulnerability for anxiety and depression could pool subjects with these disorders. Another possibility would be to search for the genes underlying neuroticism. Environmental risk factors, on the other hand, seem to differ between anxiety and depression. Therefore, subjects with different disorders should be studied separately when these risk factors are investigated. An example of the latter is a recent study on life events as predictors of MDD, GAD or the co-morbid condition (Kendler et al., 2003). It appeared that loss and humiliating events were strongly linked to risk for depressive episodes, loss and danger events were linked to risk for generalized anxiety and that the sum of those events preceded mixed anxiety and depression.

It is recommended for future twin and family studies on co-morbidity of anxiety and depression to test all models. However, when all these models are tested separately, it is still impossible to decide whether one specific model or the combination of the two models of overlapping etiological factors and multiformity explain the co-morbidity. Therefore, we propose an additional model. Since it seems likely that neuroticism is the personality trait underlying all these disorders, neuroticism should be included in the analyses as a factor explaining part of the covariance. Subsequently, the co-morbidity models can be tested on the residual covariance of the disorders not due to neuroticism. When the theory of Gray & McNaughton (2000) is right, the best fitting model will include neuroticism explaining part of the covariance with the residual covariance explained by multiformity in both directions. Yet, this model does not completely cover the theory of Gray & McNaughton (2000) either. Therefore, three latent factors, namely fear, panic and anxiety should be included in the model too. Two factor analyses on epidemiological data have already shown that MDD, dysthymia and GAD load on an "anxious misery"

factor and the other anxiety disorders load on a “fear” factor. In turn, the anxious misery factor and the fear factor loaded on an internalizing factor (Krueger 1999; Vollebergh et al., 2001). By adding a third “panic” factor to the model, the theory of Gray and McNaughton (2000) could be tested.

There are several other issues that need some attention when investigating co-morbidity. To test causal relations properly in twin and family studies, information on the time sequence of disorders is necessary (Goldberg & Ramakrishnan, 1994). Mood disorders, for example, tend to be secondary when co-morbid with anxiety disorders (De Graaf et al., 2003). This suggests that anxiety disorders are not an epiphenomenon of MDD and are probably not caused by MDD in most cases. This also applies to studies investigating the relation between neuroticism and anxiety and depression. Findings from the Munich Vulnerability Study, suggest that neuroticism is a risk factor for MDD, since one third of the, still healthy, adult relatives of patients with an affective disorder have increased neuroticism scores (Krieg et al., 2001). However, several studies have shown that current or past MDD also leads to increased scores of neuroticism (Kendler et al., 1993a; Duggan et al., 1995; Ouimette et al., 1996; Farmer et al., 2003).

The possible effect of age or sex on causes of co-morbidity should also be considered. Interestingly, the results of Wickramaratne & Weissman (1993) and Weissman et al. (1993) suggest that a different model might explain co-morbidity in late onset MDD (after 30 years). If only relatives with MDD with disease onset after 30 years are considered, no differences are found between the proband groups. This might indicate that late onset MDD is less familial (Weissman et al., 1993; Wickramaratne & Weissman, 1993). Furthermore, in univariate analyses, some studies have indicated that genes influencing neuroticism, anxiety and depression are not entirely the same in men and women (Jardine et al., 1984; Kendler et al., 1987; Kendler & Prescott, 1999; Kendler et al., 2001a; Fanous et al., 2002) and that heritability of neuroticism, anxiety and depression is higher in women than in men (Jardine et al., 1984; Bierut et al., 1999; Boomsma et al., 2000; Kendler et al., 2001a). However, other studies have found no difference between sexes (Roy et al., 1995; Hettrema et al., 2001b; Kendler et al., 2001b; Ono et al., 2002). It remains to be tested whether different models explain co-morbidity in females and males.

In conclusion, this review shows that, as proposed by Gray & McNaughton (2000) anxiety disorders and MDD are distinct disorders with co-morbidity probably partly explained by shared genetic factors, which also influence neuroticism. Whether neural recursive interconnections do also play a role remains to be investigated. Future co-morbidity research should include testing of various co-morbidity models. Finally, to be able to decide whether either one or two models play a role (i.e. overlapping etiology as well as multiformity), a model should be tested that specifically includes neuroticism.

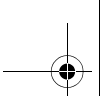
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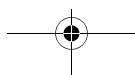
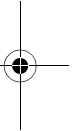
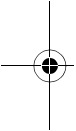
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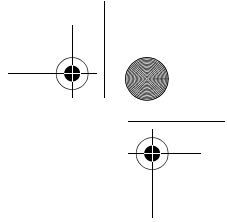
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Chapter
2





Chapter

3

The Association of Personality with Anxious and Depressive Psychopathology

This chapter is based on:

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Chapter
3

It is still unresolved to what extent and in which way personality dimensions are associated to anxious and depressive psychopathology. We performed two studies to investigate the association between neuroticism, extraversion and sensation seeking, on the one hand, and anxious and depressive psychopathology, on the other. In both studies, co-morbidity between depression and the other psychopathologies was explicitly taken into account.

In study I, data from 7969 twins and siblings of the Netherlands Twin Register were analyzed. Correlations were estimated within and between self-report measures of the three personality dimensions, anxiety and depression. Next, the sample was divided into normal controls and cases. Personality scores of subjects with only anxious or depressive symptoms and subjects with more symptoms were compared to scores of controls. In study II, analyses were performed on DSM IV diagnoses of major depression, dysthymia, social phobia, generalized anxiety disorder and panic disorder. These data were obtained for a selected sample of 1240 individuals. Personality scores were compared between groups, correcting for co-morbidity by including all disorders in the model. Additionally, personality scores were compared of subjects with zero, one, two or three or more diagnoses.

Study I showed that high neuroticism and low extraversion were related to anxiety as well as depression. Sensation seeking was related to neither to them. These results were the same for subjects with a score above the 95th percentile for anxiety or depression only or for both. In study II neuroticism was related to all disorders, except dysthymia. Low extraversion was related to social phobia and panic. Neuroticism and low extraversion were both related to the number of disorders. No associations were found with sensation seeking. Thus, neuroticism and extraversion are related to anxiety and depression, also when co-morbidity is taken into account. Sensation seeking seems an independent personality dimension, which is not associated with anxious and/or depressive psychopathology.

Introduction

The questions of to what extent and in which ways personality dimensions are associated with anxious and depressive psychopathology are still unresolved. Most research has focused on neuroticism and extraversion or traits related to these personality dimensions. Neuroticism was originally described as reflecting emotional instability and anxiety proneness (Eysenck & Rachman, 1965). This trait was hypothesized to be related to the visceral brain, more often called the limbic system, which was supposed to regulate emotional expression and to control autonomic responses. According to Eysenck (1967), neurotic subjects are characterized by higher levels of autonomic activity (or reactivity), mediated by the visceral brain.

Extraversion was described as reflecting sociability, liveliness, impulsivity and the level of ease and pleasure felt in the company of others (Eysenck & Rachman, 1965). The last mentioned trait was theorized to be related to the ascending reticular activating system, with a higher level of arousal in introverts and a higher level of inhibition in extraverts (Eysenck, 1967). A wide range of electrophysiological and other psychophysiological studies confirmed this hypothesis (Stelmack, 1981).

Cloninger (1986) proposed that harm avoidance, an anxiety related trait, is positioned between neuroticism and extraversion. This positioning was confirmed by a strong positive correlation with neuroticism ($r = 0.63$) and a strong negative correlation with extraversion ($r = -0.55$) as measured with the Eysenck Personality Questionnaire (EPQ) (Heath et al., 1994). Two dimensions related to neuroticism and extraversion are positive and negative affectivity. Negative affectivity is a general dimension of subjective distress and unpleasurable engagement, whereas positive affectivity reflects the extent to which a person feels enthusiastic, active, and alert (Watson et al., 1988). There is general consensus that individuals scoring high on neuroticism exhibit negative affectivity (Shankman & Klein, 2003). Therefore, negative affectivity and neuroticism are often used interchangeably in the literature. However, this does not hold for the relation between extraversion and positive affectivity. Since extraversion does not only measure positive affectivity, but also impulsivity and sociability, this dimension encompasses more than positive affectivity only (Clark et al., 1994).

A further personality trait is sensation seeking, which was considered to be a measure of the impulsivity and sociability parts of Eysenck's broader extraversion dimension and to be independent of neuroticism (Zuckerman, 1979). Zuckerman (1979) defined this trait as "the need for varied, novel, and complex sensations and experiences and the willingness to take physical and social risks for the sake of such experience" (p. 10). Sensation seeking was also supposed to be related to an individual's level of arousal. Different studies investigating the relation between sensation seeking and Eysenck's personality

dimensions found correlations between extraversion and sensation seeking from 0.09 to 0.42 in men and from 0.11 to 0.44 in women (Zuckerman, 1979). The correlations of neuroticism and sensation seeking were non significant (Zuckerman, 1979).

Several hypotheses regarding the relationships of these personality dimensions to anxious and/or depressive psychopathology have been put forward. Eysenck & Rachman (1965) hypothesized that subjects with symptoms of anxiety and/or depression would be high in neuroticism and low in extraversion. Gray (1982) suggested that these two dimensions could be combined into one trait, reflecting the level of activity in the behavioral inhibition system and indicating a person's vulnerability for anxiety and depression. This led to the harm avoidance dimension (Cloninger, 1986). Clark & Watson (1991) developed the tripartite model, which agrees with Eysenck's model that negative affectivity is a risk factor for both anxiety and depression. However, according to the tripartite model, low positive affectivity is related to depression only, whereas autonomic hyperarousal (e.g. racing heart, trembling, shortness of breath, dizziness) is related to anxiety. Finally, sensation seeking was hypothesized to be unrelated to depression and anxiety disorders, since it is not associated with neuroticism (Zuckerman, 1979).

Research so far has confirmed that negative affectivity / neuroticism is related to both depression and anxiety (for reviews see Bienvenu & Stein (2003), Clark et al. (1994), Shankman & Klein (2003)). This also applies to harm avoidance (Brown et al., 1992; Cloninger, 2002; Shankman & Klein, 2003). Results have been contradictory concerning the association between low positive affectivity / extraversion and depression or anxiety disorders (see Shankman & Klein (2003) for a review). A possible source of confounding, which is not taken into account in most studies, is the highly prevalent co-morbidity between anxiety and depression. If, for example, high neuroticism is a risk factor for both anxiety and depression, but low extraversion only for depression (as supposed in the tripartite model), it may be hypothesized that subjects with pure anxiety disorders are only high in neuroticism, while subjects with both anxiety and depression are low in extraversion as well. As a consequence, whether or not a study focusing on anxiety observes that low extraversion is related to anxiety, will depend on the number of subjects with co-morbid anxiety and depression. This is just one example of how co-morbidity may modify the association between personality and psychopathology.

Several approaches can be used to take co-morbidity into account, when investigators are examining the association between personality and psychopathology. One way is to study subjects with the pure disorders separately from the subjects with the co-morbid condition. Another possibility is to compare the mean scores on personality dimensions of normal controls and affected subjects while correcting for co-morbid disease. For example, in an analysis of variance (ANOVA) or a regression analysis, all disorders can be

included in one model. Finally, factor analyses or structural equation modeling can be used to investigate the etiology of the correlation between measures of personality and anxious or depressive psychopathology.

In all studies taking these approaches, neuroticism was related to major depression and anxiety disorders (Bienvenu et al., 2001; Brown et al., 1998; de Graaf et al., 2004; Johnson et al., 2003; Krueger et al., 2001; Trull & Sher, 1994). In addition, all studies except one (Johnson et al., 2003) found a relation between low extraversion and one or more of the anxiety disorders, although results were not always consistent on the level of specific diagnoses (Bienvenu et al., 2001; Brown et al., 1998; Trull & Sher, 1994). Results were contradictory regarding the relation between low extraversion and major depression. Brown et al. (1998) and Trull & Sher (1994) did find an association whereas Bienvenu et al. (2001) and Johnson et al. (2003) did not. Krueger et al. (2001) found that internalization a factor on which depression and anxiety disorders loaded correlated negatively with positive emotionality in women, but not in men. These studies also revealed that co-morbidity between anxiety and depression is associated with neuroticism (Andrews et al., 2002; Bienvenu et al., 2001; de Graaf et al., 2004) and, to a limited extent, with low extraversion (Bienvenu et al., 2001). Andrews et al. (2002) even found a linear relationship between neuroticism and the number of disorders. To summarize, studies that take co-morbidity into account find in general that high neuroticism and low extraversion are related to depression as well as anxiety; this is in agreement with Eysenck's theory and in contradiction to the tripartite model.

The association between sensation seeking and anxious or depressive psychopathology has been studied far less often, and results are contradictory. To our knowledge, no previous studies have investigated this relation while taking co-morbidity into account. Zuckerman (1979) concluded that although there is no association between sensation seeking and depression and general trait anxiety, sensation seeking could be negatively related to fearfulness of more specific types. However, in two recent studies low levels of sensation seeking appeared to be related to major depression (Carton et al., 1995; Farmer et al., 2001).

In this chapter we describe two studies that investigated the relationship between the personality dimensions of neuroticism, extraversion and sensation seeking on the one hand and anxiety and depression on the other. In both studies, co-morbidity was taken into account. The goals of these studies were to test whether Eysenck's model or the tripartite model best describes the data and to test the extent to which sensation seeking is related to anxious and depressive psychopathology. The latter issue is interesting, because Zuckerman (1979) based his hypothesis that sensation seeking is not associated to anxiety and depression on the absence of a correlation between neuroticism and

sensation seeking. However, as he also acknowledged, sensation seeking is correlated with extraversion. Since low extraversion may be related to anxiety and depression, this could be the case for sensation seeking as well.

The first study was based on self-report questionnaire data of personality and psychopathology from twins and their siblings registered in the Netherlands Twin Register (NTR). In 1991, 1993, and 1997, a survey was sent to twins and in 1997, their siblings were also approached. These three waves were combined for the analyses, in order to obtain one of the largest samples so far used to investigate the association of neuroticism, extraversion, and sensation seeking with symptoms of anxiety and depression. Correlations were calculated within and between the personality and psychopathology dimensions. Furthermore, to take co-morbidity into account, subjects were divided into cases and normal controls on the measures of anxiety and depression, with the 95th percentile used as a cutoff score. Next, the mean scores of the pure cases and the co-morbid cases were compared with the means of the normal controls.

In the second study, data from a diagnostic psychiatric interview administered to a selected sample of twins and their siblings were analyzed. Scores on neuroticism, extraversion and sensation seeking were compared between subjects without psychopathology and subjects with a depression or an anxiety disorder defined according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV (American Psychiatric Association, 1994). This analysis was performed while correcting for co-morbidity, by comparing the means between normal controls and affected subjects with all disorders included in the same model. Finally, mean personality scores were compared between subjects with zero, one, two or three or more of disorders. The two studies are described separately followed by an overall discussion.

Study I: The Association of Personality and Anxious and Depressive Psychopathology Measured Dimensionally.

Method

Subjects

The first study was part of an ongoing longitudinal survey study of the NTR, which has assessed families with adolescent and adult twins roughly every two years since 1991. Sample selection and response rates are described in detail in Boomsma et al. (2002). Each survey was sent to the twins and additional family members, namely parents in 1991 and 1993, parents and siblings in 1995, and siblings in 1997. Each survey, with the exception of the 1995 wave, collected information on personality and psychopathology. For this study, data from twins and siblings from the 1991, 1993, and 1997 surveys were used. In these years, questionnaires were returned at least once by 2825 male and 3636 female twins, and 668 brothers and 840 sisters, from 3349 families. Forty-two percent of the subjects participated two or three times, and 58% participated once. The mean ages of the subjects at the time of the three waves was 18, 20, and 27 years with standard deviations of respectively 2.3, 8.4 and 10.5 years.

Instruments

On all three occasions, sensation seeking was measured with the Dutch translation of the Zuckerman sensation seeking scale (Feij & van Zuilen, 1984; Zuckerman, 1971). Neuroticism, extraversion and somatic anxiety were measured with the Amsterdamse Biografische Vragenlijst (ABV) (Wilde, 1970). The ABV neuroticism and extraversion scales are very similar to those of the EPQ (Eysenck & Eysenck, 1964). Somatic anxiety is measured with items such as "Do you often have a headache?" and "Do you have heart palpitations?". Anxiety was measured with the Dutch translation of the Spielberger State Trait Anxiety Inventory - Trait version (STAI) (Spielberger et al., 1970; Van der Ploeg et al., 1979). Depression was measured with two different inventories in the three surveys. In 1991, the anxious/depression symptom scale of the Young Adult Self Report (YASR) (Achenbach, 1990; Verhulst et al., 1997) was used, in 1993, the 13-item version of the Beck Depression Inventory was used (Beck et al., 1974) and in 1997 both instruments were used.

Statistical methods

For all personality and psychopathology measures, normalized scores were calculated according to Blom (1958) so that we could compare the scores across scales and time. These scores were averaged over time when a subject had participated more than once in the survey study. Mean scores were compared between sexes with Student's t-test. Pearson correlations were calculated within and between the personality and psychopathology dimensions for men and women separately. Furthermore, for the four psychopathology measures (depression (BDI), anxious depression (YASR), somatic anxiety (ABV) and anxiety (STAI), the population was divided in cases and normal controls with the 95th percentile as cutoff score. Cases were further divided into subjects with pure "disorders" and with co-morbid conditions. It follows that only subjects that had scores on all four instruments were included in this analysis. In a Multivariate Analysis of Variance (MANOVA) for each group of cases personality scores were compared with the normal controls. All analyses were completed using SPSS for Windows, Release 11.0.

Results

Figures 3.1a to 3.1g show the distributions of the mean normalized scores for neuroticism, extraversion, sensation seeking, depression, anxious depression, somatic anxiety and anxiety respectively. All variables were more or less normally distributed, with the exception of the depression scores.

All dimensions differed significantly ($p < 0.0001$) between men and women, with men scoring lower on neuroticism and all psychopathology measures, and higher on extraversion and sensation seeking (Table 3.1).

Table 3.1: Mean raw and normalized scores and standard deviations (SD) for Neuroticism, Extraversion, total score on Sensation Seeking, Beck Depression Inventory, Somatic Anxiety, Anxious Depression, anxiety for men and women.

	Men		Women	
	Raw (SD)	Normalized (SD)	Raw (SD)	Normalized (SD)
Neuroticism	46.59 (21.34)	-.19 (.92)	55.18 (23.38)	.19 (.94)
Extraversion	60.77 (15.32)	.03 (.96)	59.88 (15.16)	-.05 (.93)
Sensation Seeking	11.74 (1.75)	.33 (.91)	10.59 (1.91)	-.24 (.95)
Depression	1.30 (2.21)	-.07 (.77)	1.98 (2.84)	.17 (.85)
Anxious Depression	3.77 (3.57)	-.22 (.86)	5.65 (4.59)	.20 (.96)
Somatic Anxiety	17.55 (4.71)	-.10 (.87)	18.85 (5.43)	.14 (.94)
Anxiety	31.90 (7.50)	-.13 (.91)	34.27 (8.59)	.15 (.95)

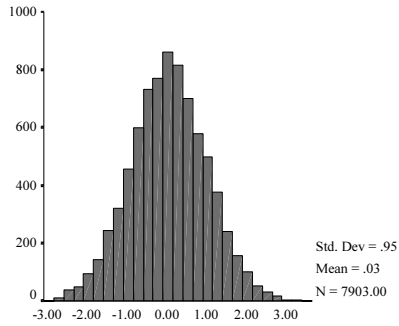


Fig 1a: Neuroticism (ABV)

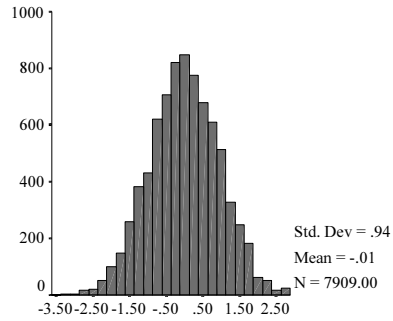


Fig 1b: Extraversion (ABV)

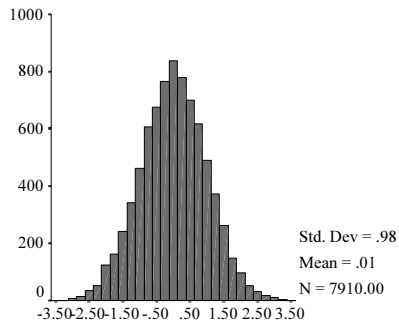


Fig 1c: Sensation Seeking (Zuckerman)

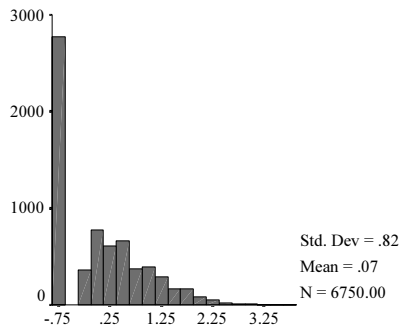


Fig 1d: Depression (BDI)

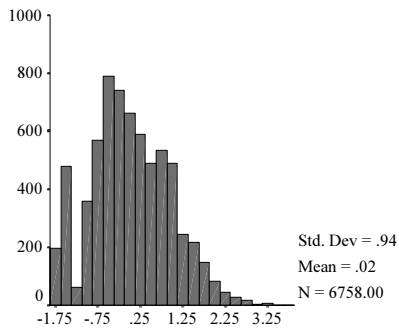


Fig 1e: Anxious Depression (YASR)

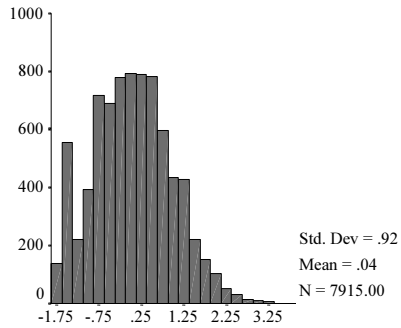


Fig 1f: Somatic Anxiety (ABV)

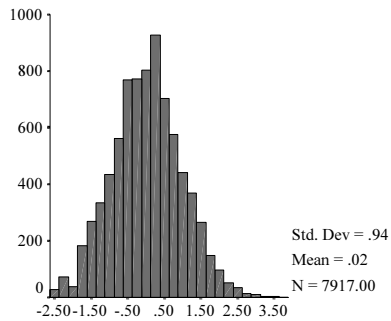


Fig 1g: Anxiety (STAI)

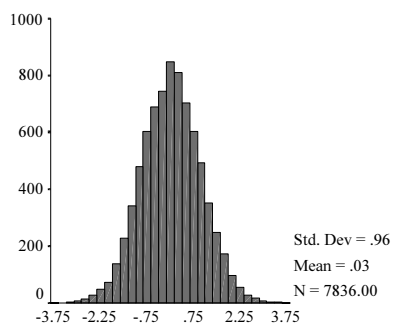


Fig 1h: Genetic factor scores

Figure 3.1: Distributions of personality and psychopathology normalized scores and genetic factor scores.

The correlations within and between the personality and psychopathology dimensions were all significant at the level of < 0.01 (Table 3.2). It is clear that measures of anxiety and depression were highly correlated. Moderate correlations were seen within the personality measures, with a negative correlation between neuroticism and extraversion. Regarding the relation between personality and psychopathology, neuroticism showed high correlations with anxiety as well as depression, while extraversion was, to a lesser extent, negatively correlated with these symptoms. Sensation seeking did not appear to be related to any of these measures, and especially not to depression. Finally, these conclusions were very similar for men and women with no differences in the size of the correlations.

Table 3.2: Correlations for Neuroticism (Neu), Extraversion (Ext), total score on Sensation Seeking (SSS), Beck Depression Inventory (BDI), Somatic Anxiety (SoA), Anxious Depression (AD), anxiety (Anx) for men (upper diagonal) and women (lower diagonal).

	Neu	Ext	SSS	BDI	AD	SoA	Anx
Neu		-.22	.19	.53	.60	.59	.69
Ext	-.22		.36	-.18	-.23	-.12	-.24
SSS	.18	.31		.08	.08	.17	.13
BDI	.58	-.20	.08		.48	.40	.58
AD	.70	-.27	.10	.56		.42	.61
SoA	.61	-.19	.13	.46	.48		.47
Anx	.75	-.22	.14	.65	.71	.53	

Correlations among the psychopathology measures were high and it was possible that the correlations between the personality measures neuroticism and extraversion and all the psychopathology measures were due to just one of the psychopathology dimensions. Therefore, for the four psychopathology measures (depression (BDI), anxious depression (YASR), somatic anxiety (ABV) and anxiety (STAI)), the population was divided into cases and normal controls with the 95th percentile as cutoff score. Cases were further divided into subjects with pure "disorders" and with co-morbid conditions. This led to 15 groups of cases, as summarized in Table 3.3, e.g. one group with pure cases of depression, one group of cases with depression and somatic anxiety, etc. Since subjects had to have a score on all four instruments to be categorized in one of the groups, 2416 subjects were excluded from this analysis. In a Multivariate Analysis of Variance (MANOVA) personality scores for each group of cases were compared to those of the normal controls. Table 3.3 shows that all groups of cases had significantly higher neuroticism scores than the normal controls ($p <$

0.0001) and almost all groups of cases had significantly lower extraversion scores ($p < 0.0001$ or $p < 0.001$), whereas just one group scored significantly higher on sensation seeking ($p < 0.05$).

Study II: The Association of Personality and Psychopathology Categorized According to DSM IV diagnoses.

Methods

Subjects

In 1998, we performed a selection to obtain a sub-sample of twin families that would be informative for a linkage study to localize the genes underlying the susceptibility to anxiety and depression. The selection strategy was based on the recommendation of Eaves & Meyer (1994) and Risch & Zhang (1995) to select sibling pairs for genotyping with extreme scores (high/high, low/low, low/high or high/low) on a quantitative scale of interest. Simulation studies have shown the optimal selection percentages for linkage analysis in sibling pairs from random samples (Dolan & Boomsma, 1998). Concordant sibling pairs were selected when both had scores in the top 12% or in the bottom 12% of the phenotypic distribution. For discordant pairs, an 'asymmetrical' criterion appeared to be optimal. Discordant sibling pairs were selected if one sibling had a score in the top 25% and the other in the bottom 20%, or if one had a score in the top 20% and the other in the bottom 25%. The quantitative scale used for the selection consisted of a genetic factor score expressing a subject's genetic susceptibility to 'anxious depression'. The formula to calculate these factor scores was derived from a multivariate genetic analysis on the anxiety, depression, neuroticism and somatic-anxiety data collected for twins and their siblings in 1991, 1993 and 1997.

Table 3.3: Mean scores and standard deviations (SD) for Neuroticism (Neu), Extraversion (Ext), total score on Sensation Seeking (SSS), for the normal controls and the fourteen groups of cases with a score above the 95th percentile on Depression (BDI), Anxious Depression (AD), Somatic Anxiety (SoA), and/or Anxiety (Anx).

	N	Neu (SD)	Ext (SD)	SSS (SD)
Normal controls	4994	-.16 (.83)	.05 (.92)	-.03 (.96)
BDI	90	.86 (.56)*	-.31 (.93)*	.02 (.93)
AD	95	1.09 (.58)*	-.46 (1.03)*	.09 (1.05)
SoA	98	1.01 (.71)*	-.20 (.96)^	-.07 (1.07)
Anx	35	1.33 (.53)*	-.54 (.97)*	-.05 (.93)
BDI + AD	14	1.41 (.41)*	-.86 (.86)*	.07 (.73)

Personality and anxious and depressive psychopathology

Table 3.3: Mean scores and standard deviations (SD) for Neuroticism (Neu), Extraversion (Ext), total score on Sensation Seeking (SSS), for the normal controls and the fourteen groups of cases with a score above the 95th percentile on Depression (BDI), Anxious Depression (AD), Somatic Anxiety (SoA), and/or Anxiety (Anx).

(Continued)	N	Neu (SD)	Ext (SD)	SSS (SD)
BDI + SoA	17	1.01 (.51)*	-.59 (.97)^	.19 (1.22)
BDI + Anx	25	1.48 (.45)*	-.23 (.84)	-.27 (1.04)
AD + SoA	9	1.40 (.55)*	-.37 (.79)	.37 (.58)
AD + Anx	41	1.72 (.49)*	-.50 (.81)*	.28 (.91)#
SoA + Anx	14	1.74 (.50)*	-.64 (.94)^	-.26 (1.20)
BDI + AD + SoA	11	1.40 (.56)*	-.96 (.99)*	-.08 (1.23)
BDI + AD + Anx	39	1.72 (.62)*	-.75 (.92)*	.01 (.94)
BDI + SoA + Anx	18	1.82 (.55)*	-.87 (.91)*	.32 (.98)
AD + SoA + Anx	10	1.93 (.25)*	-.33 (.40)	-.20 (1.03)
BDI + AD + SoA + Anx	43	2.11 (.48)*	-.89 (.91)*	-.01 (.96)

* $p < 0.0001$ versus normal controls

^ $p < 0.001$ versus normal controls

$p < 0.05$ versus normal controls

This analysis revealed that covariances for these traits could be fully attributed to a common genetic factor (Boomsma et al., 2000). The value of this common genetic factor could be estimated for each individual by using the individual scores on the traits and the factor loadings on the common genetic factor. Since the factor loadings on the common genetic factor were different for males and females, the formulas to estimate the genetic factor score were different for males and females. Furthermore, genetic factor scores depended on whether the BDI or the YASR depression scale was used in the construction. For example, this was the formula for males when the score on the YASR was used: Genetic factor score = $0.144 \times \text{Anxiety} + 0.117 \times \text{Neuroticism} + 0.039 \times \text{Somatic anxiety} + 0.064 \times \text{Depression (YASR)}$. More detailed information on how the factor scores were calculated is provided elsewhere (Boomsma et al., 2000). The correlation between the factor scores calculated with the score on the BDI and the score on the YASR in the 1997 survey was 0.98.

A factor score could be calculated for 7836 twins and siblings who participated at least once in the 1991, 1993 or 1997 survey (see Figure 3.1h). Subjects who missed one or more of the inventories that measured neuroticism, anxiety, somatic anxiety, or depression were excluded. Based on these factor scores, 561 families were selected in which both members of a sibling pair had extreme factor scores. All members of the selected families, regardless of their genetic factor scores, were asked to provide a buccal swab for DNA isolation. Twins and siblings in these families were also asked to participate in a diagnostic psychiatric interview. For example, in monozygotic

twin pairs in which one (or both) of the twins formed an extreme pair with an additional sibling, both the twins and the additional sibling were invited to take part in the study. Finally, a sub-sample of concordant and discordant monozygotic twins and seven unselected families participated in the interview. In 143 families, not all family members were approached. Eventually, 332 male and 504 female twins, and 193 brothers and 227 sisters, from 479 families were interviewed. One hundred and seven subjects were not available, e.g. because the phone was not answered several times, and 154 subjects refused to participate.

Table 3.4 shows the consequences of the selection on the distribution of the factor scores on an individual level. Eighty percent of the interviewed subjects had extreme scores (i.e. above the 75th or below the 25th percentile of the total population). Subjects who refused to participate had less extreme scores than the subjects who participated, whereas subjects who were not available for the interview had more extreme scores. For 17 twins and siblings, no genetic factor score was available. They participated in the interview, because they were family members of an extreme scoring sibling pair. Twelve of them had not returned a questionnaire. Five participants had filled out a questionnaire, but missed items on the scales used to calculate the factor scores. Mean age of the participants at the time of the interview was 28.3 years.

Table 3.4: Interview participation and factor scores (fs)*.

	Not approached (N / %)	Participated (N / %)	Refused participation (N / %)	Respondent not available (N / %)
fs \geq 75 th %	180 (28.5%)	460 (37.1%)	45 (29.4%)	52 (48.6%)
fs \leq 25 th %	167 (26.4%)	480 (38.7%)	70 (45.8%)	34 (31.8%)
fs between 25 th % and 75 th %	280 (44.3%)	256 (20.6%)	31 (20.3%)	20 (18.7%)
fs \geq 75 th % and \leq 25 th %	54 (0.9%)	44 (3.5%)	7 (4.6%)	1 (0.9%)
Total	6336 (100%)	1240 (100%)**	153 (100%***)	107 (100%)

* Factor scores were calculated in 1991, 1993 and 1997. A subject is assigned to a group based on his lowest or highest score of these three occasions. Subjects who score above the 75th percentile on one occasion and below the 25th percentile on another are classified in a separate group.

** For sixteen twins and siblings, who participated in the CIDI, a factor score is missing.

*** For one sibling, who refused to participate, a factor score is missing.

Correlations within and between the personality and psychopathology dimensions were somewhat higher in the selected sample than in the total population. The highest correlations in the selected population were found between neuroticism and anxiety, namely 0.80 in men and 0.84 in women. In the total population, these correlations were 0.69 and 0.75 respectively.

Instruments

During the telephone interview, the following sections from the lifetime computerized version of the Composite International Diagnostic Interview (CIDI) (World Health Organization, 1992) were administered to obtain lifetime DSM-IV diagnoses (American Psychiatric Association, 1994): Demographics (Sections A); Social Phobia, Agoraphobia, Panic Disorder and Generalized Anxiety Disorder (D33 and further); Depression and Dysthymia (E); Mania Screen and Bipolar Affective Disorder (F) and Obsessive-Compulsive Disorder (K1-22). The CIDI is a fully standardized diagnostic interview. No information on the reliability and validity of the Dutch version of the CIDI is available, but good reliability and validity have been reported for the American CIDI (Andrews & Peters, 1998). All interviewers were trained by the Dutch World Health Organization training center. The interviews were taped, and a trained clinician (CM) reviewed 126 interviews (10%) to check whether the interviewers had administered the CIDI appropriately. This appeared to be the case. However, it was apparent that questions regarding age of onset and age of recency were not reliably answered because of comments made by the subjects such as "I have to guess" or "I do not know. I suppose I was around .. years of age". This was also the case with respect to the number of episodes reported in major depression.

According to the diagnostic algorithm as obtained with the CIDI, subjects could be classified to one of three categories: "not affected", "affected", "fulfilling the positive criteria, but not the exclusion criteria". The third category consisted of subjects with more than one anxiety disorder, subjects who exhibited symptoms of generalized anxiety disorder exclusively during a depressive episode, and subjects who fulfilled the criteria for an anxiety disorder but did not seek help for their symptoms. Subjects in this category were classified as affected.

We analyzed data on major depression, dysthymia, generalized anxiety disorder, social phobia, panic disorder with or without agoraphobia and agoraphobia without a history of panic disorder. Subjects with one of the latter three diagnoses were considered as one group, which is further referred to as 'panic/agoraphobia'. Subjects with bipolar disorder and/or obsessive-compulsive disorder without any other condition were excluded from the analyses (N=8).

Statistical methods

MANOVA were performed with the mean scores on the personality dimensions as dependent variables. In the first analysis the diagnoses major depression, dysthymia, social phobia, generalized anxiety disorder or panic constituted the independent variables. By including these variables in the model at the same time, we could control for co-morbidity. In the second analysis the number of diagnoses was the independent variable.

Results

Table 3.5 shows the number of subjects with no, one, two, three, four, or five diagnoses and the distribution of the disorders in these groups. Co-morbidity was very common, especially in women or when an anxiety disorder was present.

Table 3.5: Frequency of the number of disorders in men (upper part) and women (lower part) with a specification of which diagnoses are made.

N disorders	Total (%)*	MDD (%)	Dys (%)	GAD (%)	Panic (%)	Social P (%)
0	454 (87.2)					
1	45 (8.6)	28 (5.4)	0	4 (0.8)	7 (1.3)	6 (1.1)
2	16 (3.1)	14 (2.7)	0	10 (1.9)	4 (0.8)	4 (0.8)
3	6 (1.1)	6 (1.1)	3 (0.6)	4 (0.8)	3 (0.6)	2 (0.4)
Total N men	521	48 (9.2)	3 (0.6)	18 (3.4)	14 (2.7)	12 (2.3)
0	532 (73.3)					
1	108 (14.8)	67 (9.2)	2 (0.3)	8 (1.1)	20 (2.7)	11 (1.5)
2	49 (6.7)	40 (5.5)	8 (1.1)	18 (2.5)	20 (2.7)	12 (1.6)
3	28 (3.8)	27 (3.7)	7 (1.0)	19 (2.6)	18 (2.5)	13 (1.8)
4	8 (1.1)	7 (1.0)	6 (0.8)	7 (1.0)	6 (0.8)	6 (0.8)
5	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)
Total N women	727	143 (19.6)	25 (3.4)	54 (7.4)	66 (9.1)	44 (6.0)

MDD: Major Depression,

Social P: Social Phobia,

GAD: Generalized Anxiety Disorder,

Dys: Dysthymia.

*Percentages are always calculated from the total group of men (N=521) or women (N=727).

MANOVA showed that mean scores on the personality and psychopathology measures differed significantly between unaffected subjects and subjects with a diagnosis of major depression, social phobia, generalized anxiety disorder or panic/agoraphobia ($p < 0.0005$) (Table 3.6). Only the scores of subjects diagnosed with dysthymia were not significantly different from

those of the group without a disorder, although their scores were the same as or even higher than those of the other subjects with depression or an anxiety disorder. Interaction between variables was not included in the analysis, because power was too low to detect significant effects. Considering the results in more detail, the univariate tests demonstrated that subjects diagnosed with major depression, social phobia, generalized anxiety disorder or panic/agoraphobia all differed significantly from the subjects without a disorder in their scores on neuroticism ($p \sim 0.005$). With regard to extraversion, only the subjects with social phobia or panic showed decreased scores in comparison with the normal group ($p < 0.05$). On sensation seeking, subjects with diagnoses did not differ from normal controls.

Table 3.6: Mean scores and standard deviations (SD) on psychopathology and personality measures for men (upper part) and women (lower part) with or without a DSM IV diagnosis of a mood or anxiety disorder.

	No diagnoses	MDD	Dys	GAD	Panic	Social P
BDI (SD)	-.16 (.72)	.91 (.97)	1.81 (.91)	.94 (.96)	.71 (.78)	1.01 (1.28)
AD (SD)	-.30 (.88)	.75 (.91)	1.33 (.07)	.97 (.57)	.17 (1.33)	.69 (.80)
SoA (SD)	-.26 (.89)	.58 (.85)	.89 (.72)	.81 (.75)	.35 (.70)	.82 (1.03)
Anx (SD)	-.33 (1.00)	.87 (1.09)	1.78 (.23)	1.30 (.61)	.70 (.87)	1.01 (1.36)
Neu (SD)	-.40 (1.03)	.75 (1.11)	1.50 (.95)	1.06 (.63)	.35 (1.22)	1.16 (1.06)
Ext (SD)	.14 (1.00)	-.04 (1.26)	-.95 (.70)	.03 (1.30)	-.54 (.88)	-.48 (1.02)
SSS (SD)	.26 (.89)	.32 (.90)	.42 (.37)	.53 (.94)	-.31 (.78)	.31 (.89)
BDI (SD)	-.01 (.79)	.92 (.96)	1.63 (.99)	1.29 (.81)	.76 (.88)	1.00 (.87)
AD(SD)	-.06 (.92)	.96 (.98)	1.43 (.90)	1.28 (.86)	.99 (.99)	1.38 (.80)
SoA (SD)	-.08 (.93)	.69 (1.05)	1.10 (1.06)	.78 (1.04)	.93 (.92)	.92 (.95)
Anx (SD)	-.17 (1.01)	.92 (1.00)	1.68 (.98)	1.39 (.88)	.91 (.94)	1.20 (.90)
Neu (SD)	-.17 (1.03)	.87 (.97)	1.36 (.99)	1.24 (.91)	.92 (.88)	1.11 (.86)
Ext (SD)	-.03 (.91)	-.37 (.90)	-.82 (1.00)	-.66 (.88)	-.44 (.89)	-.69 (.74)
SSS (SD)	-.41 (.96)	-.39 (.97)	-.55 (1.10)	-.56 (.96)	-.32 (.95)	-.25 (.90)

MDD: Major depression,
GAD: Generalized Anxiety disorder,
BDI: Beck Depression Inventory,
SoA: Somatic Anxiety, Anx: Anxiety,
Ext: Extraversion,

Social P: Social Phobia,
Dys: Dysthymia,
AD: anxious depression,
Neu: Neuroticism,
SSS: Sensation Seeking.

A second MANOVA, with the personality dimensions as independent variables and with the number of CIDI diagnoses as independent variable (zero, one, two or three or more) did also reach significance ($p < 0.0001$) (Table 3.7). The univariate tests showed that neuroticism and extraversion, but not sensation seeking, were significantly different among the four groups of subjects. Figure 3.2 shows a positive relation between neuroticism and the number of disorders, and a negative relation between extraversion and the number of disorders.

Table 3.7: Mean scores and standard deviations (SD) on psychopathology and personality measures for men (upper part) and women (lower part) with zero, one, two or three or more disorders.

	0	1	2	3 or more
BDI (SD)	-.16 (.72)	.71 (.91)	1.15 (1.00)	.90 (.90)
AD (SD)	-.30 (.88)	.45 (1.01)	.83 (.92)	.91 (.66)
SoA (SD)	-.26 (.89)	.39 (.93)	.83 (.73)	.75 (.52)
Anx (SD)	-.33 (1.00)	.51 (1.14)	1.29 (.81)	1.32 (.47)
Neu (SD)	-.40 (1.03)	.43 (1.16)	1.24 (.78)	1.03 (.81)
Ext (SD)	.14 (1.00)	-.26 (1.31)	.15 (1.19)	.12 (1.12)
SSS (SD)	.26 (.89)	.04 (.85)	.64 (1.10)	.26 (.46)
BDI (SD)	-.01 (.79)	.66 (.93)	.93 (1.02)	1.33 (.72)
AD (SD)	-.06 (.92)	.74 (1.01)	1.14 (.91)	1.38 (.81)
SoA (SD)	-.08 (.93)	.53 (.98)	.86 (1.01)	1.00 (.99)
Anx (SD)	-.17 (1.01)	.65 (.94)	.93 (1.02)	1.47 (.79)
Neu (SD)	-.17 (1.03)	.70 (.98)	.88 (.91)	1.31 (.81)
Ext (SD)	-.03 (.91)	-.28 (.94)	-.40 (.73)	-.42 (.92)
SSS (SD)	-.41 (.96)	-.28 (.93)	-.75 (.87)	-.47 (1.02)

BDI: Beck Depression Inventory,
SoA: Somatic Anxiety,
Neu: Neuroticism,
SSS: Sensation Seeking.

AD: anxious depression,
Anx: Anxiety,
Ext: Extraversion,

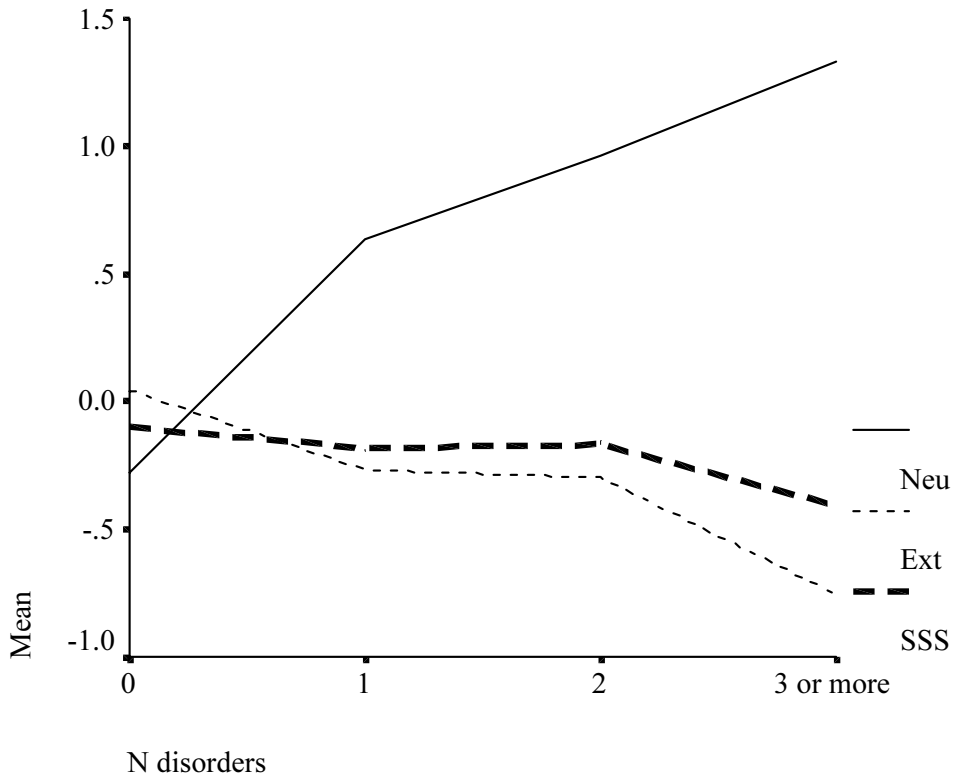


Figure 3.2: Relation between number of disorders and scores on neuroticism (Neu), extraversion (Ext) and sensation seeking (SSS).

Discussion

We have presented results from two studies, which aimed to explore whether Eysenck's model or the tripartite model best describes the relation of neuroticism and extraversion to depressive and anxious psychopathology. Both models hypothesize that anxiety and depression are related to high neuroticism. Eysenck theorized that depression and anxiety are both also related to low extraversion. The tripartite model, on the other hand, hypothesizes that depression, but not anxiety, is related to low positive affectivity, whereas anxiety is related to symptoms of autonomic hyperarousal. A second goal was to examine the relation of sensation seeking to anxious and depressive psychopathology. The analyses clearly showed that neuroticism is highly correlated with all measures of anxiety and depression. Low extraversion is also related to anxiety and depression, but to a lesser extent. Sensation seeking is not associated with anxiety and/or depression. In study I, subjects with a score above the 95th percentile on anxious depression and anxiety had

significantly higher sensation seeking scores than normal controls ($p < 0.05$). This may simply reflect a consequence of multiple testing. The results support Eysenck's theory that depressive and/or anxious subjects score high on neuroticism and low on extraversion as well as Zuckerman's hypothesis that sensation seeking, although weakly correlated with extraversion, is not related to anxiety and/or depression. These results thus suggest that the tripartite model can be rejected.

In all analyses co-morbidity between depression and anxiety was considered. In the first study, we used a cutoff score of the 95th percentile on the psychopathology questionnaires to divide subjects into groups consisting of normal controls, subjects with pure 'disorders' and subjects with co-morbid 'disorders'. Differences in personality measures with the normal controls were tested separately for all affected groups. In the second study, co-morbidity was controlled for by including all disorders in the model, when personality scores were compared between subjects with and without a disorder. Finally, the effect of co-morbidity was directly investigated by analyzing the association between personality and the number of disorders. All analyses showed very similar results, although in the first study the division between the groups of affected and unaffected is based on self-report questionnaires and not on clinical criteria. The STAI, for example, has been shown not to assess anxiety only, but also depression and general negative affectivity (Bieling et al., 1998; Kennedy et al., 2001). In our own sample, all four questionnaires (the BDI, the YASR, the STAI and the ABV subscale for somatic anxiety) do not seem to distinguish between disorders (Table 3.6). Furthermore, the ABV subscale for somatic anxiety and the STAI – trait version ask subjects to indicate how they generally feel and the YASR asks about the last 6 months. Therefore, it is questionable whether state is measured with these questionnaires. However, the results are remarkably the same as the results of study II. First, the relationship to the personality dimensions was the same for anxiety and depression measured either dimensionally or categorically. Second, neuroticism scores were higher and extraversion scores were lower when subjects suffered from more than one disorder.

Some results deserve further attention. In study II, dysthymia was the only disorder that was not associated with neuroticism although the neuroticism scores of subjects with dysthymia were comparable to those of the other groups diagnosed with a psychiatric disorder. This result might be a consequence of the low prevalence of dysthymia. Another explanation could be that the high neuroticism scores of subjects with dysthymia were due to co-morbid disorders, since most of them also had another diagnosis, mainly major depression. This appears in accordance with Klein & Santiago (2003) who argue that the distinction between dysthymia and chronic depression is not

meaningful. To our knowledge, there are no studies that have investigated the relation between neuroticism and dysthymia as a separate disorder while taking co-morbidity into account.

Another interesting point is that in the first analysis of study II low extraversion only seemed related to social phobia and panic/agoraphobia and not to the other disorders, whereas this did not appear to be the case in study I or in the second part of study II. This might be due to a lack of power, since the trend was clearly the same for all disorders (Table 3.6). However, in other studies that took co-morbidity into account, low extraversion did not appear to be associated with all disorders either. One of the studies found that low extraversion was related to social phobia and agoraphobia, but not to panic disorder and major depression (Bienvenu et al., 2001). Another study found that low extraversion was related to social phobia and major depression, but not to generalized anxiety disorder and panic disorder/agoraphobia (Brown et al., 1998). An explanation for these somewhat divergent findings could be that whereas neuroticism seems to be an independent risk factor, extraversion may interact with other risk factors, for example, life events. In other words, subjects who score high on extraversion may be less sensitive to the effect of life events or subjects with high extraversion may be less prone to adverse events that are associated with these disorders. For example, an extraverted, highly social individual may be at lower risk for a divorce. A recent study investigated the opposite of the latter hypothesis for sensation seeking, life events and depression (Farmer et al., 2001). They hypothesized that subjects with high levels of sensation seeking might be more at risk for adverse events, which are related to major depression because of their accident-prone behavior. This did not appear to be the case. However, this seems a promising direction of research. Interaction effects could lead to conflicting results as in the case of the relation with low extraversion. When the group of affected subjects includes a relatively high number of patients who have experienced adverse effects and get a disorder because they are also low in extraversion, a relationship between extraversion and the disorder will be found. When, on the opposite, the group of affected subjects consists mainly of highly neurotic patients who already have a high risk of developing a psychiatric disorder, the relationship may be missed. This might explain why in our study low extraversion did not seem to be associated with all of the disorders we examined, while extraversion scores were found to decrease with the number of disorders. Subjects with co-morbidity are probably more vulnerable to disorders, e.g. because of high neuroticism scores in combination with low extraversion scores, than subjects with a pure disorder.

The finding that sensation seeking is not related to anxiety and depression, but is weakly correlated to extraversion, is consistent with the view, which emerged after the development of the first version of the EPQ and the ABV, that impulsivity may reflect a third personality dimension independent of extraversion and neuroticism (Clark et al., 1994; Zuckerman, 1994).

Concerning the etiology of depression and anxiety, the linear relation between neuroticism and low extraversion on the one hand and the number of disorders on the other, links nicely to the hypothesis that anxiety and depression are polygenic disorders with a partly shared common genetic background (Gray & McNaughton, 2000; Jardine et al., 1984; Kendler et al., 1995; Kendler et al., 1993). The higher an individual's neuroticism score and perhaps the lower the person's score on extraversion, the more genes the individual probably has that increase the vulnerability for depression and/or anxiety. This might also explain part of the co-morbidity, as Bienvenu et al. (2001) has already suggested, because subjects scoring high on neuroticism and low on extraversion have an increased chance to have depression or an anxiety disorder and, as a consequence, have a higher chance to have both disorders as well.

In addition, in both studies, although this was not formally tested, the relation between the personality dimensions and anxious or depressive psychopathology appeared to be the same for men and women. This signifies that the higher prevalence rates for anxiety and depression in women are more likely to be explained by the higher neuroticism scores than by a different etiological background for anxiety and depression. This is confirmed by Goodwin & Gotlib (2004) who found that higher neuroticism scores in women might explain the gender difference in prevalence of major depression. The question of why women have higher neuroticism scores than men remains.

To conclude, high neuroticism and low extraversion are related to anxiety and depression, even when co-morbidity between these disorders is taken into account. Sensation seeking seems an independent personality dimension, which is not associated with anxious and depressive psychopathology.

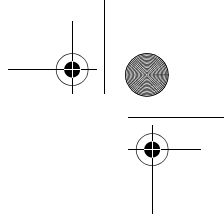
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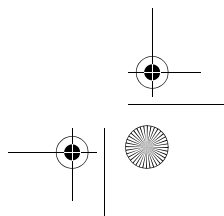
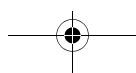
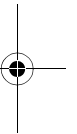
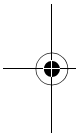
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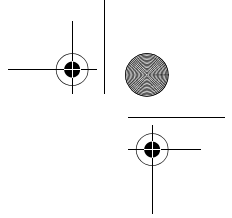


Chapter
3

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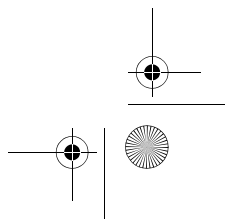
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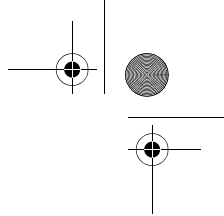
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Familial clustering of major depression and anxiety disorders in Australian and Dutch twins and siblings

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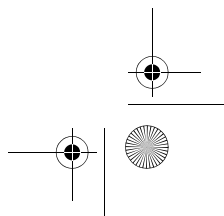
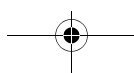
Middeldorp C.M., Birley A.J., Cath D.C., Gillespie N.A., Willemsen G., Statham D., De Geus E.J.C., Andrews J.G., Van Dyck R., Beem A.L., Sullivan P.F., Martin N.G., Boomsma D.I. (2005). Familial clustering of major depression and anxiety disorders in Australian and Dutch twins and siblings. *Twin Research and Human Genetics*, 8, 609-615.





Abstract

The aim of this study was to investigate familial influences and their dependence on sex for panic disorder and/or agoraphobia, social phobia, generalized anxiety disorder and major depression. Data from Australian (N=2287) and Dutch (N=1185) twins and siblings who were selected for a linkage study and participated in clinical interviews to obtain lifetime DSM-IV diagnoses were used. In a liability model, tetrachoric correlations were estimated in sibling pairs and sex differences between sibling correlations were tested. For each diagnosis, the sibling correlations could be constrained to be equal across the Australian and Dutch samples. With the exception of panic disorder and/or agoraphobia, all sibling correlations were the same for brother, sister and opposite-sex sibling pairs and were around 0.20. For panic disorder and/or agoraphobia, the correlation was 0.23 in brother and sister pairs, but absent in opposite-sex sibling pairs. From these results can be concluded that upper heritability estimates, based on twice the correlations in the sibling pairs, vary between 36% (major depression) and 50% (social phobia). Furthermore, different genetic risk factors appear to contribute to the vulnerability for panic disorder and/or agoraphobia in men and women. No other sex differences were found.



Introduction

Anxiety disorders and major depression (MDD) are common disorders. In epidemiological studies lifetime prevalences in women are found of around 30% for some kind of anxiety disorder and around 20% for MDD (Bijl et al., 1998; Kessler et al., 1994). Although these prevalences are lower in men, they are still high with figures ranging between 14%-19% for anxiety disorders and between 11%-13% for MDD (Bijl et al., 1998; Kessler et al., 1994). These prevalences may be even higher since cross-sectional surveys are biased by recall problems. When recall bias is considered, the prevalence of lifetime MDD is estimated at 30% in men and 40% in women (Kruijshaar et al., 2005). These disorders constitute a huge public health problem, mainly due to the chronic and disabling course, but, in the case of MDD, also as a result of the increase in risk for other major diseases, such as cardiac mortality (Musselman et al., 1998; Penninx et al., 2001),

Consequently, the etiology of these disorders is an important topic of research. Over the last 20 years, several family and twin studies have been performed to investigate the influence of familial factors on anxiety and depression. In the description of the results, we will focus on MDD, panic disorders and/or agoraphobia, social phobia and generalized anxiety disorder (GAD). Sullivan et al. (2000) and Hettema et al. (2001a) discussed the results of family and twin studies on lifetime diagnoses of MDD and anxiety disorders respectively and performed a meta-analysis when possible. They included studies in which the disorders were defined by operationalized diagnostic criteria, such as the DSM-III, III-R or IV (American Psychiatric Association, 1980; American Psychiatric Association, 1987; American Psychiatric Association, 1994). The family studies that compared the risk on MDD or anxiety disorders between first-degree relatives of probands and controls showed a significant familial risk with summary odds ratios for these disorders varying between 2.8 and 6.1 (Hettema et al., 2001a; Sullivan et al., 2000). However, in most family studies, data were collected in clinical samples, which might have biased the results. Twin studies are often population based. A meta-analysis of five twin studies performed in different continents showed that familial resemblance in MDD was entirely due to shared genes with genetic factors explaining 37% of the variance (Sullivan et al., 2000). For the anxiety disorders, meta-analyses could only be performed on panic disorder and GAD due to the scarcity of twin studies on this issue (Hettema et al., 2001a). Genetic factors appeared to explain 43% of the variance in panic disorder and 32% in GAD (Hettema et al., 2001a). These meta-analyses were based on two large community based twin samples only, which are both from the United States (Hettema et al., 2001a). The Virginia Twin Registry originally consisted of female twins, but has been extended with male twins and twins of opposite-sex (Kendler & Prescott, 1999). The Vietnam Era Twin Registry consists of male twins only (Scherrer et al.,

2000). In the Virginia Twin Registry, phobias were also investigated. It was found that, overall, familial resemblance was due to shared genetic influences, which explained 30% and 39% of the variance in women for social phobia and agoraphobia respectively and 20% and 37% of the variance in men (Kendler et al., 1992; Kendler et al., 2001c).

Sex differences in the influence of familial factors is an important issue when investigating specific risk factors, e.g. in linkage studies. In the absence of sex differences, for example, data from men and women can be analyzed simultaneously, which increases statistical power. The majority of the studies indicates that genetic effects influence variation in MDD in men and women to the same extent with most, but not all, genetic influences shared in men and women (Kendler et al., 2001a; Sullivan et al., 2000). Sex differences in the etiology of anxiety disorders have been studied in the Virginia Twin Registry only. No consistent differences in genetic architecture between men and women were found in GAD, social phobia and panic disorder (Hettema et al., 2001b; Hettema et al., 2005; Kendler et al., 2001b; Kendler et al., 2002; Kendler et al., 2003). In agoraphobia, results indicated that the genes conveying the risk are probably not entirely the same (Kendler et al., 2002).

This overview of the current literature shows that knowledge about familial influences on anxiety disorders and MDD and especially about sex differences in these influences is limited. In this paper, data on lifetime panic disorder and/or agoraphobia, social phobia, GAD and MDD, all defined according to DSM IV criteria, were analyzed in samples of male, female and opposite-sex dizygotic (DZ) twin and sibling pairs from the Australian and Netherlands population based Twin Registers. The participants were selected for a linkage study on anxiety and depression, based on scores on self-report measures. Since these scores were available for the total samples of twins and their siblings, a correction for ascertainment bias could be carried out (Little & Rubin, 1987).

Methods

Subjects

Data were collected in the Australian and Netherlands Twin Registers as part of a project aiming to find the genes underlying the susceptibility to anxiety and depression. For a detailed description of the data collection, see Kirk et al. (2000), Boomsma et al. (2000) and Middeldorp et al. (2006). In short, in 1998, the most informative families for a linkage study on anxiety and depression were selected. These were families with sibling pairs scoring extreme discordant (low-high) or concordant (high-high and low-low) on a quantitative scale that correlates with a diagnosis of MDD or an anxiety disorder (Dolan & Boomsma, 1998; Eaves & Meyer, 1994; Risch & Zhang, 1995). In Australia, the

selection variable was a normalized neuroticism score, adjusted for age and sex, obtained in 1989. This score was available for 18578 twins, siblings and adult offspring of twins (Kirk et al., 2000). In the Netherlands, the selection variable was a genetic factor score expressing a subject's genetic susceptibility to 'anxious depression'. These factor scores were calculated as a weighted sum of the scores on four measures of neuroticism, anxiety and depression assessed on three different occasions (1991, 1993 and 1997). The weights were derived from a multivariate genetic analysis on these four scales and were different for men and women. The calculation of the factor scores is described in detail by Boomsma et al. (2000). A factor score was available for 7836 Dutch twins and siblings (Middeldorp et al., 2006). In both Australia and the Netherlands, extreme discordant and concordant scoring sibling pairs were asked to participate in a diagnostic psychiatric interview. In addition, all other twins and siblings in these families, regardless of their value on the selection variable, were invited to take part in the study.

In the Australian and Netherlands Twin Register, 2918 and 1517 subjects respectively were approached to participate in the interview. In Australia, 256 subjects declined to participate and 192 subjects could not be contacted (Kirk et al., 2000). In the Netherlands, 154 subjects refused and 107 subjects could not be contacted (Middeldorp et al., 2005). Eventually, 2470 Australian and 1256 Dutch individuals were interviewed. Thus, a participation rate of around 90% was achieved in both samples.

Analyses were carried out on the data from DZ twins, siblings, and, in the Australian sample, adult children of twins, who have a score on the selection variable and at least one additional full sibling with a score on the selection variable. Half siblings, twin pairs with unknown zygosity, and subjects without additional siblings were excluded. Monozygotic twins were included if there was a sibling available with a score on the selection variable. This resulted in a total population for the analyses of 11291 Australian and 5836 Dutch subjects with scores on the selection variables of which 2287 Australian and 1185 Dutch subjects had participated in the interview.

Instruments

In Australia, neuroticism was measured using the revised short form of the EPQ-R with a 12-item neuroticism scale (Eysenck et al., 1985). In The Netherlands, genetic factor scores were calculated from the scores on the neuroticism and somatic anxiety scales of the Amsterdamse Biografische vragenslijst (Wilde, 1970), the Spielberger State Trait Anxiety Inventory - Trait version (STAI) (Spielberger et al., 1970; Van der Ploeg et al., 1979), the Beck Depression Inventory (BDI) (Beck et al., 1974) and the Young Adult Self Report (YASR) (Achenbach, 1990; Verhulst et al., 1997). The 30-item neuroticism scale is similar in content to the neuroticism scale of the Eysenck Personality Questionnaire (Eysenck & Eysenck, 1964).

In both samples, all offspring of selected families were asked to participate in a telephone interview, during which the computerized version of the Composite International Diagnostic Interview (CIDI) (World Health Organization, 1992) was administered to obtain lifetime DSM IV diagnoses of mood and anxiety disorders. The CIDI is a fully standardized diagnostic interview. No information on the reliability and validity of the Dutch version of the CIDI is available, but good reliability and validity have been reported for the English version of the CIDI (Andrews & Peters, 1998). All interviewers were trained by the Dutch and Australian World Health Organization training center. In order to minimize observer bias, interviewers were unaware of interviewees' scores on the initial selection variables throughout the study. According to the diagnostic algorithm as obtained with the CIDI, subjects can be classified in three categories: "not affected", "affected", "fulfilling the positive criteria, but not the exclusion criteria". The latter category consists of subjects with more than one anxiety disorder at the same time, subjects who exhibit symptoms of GAD exclusively during a depressive episode and subjects who fulfill the criteria for an anxiety disorder but did not seek help for their symptoms. Subjects in this category were classified as affected as well.

We analyzed diagnoses of MDD, GAD, social phobia, panic disorder with or without agoraphobia and agoraphobia without a history of panic disorder. Subjects with one of the latter three diagnoses were grouped together.

Statistical methods

The CIDI was administered in a selected sample, so a correction for ascertainment was applied by including the selection variables in the analyses (Little & Rubin, 1987). This correction assumes that in the total sample missing values are only due to the selection variables and to random factors (Little & Rubin, 1987). Therefore, for all diagnoses, a bivariate analysis was carried out including the scores of the selection variables of all participants and the information on the diagnosis of the selected sample.

The saturated bivariate model thus included neuroticism in the Australian sample, the genetic factor scores in the Dutch sample and one of the diagnoses under study in both the Australian and Dutch sample, i.e. MDD, GAD, social phobia or panic disorder and/or agoraphobia. The diagnoses are assessed on a dichotomous scale. The selection variables were analyzed as ordinal data by dividing the scores in four categories based on the 25th, 50th and 75th percentile. Thresholds for the selection variables and for the diagnosis were estimated separately for the Australian and Dutch sample and for men and women. Polychoric (cross) correlations for the selection variables and the diagnosis were calculated for DZ and sibling pairs of brothers, sisters and siblings of opposite-sex. The correlations for the selection variables and the cross correlations between the selection variables and the diagnosis were

estimated separately in the Australian and Dutch samples. For each diagnosis we explicitly tested whether the Dutch and Australian correlations between brothers, sisters and opposite-sex siblings were similar.

Sex differences in genetic influences on the diagnoses were analyzed in two ways. First, quantitative differences between men and women were investigated by testing whether the correlations were different in same-sex male and female sibling pairs. Second, qualitative differences were investigated. If the same genetic factors are of importance in men and women, the correlation of opposite-sex sibling pairs should not differ significantly from the product of the square roots of correlations in men and women. This formula can be derived from the tracing rules of path analysis (Neale & Cardon, 1992). After analyzing sex differences, the significance of the sibling correlations for the diagnosis was tested by fixing this correlation to zero. A significant correlation indicates that members of a sibling pair are more alike than would be expected by chance.

Statistical analyses were performed on raw data using the raw likelihood method implemented in the software programme Mx (Neale et al., 1999). To test whether correlations were significantly different between the groups of sibling pairs or from zero, the likelihood of the model in which all parameters were estimated, was compared to the likelihood of the model in which the parameters were constrained to be equal across different groups or to zero. The difference between $-2 * \log\text{likelihood}$ of two models is distributed asymptotically as χ^2 . The degrees of freedom for these tests are equal to the difference in parameters being estimated. Utilizing the principle of parsimony, the most restrictive model was accepted as the best fitting model if the difference between a nested and a more comprehensive model was not significant (Neale & Cardon, 1992). Analyses were carried out on all possible pairs (Hottenga et al., 2005).

Results

Table 4.1 shows the mean ages at the time of the interview and the frequencies of the diagnoses in men and women in the Australian and Dutch samples. The Australian subjects were significantly older than the Dutch participants. This age difference probably explains the higher frequencies of all diagnoses in the Australian sample. However, the difference in frequencies could also be partly explained by coincidental differences in the selection. In Australia, 43% of the interviewed subjects had an extreme neuroticism score, while in The Netherlands a smaller proportion of the interviewed subjects, namely 32%, had an extreme genetic factor score. Earlier analyses have shown that subjects with high scores on neuroticism (Australia) or on the questionnaires used to

calculate the genetic factor scores (The Netherlands) are more likely to get a diagnosis (Kirk et al., 2000; Middeldorp et al., 2006). In both countries, all disorders were more common in women than in men.

Table 4.1: Age and frequencies of lifetime MDD, panic disorder and/or agoraphobia, social phobia and GAD in the selected Australian and Dutch samples.

	Australia		The Netherlands	
	Men (N=885)	Women (N=1402)	Men (N=499)	Women (N=686)
Age at interview (sd)	41.8 (10.4)	42.4 (11.3)	28.5 (10.8)	28.6 (11.0)
MDD (%)	191 (21.6)	374 (26.7)	46 (9.3)	137 (20.0)
Panic disorder and/ or agoraphobia (%)	79 (8.9)	197 (14.1)	19 (3.8)	79 (11.5)
Social Phobia (%)	85 (9.6)	142 (10.2)	12 (2.4)	38 (5.5)
GAD (%)	71 (8.0)	140 (10.0)	18 (3.6)	52 (7.6)

Differences between twins and siblings were also investigated in both countries. Twins and siblings did not differ regarding their scores on the selection variables. Nor was the percentage of subjects who got a diagnosis different in twins and siblings. These results indicate that in both the Australian and Dutch samples the twin and sibling populations were equivalent to each other.

Table 4.2 shows for each diagnosis the differences in $-2 \times \log$ likelihood between the different models. For each diagnosis, the correlations could be constrained to be equal across the Australian and Dutch populations. Further analyses were therefore performed on the combined samples. First, the correlations were constrained to be equal across the male and female same-sex sibling pairs. Second, the correlation between the opposite-sex sibling pairs was constrained to be equal to the product of the square roots of correlations in the same sex pairs. Next, the correlations were fixed to zero. This last test had to be performed on one, two or three correlations, depending on the outcome of the first two steps in the model fitting procedure. Table 4.3 gives the estimates of the correlations and confidence intervals in the full bivariate model as well as in the best fitting model resulting from the model fitting procedure. For the sake of clarity, only the results for the diagnoses are shown and the results for the selection variables are left out of consideration.

Table 4.2: Tests of equality of correlations (r) between 1. Australia and The Netherlands, 2. brother-brother and sister-sister pairs, 3. same-sex and opposite-sex pairs and 4. for the overall significance of the correlations; the test-statistic is based on the difference in $-2 \times \log\text{likelihood}$ between nested models and is distributed as χ^2 with degrees of freedom (df) as shown.

	1. $r_{Aus} = r_{NL}$ ($\Delta df = 3$)	2. $r_M = r_F$ ($\Delta df = 1$)	3. $r_{OS} = r_{SS}$ ($\Delta df = 1$)	4. $r = 0$ ($\Delta df = 1$) ^a
MDD	2.60	.03	.61	24.32***
Panic Disorder and/or Agoraphobia	1.53	1.30	4.36*	10.04** / .92
Social Phobia	3.00	.01	2.70	18.07***
GAD	2.41	.79	1.01	11.37***

r_M : correlations in male twin pairs,

r_F : correlations in female twin pairs,

r_{OS} : correlations in opposite sex pairs,

r_{SS} : correlations in same sex pairs.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

^a For panic disorder and/or agoraphobia, the correlation between opposite-sex sibling pairs was not equal to the correlation in same-sex sibling pairs. Therefore, two correlations were tested, i.e. the correlation in same-sex sibling pairs (left χ^2 : significant) and the correlation in the opposite-sex sibling pairs (right χ^2 : not significant).

Table 4.3: Maximum-likelihood estimates of tetrachoric sibling correlations (and 95% Confidence Intervals) under the full and the best fitting model.

(N pairs total/N pairs selected)	Full Model			Best Fitting Model		
	Brothers (3134/497)	Sisters (5913/1007)	OS siblings (8145/1403)	Brothers	Sisters	OS siblings
MDD	.22 (.04-.39)	.20 (.08-.31)	.15 (.05-.25)	.18 (.11-.25)	.18 (.11-.25)	.18 (.11-.25)
Panic disorder and/or agoraphobia	.15 (-.14-.42)	.25 (.10-.39)	-.01 (-.18-.16)	.23 (.11-.36)	.23 (.11-.36)	0 (-.18-.16)
Social Phobia	.33 (.04-.63)	.34 (.17-.49)	.15 (-.02-.31)	.25 (.14-.35)	.25 (.14-.35)	.25 (.14-.35)
GAD	.15 (-.14-.40)	.14 (-.06-.33)	.26 (.10-.41)	.20 (.09-.31)	.20 (.09-.31)	.20 (.09-.31)

For MDD, social phobia and GAD, the correlations in the brothers, sisters and opposite-sex pairs could be constrained to be equal and the final correlations were significant with estimates around 0.20 (Table 4.2 and 4.3). In panic disorder and/or agoraphobia, the correlation between the opposite-sex pairs was significantly different from the correlation calculated in the same-sex

brother and sister pairs. The correlation in the brother and sister pairs was estimated at 0.23, whereas the correlation between the opposite-sex pairs could be fixed to zero.

Discussion

Chapter 4

The resemblances found in these combined analyses of Australian and Dutch twin and sibling data indicate significant familial risk for the development of MDD, panic disorder and/or agoraphobia, social phobia and GAD. No sex differences were found in the familial influences on MDD, social phobia and GAD. The results for panic disorder and/or agoraphobia indicate that familial factors contribute to a similar degree to the variance in liability in men and women, but the familial factors themselves are different between the sexes. Because monozygotic twins pairs were not selected for this study, it is, strictly speaking, not possible to decide whether the familial resemblance is due to genetic or common environmental factors and only upper limits for heritability estimates, based on twice the DZ/sibling pair correlations, can be given. These upper heritability estimates vary between 36% (major depression) and 50% (social phobia). However, earlier research in these samples indicates that twin resemblance for self-report measures of neuroticism, anxiety and depression is entirely explained by genetic factors (Boomsma et al., 2000; Jardine et al., 1984; Martin et al., 1988). This also accounts, in general, for twin studies on DSM anxiety disorders and MDD (Hettema et al., 2001a; Sullivan et al., 2000). Therefore, we think that it is reasonable to assume that our results also indicate genetic and not common environmental influences on MDD, panic disorder and/or agoraphobia, social phobia and GAD.

The upper heritability estimates are comparable to earlier studies (Hettema et al., 2001a; Sullivan et al., 2000). Regarding the sex differences, the results were somewhat different from the results of the Virginia Twin Registry. We did not find any sex specific genetic influences for MDD in contrast to Kendler et al. (2001a), who found that 50% of the genes that influence the vulnerability to MDD might be different in men and women. By controlling for unreliability of measurement their study probably had more power to detect sex differences. Furthermore, we found sex specific genetic risk factors for panic disorder and/or agoraphobia, whereas their analyses of panic syndromes showed no sex differences (Kendler et al., 2001b). However, their results for agoraphobia also suggested sex-specific genetic risk factors (Kendler et al., 2002). In the current study, subjects with panic disorder and/or agoraphobia were considered to be one group, containing over 50% of subjects with agoraphobia with or without panic disorder. This may have caused the differential outcomes.

This is the first non-clinical twin-family study outside the United States that investigates not only familial risk in anxiety disorders as defined according to the DSM IV but also the presence of sex differences in familial influences. The sample size is large due to the combination of the Australian and Dutch twin-family samples. Combining these samples was possible since the way in which the twins and siblings were recruited was similar. Moreover, differences between the correlations in the two samples were statistically tested and appeared to be absent.

Still, one might argue that the samples were not comparable since the Australian subjects were older than the Dutch participants. As a consequence, more Australian twins and siblings were diagnosed with one or more disorders. However, a recent study found that genetic and environmental determinants of anxiety and depression hardly show any change with age, so this age difference has probably not influenced our results (Gillespie et al., 2004). Another limitation is that test-retest data were not available for our samples, which made it impossible to estimate the reliability of the lifetime interviews. In studies in which unreliability of measurement was taken into account, heritability estimates were around 50% for phobias (Kendler et al., 1999) and 66% for MDD (Foley et al., 1998). These studies demonstrate that in our study the effect of familial influences might be underestimated. Finally, despite the large sample size, power to detect sex differences was relatively small as can be seen from the relatively broad confidence intervals (Table 4.3).

To summarize, in these two large family studies, performed in different continents, MDD, panic and/or agoraphobia, social phobia and GAD show sibling correlations around 0.20, suggesting that genetic factors explain approximately 40% of the variance. Panic and/or agoraphobia might be influenced by different familial factors in men and women. No sex differences were found for the other disorders. Overall, these results are in accordance with earlier studies. This means for future linkage and association studies that analyses on panic disorder and/or agoraphobia should be carried out in men and women separately. This does not appear to be necessary for MDD, social phobia and GAD in which the results suggest considerable overlap in genetic risk factors for men and women.

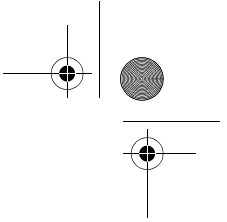
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 Familial clustering in anxiety and depression

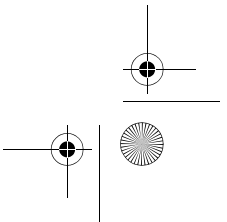
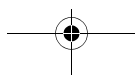
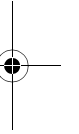
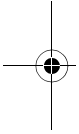
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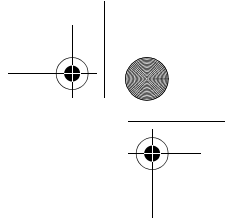
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Familial clustering in anxiety and depression

Chapter
4





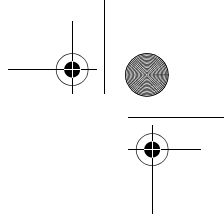
Chapter

5

Family based association analyses of the serotonin transporter gene polymorphism and neuroticism, anxiety or depression

This chapter is submitted as:

***Middeldorp C.M., De Geus E.J.C., Beem A.L., Lakenberg N., Hottenga J.J.,
Slagboom P.E., Boomsma D.I. Family based association analyses of the
serotonin transporter gene polymorphism and neuroticism, anxiety or
depression.***



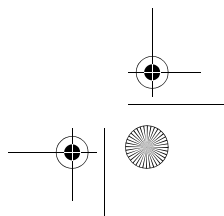
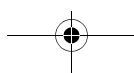
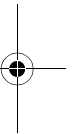
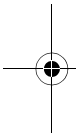
Abstract

Background Research on the association between the promoter-based length polymorphism of the serotonin transporter gene (5-HTTLPR) and neuroticism, anxiety or depression has shown conflicting results.

Methods 559 parents and 1245 offspring of 466 families were genotyped for 5-HTTLPR. These families were selected from the Netherlands Twin Register to include sibling pairs scoring extremely high or low on a composite score of neuroticism, anxiety and depression. The subjects had participated between one and five times in a survey study measuring neuroticism, anxiety or depression. Within family association and total association between 5-HTTLPR and these traits were tested in QTDT.

Results Only 3 of the 36 association tests showed a significant effect of 5-HTTLPR ($p < 0.05$). These effects were in opposite directions, i.e. both negative and positive regression coefficients were found for the s allele.

Conclusions There does not seem to be a straightforward association between 5-HTTLPR and neuroticism, anxiety or depression.



Introduction

In 1996, Lesch et al. (1996) reported an association between the promoter-based length polymorphism of the serotonin transporter gene (5-HTTLPR) and anxiety-related personality traits, such as neuroticism. Since then, the association between 5-HTTLPR and anxiety-related personality traits or depressive psychopathology has been investigated in numerous studies, but with conflicting results. Even meta-analyses on the association between 5-HTTLPR and personality traits (Munafo et al., 2003; Munafo et al., 2005a; Schinka et al., 2004; Sen et al., 2004) or affective disorders (Lasky-Su et al., 2005; Lotrich & Pollock, 2004) did not come to the same conclusions. This might be partly due to methodological differences (Munafo et al., 2005b; Schinka, 2005; Sen et al., 2005). Munafo et al. (2005b) therefore stated that "Very large, well designed primary studies remain the most reliable way of obtaining reproducible results".

Willis-Owen et al. (2005) performed an association study in a sample of selected subjects scoring high or low on neuroticism. Their sample retained 100% power to detect a genetic effect accounting for just 0.5% of phenotypic variance. They did not find any significant association between 5-HTTLPR and neuroticism measured with the Eysenck Personality Questionnaire (Eysenck & Eysenck, 1975) or major depression as defined by the DSM IV (American Psychiatric Association, 1994). However, population stratification was not considered in their analyses. Therefore, we present the results of family based association analyses of 5-HTTLPR and neuroticism, anxiety or depression in a large sample of siblings and their parents.

Methods

Subjects

In 466 families selected from the Netherlands Twin Register, 254 fathers, 305 mothers, 501 male and 744 female offspring, all aged between 16 and 65 years, were genotyped for

5-HTTLPR. All these subjects had participated at least once in a longitudinal survey study collecting information on personality and psychopathology roughly every two years. Most had participated more than once (Boomsma et al., 2000).

Families were selected which included sibling pairs scoring extremely discordant or concordant on a genetic factor score expressing a subject's genetic susceptibility to 'anxious depression'. The factor scores were calculated as a weighted sum of the scores on self-report measures of neuroticism, anxiety and depression assessed on three different occasions (1991, 1993 and

5-HTTLRP and anxiety-related traits

1997). The weights were derived from a multivariate genetic analysis on these four scales and were allowed to be different for men and women. In addition to the extreme scoring sibling pairs, all other family members were asked to provide DNA. The calculation of the factor scores and the composition of the sample is described in detail by Boomsma et al. (2000).

Instruments

In 1991, 1993, 1997, 2000 and 2002, anxiety was measured with the Spielberger State Trait Anxiety Inventory – Trait version (STAI) (Spielberger et al., 1970; Van der Ploeg et al., 1979) and neuroticism was measured with the Amsterdamse Biografische Vragenlijst (Wilde, 1970), which 30-item neuroticism scale is modelled after the neuroticism scale of the Eysenck Personality Questionnaire (Eysenck & Eysenck, 1964). In 1991, 1995, 1997, 2000 and 2002, anxious depression was measured with the Young Adult Self Report (YASR) (Achenbach, 1990; Verhulst et al., 1997). Correlations between the scores on these three scales varied from 0.60 to 0.75 (Middeldorp et al., 2006). Association analyses were carried out on the scores from each survey separately and on the mean neuroticism, anxiety and depression scores over all surveys in which each subject had participated.

Genotyping

The 5-HTT regulatory gene region was amplified using a polymerase chain reaction (PCR) of oligonucleotide primers 5'-GAGGGACTGAGCTGGACAACCCAC (Greenberg et al., 1999) and 5'-ATGCCAGCACCTAACCCCTAATGT (Gelernter et al., 1997). PCR was performed in a 40 µl volume containing 10 ng of genomic template, 0.33 mM of each primer, 0.4 mM deoxynucleotide triphosphates, 2.5% dimethyl sulfoxide (DMSO), 1.6 units of rTaq DNA polymerase (Amersham Biosciences). Initial denaturation at 94 °C for 3 min. was followed by denaturation at 94 °C for 30 s, annealing at 59 °C for 30 s, and extension at 72 °C for 1 min. 30 s for 35 cycles. The PCR procedure was terminated by extension at 72 °C for 6 min. Amplified 469/513 bp fragments were electrophoresed through 2% agarose and were visualized by ultraviolet illumination upon ethidium bromide staining.

Statistical methods

The association between the *ss*, *sl* and *ll* variants of 5-HTTLPR, and the traits were investigated, modeling an additive effect of the *s*-allele with sex included as a fixed effect. A sample consisting of subjects who are related to each other provides the opportunity to decompose the association into a between- and within-family association effect (Abecasis et al., 2000). While a significant between-family effect of a genotype might be due to population stratification, a

significant within-family effect indicates genuine association since family members are of the same background. Equal within- and between-family effects indicate the absence of population stratification (Abecasis et al., 2000). Then, a total association effect can be tested in a model without a separate within- and between-family effect. All these analyses were performed in QTDT (Abecasis et al., 2000).

Results

The null hypothesis of Hardy Weinberg Equilibrium was not rejected. Table 5.1 shows the mean neuroticism, anxiety and depression scores for each occasion and across the five occasions as well as the results of the tests for association and population stratification. Most association tests did not reach significance. Anxiety and neuroticism measured in 1991 were significantly associated with 5-HTTLPR with a negative within-family regression coefficient for the *s* allele. Population stratification seemed to counteract the effect, since the total association tests for anxiety and neuroticism measured in 1991 were not significant.

Depression measured in 1991 showed a trend in the same direction. The total association test was significant for neuroticism measured in 2000 and showed a trend for neuroticism measured in 2002, but the effect was in the opposite direction, i.e. the regression coefficient was positive for the *s* allele. The test for population stratification was significant for neuroticism in 2002, which might indicate a spurious association.

No significant results were found with the mean neuroticism, anxiety and depression scores over the five occasions, neither for the within family association tests nor for the total association tests.

Discussion

The general picture emerging from these analyses clearly suggests no association between 5-HTTLPR and neuroticism, anxiety or depression. These results support the conclusion of Willis-Owen et al. (2005) that the 5-HTTLPR variant does not contribute significantly to neuroticism, anxiety or depression and exclude the possibility that their results were due to population stratification.

These analyses also show how associations can be found by coincidence. Had we chosen to report exclusively on the results of the 1991 survey, we would have drawn the conclusion that a significant association between 5HTTLPR and anxiety-related traits is present, although the effect was in the other direction than expected.

5-HTTLRP and anxiety-related traits

Table 5.1: Association tests between the three variants of the serotonin transporter gene (*ss*, *sl* and *ll*) and neuroticism (*neu*), anxiety (*anx*) or depression (*dep*). Phenotypes were measured on five different occasions (first 15 rows). The last 3 rows give results for mean scores over these five occasions. *P*-values below 0.10 are shown.

	N	Mean scores (SD) per genotype			Total association	Within family association	Population stratification
		<i>ss</i>	<i>sl</i>	<i>ll</i>			
Neu 1991	680	19.4 (2.6)	19.2 (2.5)	19.3 (2.6)	ns	0.001	0.001
Neu 1993	986	18.4 (2.9)	18.6 (2.9)	18.4 (3.1)	ns	ns	ns
Neu 1997	1019	18.5 (3.1)	18.4 (3.1)	18.3 (3.0)	ns	ns	ns
Neu 2000	833	18.6 (3.0)	18.5 (3.0)	17.8 (3.2)	0.02	ns	ns
Neu 2002	1160	18.7 (2.8)	18.4 (2.9)	18.1 (3.1)	0.06	ns	0.02
Anx 1991	683	34.9 (2.6)	34.9 (2.5)	35.1 (2.8)	ns	0.01	0.02
Anx 1993	985	34.5 (2.7)	34.9 (2.7)	34.5 (2.9)	ns	ns	ns
Anx 1997	1019	34.4 (2.9)	34.6 (3.0)	34.3 (2.9)	ns	ns	ns
Anx 2000	856	34.8 (2.8)	34.7 (2.8)	34.4 (2.9)	ns	ns	ns
Anx 2002	1182	35.0 (2.5)	34.8 (2.7)	34.6 (2.6)	ns	ns	ns
Dep 1991	332	18.3 (10.0)	20.7 (9.4)	20.0 (10.7)	ns	0.09	ns
Dep 1993	521	17.0 (11.0)	18.2 (11.1)	18.5 (10.6)	ns	ns	ns
Dep 1995	1024	18.4 (10.7)	19.3 (10.6)	18.8 (10.6)	ns	ns	ns
Dep 2000	852	20.7 (10.0)	20.6 (10.4)	19.7 (10.4)	ns	ns	ns
Dep 2002	1171	20.8 (10.8)	20.4 (10.4)	20.0 (10.6)	ns	ns	0.097
Mean neu	1558	18.7 (2.7)	18.6 (2.7)	18.5 (2.7)	ns	ns	ns
Mean anx	1721	34.7 (2.4)	34.9 (2.5)	34.7 (2.5)	ns	ns	0.06
Mean dep	1717	19.8 (9.6)	20.0 (9.6)	20.0 (9.4)	ns	ns	ns

ns: non significant

Therefore, not only different phenotypes should be measured, as suggested by Munafo et al. (2005b), but they should also be measured repeatedly.

Moreover, if measurements at different occasions are available, mean scores should be analyzed. This is illustrated by our results on neuroticism. Two out of the five total association tests were (nearly) significant with the effect in the expected direction. However, the total association test with the mean score over the five occasions did not show significance. The latter test had more power because of the high number of subjects and the reduction of measurement error.

The analyses in our and Willis-Owen et al. (2005) study were performed in a sample of subjects selected for their high or low neuroticism scores. It is possible that extremely low or high levels of neuroticism might be due to risk factors different from those that operate in the middle of the distribution (Sirota et al., 1999). However, in our sample, all family members of extreme scoring sibling pairs were included. This led, for example, in 2002, to a sample with 44%, 47% and 43% of the subjects scoring between the 25th and 75th percentile of the neuroticism, anxiety and depression scores respectively. Thus, although in our sample the scores were slightly kurtose, more than 40% of our subjects did not score extremely high or low.

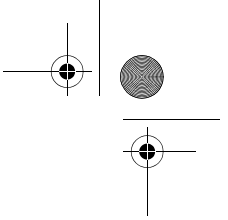
To summarize, there does not seem to be a straightforward association between 5-HTTLPR and neuroticism, anxiety or depression, even in a large sample with three different phenotypes measured at five occasions.

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5-HTTLRP and anxiety-related traits

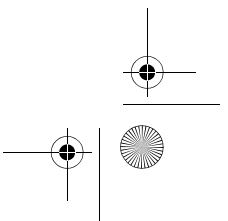
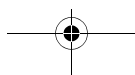
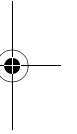
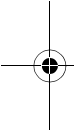
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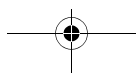
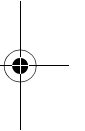
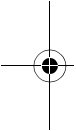


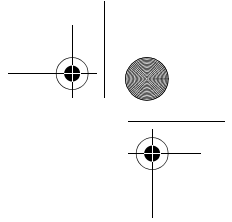
Part

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Life Events







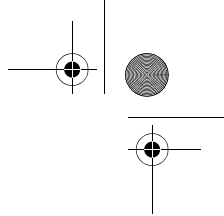
Chapter

6

Familial clustering in burnout. A twin-family study.

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Abstract

Background. Research on risk factors for burnout has mainly focused on circumstances at work and on personal characteristics. The aim of this study was to investigate whether burnout clusters within families and, if yes, whether this is due to genetic influences or to environmental factors shared by family members. Finally, we tried to identify specific risk factors for burnout.

Methods. In 2707 twins, 736 of their siblings and 575 of their spouses from a population based twin-family sample, burnout was measured using a self-report questionnaire. Correlations in burnout scores were obtained for monozygotic and dizygotic twin pairs and sibling pairs conditional on pairs' sex. Correlations for twins and their spouses were derived conditional on the length of the relationship.

Results. In the final model, correlations of the monozygotic and dizygotic twin pairs and sibling pairs were significantly different from zero, but not significantly different from each other. The correlation was estimated at 0.22. The correlation between spouses was also significant. This was mainly due to the group with a relationship longer than 5 years in which the correlation was 0.24. Burnout scores were higher in subjects whose parents had a high level of education.

Conclusions. There is familial clustering for burnout due to environmental factors shared by family members, explaining 22% of the variance. Genetic factors do not seem to be of importance. The significant correlation between spouses supports the conclusion that common environment plays a role in burnout. A high parental education is one of the familial risk factors.

Introduction

Burnout encompasses a work related syndrome, which is defined by three dimensions: an overwhelming exhaustion, feelings of cynicism and detachment from the job, and a sense of ineffectiveness and lack of accomplishment at work (Maslach et al., 2001). Emotional exhaustion is regarded to be the key dimension of the syndrome, and refers to feelings of being overextended and depleted of one's emotional and physical resources (Maslach et al., 2001). There has been considerable debate whether burnout is a distinct entity from depression. However, most research indicates that depression and burnout are not identical, although their symptoms are positively related (Leiter & Durup, 1994; Glass & Mcknight 1996; Brenninkmeyer et al., 2001). Burnout is a common problem. A study performed in the Dutch general population revealed, for example, that ten percent of the people participating in labour had symptoms of burnout (CBS 1997).

Research on risk factors (for a review see Schaufeli & Enzmann, 1998) indicated that several job characteristics, such as experienced workload and time pressure, role conflict and role ambiguity, lack of social support at work, lack of feedback, little participation in decision-making and lack of autonomy, are related to burnout. Furthermore, some personality characteristics are linked to burnout, e.g. high levels of neuroticism, an avoidant coping style and high levels of type A behavior (competition, time-pressured lifestyle, hostility, and an excessive need for control). Age has also been consistently related to burnout. Among younger employees the level of burnout is reported to be higher than among those over 30 or 40 years of age. This could be a result of survival bias i.e. those who burn out early in their careers are likely to quit their jobs, leaving behind the survivors who consequently exhibit lower levels of burnout. Data on the effect of gender are contradictory. Some studies show that burnout occurs more often in women than in men, some show the opposite and others find no overall differences. Most research suggests that characteristics of the work environment, particularly job stressors such as workload, work pressure etc. are more strongly related to burnout than are personality and demographic factors (Lee & Ashforth, 1996; Schaufeli & Enzmann, 1998). This is confirmed in a recent study among Dutch medical specialists, which revealed that the organizational factors are more important in managing stress than the personal factors (Visser et al., 2003).

So far, to our knowledge, no studies have investigated whether burnout clusters in families. In general, familial clustering can be due to shared genetic or common environmental factors. When familial clustering is absent, unique environmental factors are primarily important. Twin-family studies provide a good method to estimate the influence of genes, common environment and unique environment on individual differences in behavioral and other traits (Boomsma et al., 2002a). These studies make use of the fact that monozygotic

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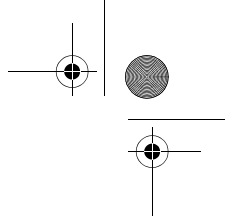
(MZ) twin pairs share all (or nearly all) their genes whereas dizygotic (DZ) twin pairs share on average half of their segregating genes. Consequently, if MZ twin pairs are more similar for a trait than DZ twin pairs, this suggests that genetic factors influence this trait. If, on the other hand, MZ twin pairs and DZ twin pairs show the same amount of similarity, then common environmental factors, shared by family members, probably play a role. The differences within MZ twin pairs are explained by unique environmental factors. Siblings, like DZ twin pairs, share on average half of their segregating genes. But twins and siblings may differ in the amount of environment they share. For example, prenatal conditions are different for singletons than for twins and twins grow up together with someone of their own age. Consequently, DZ twin pairs are the perfect controls for MZ twin pairs. Additional information on the similarity between siblings increases the power of a study to detect effects of common environment (Posthuma & Boomsma, 2000). Finally, by including the spouses of twins in the sample, assortative mating can be studied. Similarities between spouses can develop during the relationship. Then, it is a consequence of shared environment. It is also possible that similarities already existed at the beginning of the relationship. Then, spouses might have chosen each other based on phenotypic similarity.

No twin or family studies have investigated whether burnout clusters in families, but there is a wealth of twin studies on related conditions and traits. Job satisfaction, which shares 20% of its variance with burnout (Schaufeli & Enzmann, 1998), has been studied in both US twins reared apart and US twins reared together (Arvey et al., 1989; Arvey et al., 1994). Job satisfaction clusters in families, but unique environmental factors explain most of the variance (around 70%). Familial clustering in job satisfaction is a result of genetic factors only.

Chronic fatigue is comparable with the dimension of emotional exhaustion in burnout, but does not require that it is work related. Twin studies on symptoms of fatigue have shown that familial clustering is present, but unique environmental factors play a significant role too, explaining between 50% and 80% of the variance (Hickie et al., 1999a; Hickie et al., 1999b; Buchwald et al., 2001; Hickie et al., 2001; Sullivan et al., 2003). Regarding causes for familial clustering, results differ between studies. Results of the volunteer Australian Twin Registry have indicated that familial clustering for fatigue is due to genetic factors only (Hickie et al., 1999a; Hickie et al., 1999b; Hickie et al., 2001), whereas in a US sample of twins partly recruited from patients support groups, both genetic and family environmental factors are causes for familial clustering (Buchwald et al., 2001). Finally, in a community sample of US twins (the Mid-Atlantic Twin Registry, formerly known as the Virginia Twin Registry) familial clustering was a result of common environmental factors in males, while in females genetic factors explained familial clustering (Sullivan et al., 2003).

With respect to personality characteristics related to burnout, the influences of genetic and environmental factors have been studied extensively, especially for neuroticism. Reviews of several population based twin studies (Eaves et al., 1989; Sherman et al., 1997; Lake et al., 2000) have concluded that familial clustering is present in neuroticism as a result of genetic factors only. Neuroticism is further influenced by unique environmental factors. The same seems to account for type A behavior, although this trait has been studied less extensively (Pedersen et al., 1989; Sims et al., 1991; Duffy et al., 1994; Sluyter et al., 2000). Regarding avoidant coping style, results are less straightforward. One twin study assessed coping with 14 items chosen from the Ways of Coping checklist. In a factor analysis, four of these 14 items were found to load on a factor called 'denial'. Twin resemblance for this factor was fully explained by common environmental factors (Kendler et al., 1991). In another twin study no such factor appeared from the factor analysis (Busjahn et al., 1999). The results of the analysis of the individual items of the questionnaire were published as well. Items comparable with the items loading on 'denial' in the paper of Kendler et al., (1999) were "Play down", "Distraction from situation", "Avoidance" and "Flight tendency". Twin resemblance for "Play down" and "Flight tendency" was explained by genetic factors, for "Distraction from situation" by common environmental factors and for "Avoidance" by both genetic and common environmental factors (Busjahn et al., 1999). Again, unique environmental factors were also found to be important in avoidant coping style, explaining 50% to 90% of the variance (Kendler et al., 1991; Busjahn et al., 1999).

The aim of the current study was to investigate in males and females whether familial clustering is present in burnout and, if so, whether this is due to genetic or common environmental factors. The results of the twin studies on job satisfaction, chronic fatigue and on the personality characteristics related to burnout lead to the expectation that burnout will cluster in families mainly as a result of genetic factors. However, since studies on the risk factors for burnout have found that work characteristics are more important than personal factors, unique environmental factors will probably explain most of the variance. A self-report questionnaire on burnout was used that was completed by MZ twins, DZ twins, their siblings and their spouses. Correlations for the burnout scores were calculated between MZ twin pairs, DZ twin pairs, sibling pairs and between twins and their spouses. As pointed out above, by comparing these correlations between the different groups the proportion of influence of genetic, common environmental and unique environmental factors can be estimated for males and females. To investigate whether assortative mating is important, correlations were calculated for three groups of twins and their spouses conditional on the length of the relationship. Finally, taking into account the results of these analyses, we tried to identify specific risk factors for burnout.



Methods

Subjects

This study is part of a longitudinal questionnaire study of the Netherlands Twin Register (NTR) that has assessed families with adolescent and young adult twins roughly every two years since 1991. Sample selection and response rates are described in detail in Boomsma et al. (2002b). For this paper, data were used from the survey in 2000, which included several items assessing burnout. Twins and their siblings were requested to complete the survey. Spouses of twins aged between 25 years and 30 years were also asked to participate. Mean duration of the relationship of twins and spouses was 6.5 years with a maximum of 16 years. The survey was completed by 6701 subjects (excluding half sibs, adoptive sibs and triplets). In the majority of the twin pairs zygosity was determined from questions about physical similarity and confusion of the twins by family members, friends and strangers. On 804 same sex twin pairs information on their zygosity was available from DNA polymorphisms. The agreement between zygosity diagnoses from questionnaire and DNA data was 98%.

Since burnout is a work related syndrome, subjects younger than 18 years or older than 65 years of age as well as subjects who were unemployed at the time they completed the questionnaire, were excluded from the study. Table 6.1 summarizes the number of subjects per inclusion criterium. It can be seen that from the population between 18 and 65 years of age, around 70% of the subjects were employed. This percentage was higher than in the general population (CBS, 1997), probably because this was a relatively young sample. In the group of people participating in labour, more men work full-time and more women work part-time. This is comparable with the general population (CBS, 1997). Of the working people, 290 subjects were excluded, because they did not complete all questions about burnout. One sibling per family was included, i.e. the sibling who was closest in age to the twin pair. This led to the exclusion of 202 siblings. Finally, 4018 subjects from 2328 families were included in the analysis.

Table 6.1: Numbers of subjects per inclusion criterium.

	Male twins	Female twins	Male sibs	Female sibs	Male spouses	Female spouses
Total Population	1502	3046	585	863	442	263
All subjects between 18yrs – 65yrs	1403	2869	531	816	431	259
All employed subjects (% full-time / % part-time)*	1008 (92/8)	1861 (58/42)	424 (95/5)	558 (51/49)	406 (95/5)	198 (70/30)
All burnout questions completed	950	1757	408	530	392	183

*Full-time is defined as working more than 32 hours per week.

Questionnaire

Burnout was measured by a Dutch version of the emotional exhaustion subscale of the Maslach Burnout Inventory – General Survey (Schaufeli et al., 1996). This questionnaire was chosen, because it was also used in the study in the Dutch general population (CBS, 1997). The subscale consists of five items with an answer range between 1-7 (never, a few times a year, monthly, a few times a month, every week, a few times a week, every day). The 5 items can be summarized as 1) emotionally exhausted because of work, 2) feeling empty after work, 3) feeling tired in the morning when confronted with work, 4) completely exhausted because of work, and 5) feeling worn out. Cronbach's alpha was 0.87 in our sample. The total score of the five items was used for the analysis. The scores were not normally distributed (skewness 2.0, kurtosis 4.4). Therefore, correlations were calculated for the logtransformed total burnout scores. This led to an improvement of the skewness and kurtosis to 0.8 and 0.1 respectively.

Statistical methods

Statistical analyses were performed with the software program Mx, modeling the dependency that exists between measures of pairs of relatives (Neale et al., 1999). Families may have different numbers of observations within the family, e.g. families with one participating twin and one sibling, families with two participating twins without sibling. To use all data, analyses were performed on raw data using the raw likelihood method. To test whether means and correlations were significantly different between the groups of male and female twins, siblings and spouses, the likelihood of the model in which all parameters were estimated was compared to the likelihood of the model in which the parameters were constrained to be equal in different groups. Twice the difference between the log-likelihood of two models is distributed asymptotically as χ^2 . The degrees of freedom for these tests are equal to the difference in parameters being estimated. Utilizing the principle of parsimony,

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the most restrictive model was accepted as the best fitting one in case the difference between a nested and a more comprehensive model was not significant (Neale & Cardon, 1992).

To investigate assortative mating, the total group of twins and their spouses was divided in three groups according to the length of the relationship: shorter than five years, between five and 10 years and more than 10 years. Correlations between burnout scores of spouses were calculated for the separate groups.

Results

Table 6.2 shows the average ages and total burnout scores in male and female twins, siblings and spouses. Total burnout scores were not significantly different between the groups. Keeping in mind that the total burnout score ranges from 7-35 it is obvious that most subjects scored low. Scores were comparable with Dutch general population based data (CBS, 1997).

Table 6.2: Average age and total burnout score.

	N	Age (SD)	Total burnout score (SD)
Male twins	950	31.0 (9.2)	9.5 (5.1)
Female twins	1757	30.5 (8.6)	9.7 (5.6)
Brothers	318	32.6 (8.9)	9.7 (5.6)
Sisters	418	31.4 (7.8)	9.6 (5.0)
Male spouses	392	30.8 (4.0)	9.3 (4.6)
Female spouses	183	27.2 (3.8)	10.0 (5.3)

Table 6.3 shows the correlations and 95% confidence intervals for the full model, in which all correlations are estimated without constraints, and for the final model for all twin and sibling pairs: monozygotic male twin pairs (MZM), dizygotic male twin pairs (DZM), monozygotic female twin pairs (MZF), dizygotic female twin pairs (DZF), dizygotic twin pairs of opposite sex (DOS), brothers (SibMM), sisters (SibFF), siblings of opposite sex (SibOS). All these correlations could be constrained to be equal. Table 6.4 shows the statistics of this procedure. The significant correlation indicates that familial clustering is present. Since the correlations between MZ and DZ twin pairs were not significantly different, familial clustering is due to common environmental factors only, explaining 22% of the variance. Unique environmental factors explain the remaining part of the variance, thus 78%.

Table 6.3: Number of family members and correlations between twin pairs and sibling pairs.

	MZM	DZM	MZF	DZF	DOS	SibMM*	SibFF*	SibOS*	
N individuals in pairs	260	124	568	264	282	156/ 104	216/ 240	332/ 272	
N twins or siblings from incomplete pairs**	159	127	327	260	336	70	125	101	
Correlations estimated in full model	0.37	0.41	0.26	0.21	0.12	0.16	0.20	0.12	
CI's for full model	lower values	0.20	0.13	0.16	0.02	-0.08	-0.07	0.05	-0.03
	upper values	0.50	0.59	0.36	0.38	0.30	0.35	0.34	0.25
Correlations in constrained model	0.22	0.22	0.22	0.22	0.22	0.22	0.22	0.22	

MZM: Monozygotic Males, DZM: Dizygotic Males,
 MZF: Monozygotic Females, DZF: Dizygotic Females,
 DOS: Dizygotic twins of Opposite Sex, SibMM: Brothers,
 SibFF: Sisters, SibOS: Sibs of Opposite Sex, CI: 95% confidence interval

* Two numbers are given for the N individuals in pairs, because siblings can form two pairs: a sib with twin 1 and a sib with twin 2.

** Incomplete pairs arise due to 1) subjects who did not participate in the survey 2) subjects who did not complete the burnout questionnaire, (e.g. because they were unemployed).

Table 6.4: Likelihood of the different models for the twin and sibling pairs.

	-2loglikelihood	Δdf	χ ²	p
1. Full model	30236.945			
2. rMZM=rDZM	30237.016	1	0.071	ns
3. rMZM=rDZM=rSibMM	30240.439	1	3.423	ns
4. rMZF=rDZF	30240.691	1	0.252	ns
5. rMZF=rDZF=rSibFF	30241.055	1	0.364	ns
6. rMZM=rDZM=rSibMM =rMZF=rDZF=rSibFF	30241.934	1	0.879	ns
7. rSame sex Twins and sibs =rDOS=rSibOS	30246.336	2	4.402	ns

MZM: Monozygotic Males, DZM: Dizygotic Males,
 MZF: Monozygotic Females, DZF: Dizygotic Females,
 DOS: Dizygotic twins of Opposite Sex, SibMM: Brothers,
 SibFF: Sisters, SibOS: Sibs of Opposite Sex, r: correlation.

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Table 6.5 shows the correlations between twins and their spouses for the total population and after division in three groups conditional on the length of relationship: shorter than 5 years, between 5 and 10 years and more than 10 years (maximum duration is 16 years). The correlation in the total group was significantly different from zero. The analysis of the three groups revealed that this significant correlation is due to the pairs of spouses with a relationship over 5 years since the correlation of the pairs with a relationship shorter than 5 years could be constrained to zero ($\chi^2=1.427$ with 1 degree of freedom). The correlations of the other two groups were significantly different from zero ($\chi^2=17.396$ with 2 degrees of freedom). They could be constrained to be equal ($\chi^2=0.330$ with 1 degree of freedom). This again suggests an influence of common environment.

Table 6.5: Spouse correlations.

		Total	Length of relation 0-5 yrs	Length of relation 5-10 yrs	Length of relation 10-16 yrs
N individuals in pairs*		956	330	408	200
N spouses from incomplete pairs		97	29	35	27
Full model		0.18	0.09	0.22	0.29
CI's for full model	Lower values	0.09	-0.06	0.09	0.08
	Upper values	0.26	0.24	0.34	0.46
Best fitting model		0.18	0	0.24	0.24

*The length of the relation was unknown in 18 individuals.

To make sure that the influence of common environment was not an effect of twins and siblings having (nearly) the same age, a linear regression analysis was performed with age and total burnout score. Only in females, there was a significant negative relation ($p < 0.001$), but this explained just 0.7% of the variance. Consequently, age cannot be responsible for the total influence of the common environment, which explains 22% of the variance. However, it is interesting that this apparent age effect is probably due to the fact that women who work part-time are, on average, older and have lower burnout scores (Table 6.6). In males this effect is absent, since only a minority of them works part-time whatever their age is.

Table 6.6: Age and Burnout scores for males and females working full-time or part-time.

	Males			Females		
	N*	Age	Burnout score	N*	Age	Burnout score
Employment > 32 hours per week	1495	31.2	9.5	1308	28.0	10.3
Employment between 12 and 32 hours per week	90	30.9	9.7	842	33.2	9.2
Employment < 12 hours	17	25.2	6.8	111	34.9	7.3

*Working hours were unknown for 58 males and 97 females.

To identify specific risk factors for burnout, a univariate analysis of variance was performed with items of the questionnaire from the year 2000 that assessed environmental factors shared by family members, i.e. religious upbringing and education of the parents. Burnout scores were significantly higher in subjects with a highly educated father or mother ($p < 0.001$ for both items). No differences were found in burnout scores between subjects with or without a religious upbringing ($p = 0.11$).

Discussion

The results indicate that familial clustering is present in burnout. This is due to common environmental factors, since the correlations of all pairs of relatives are significant and equal. Furthermore, it is apparent that unique environmental factors are most important in the symptoms of burnout, explaining 78% of the variance. These results are the same for males and females. The significant spouse correlation supports the finding that common environment is of importance in burnout; especially since the partner correlation tends to increase with the length of the relationship. Age cannot account for the effect of common environment. A possible common environmental risk factor is a high level of education of the parents.

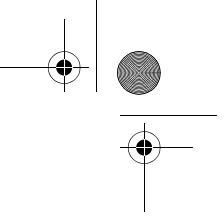
A limitation of this study and of all other studies on symptoms of burnout is that subjects need to be working to complete the questionnaire. This means that if subjects do not work any more, because they suffer from burnout, they are not included in the study. In our sample with regard to the males this does not seem to be a problem (Table 6.1). The majority works full-time and most subjects who do not work are students. With respect to the women, a survival bias might have influenced our results. Around forty percent is working part-time or engaged in housekeeping. Possibly these women choose not to work

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full-time because of symptoms of burnout. However, the results of a study on non-response bias in the same population of twins and siblings suggested that the data collected on health, personality and lifestyle are relatively unbiased (Vink et al., 2005). The analyses in this study were based on the idea that when the variable of interest has a familial component, data from respondents can be used as proxy for the data from their non-responding family members. Therefore, mean burnout scores of participants from families with a high response rate (more than 80% of the family members participated) were compared with mean burnout scores of participants from families with a low response rate (less than 80% of the family members participated). No significant difference in burnout scores was found.

It is consistent with earlier studies, which have found that work characteristics are more related to burnout than personal factors, that unique environmental factors are most important. It follows that circumstances at work should stay a focus of research. However, caution is needed in defining a risk factor as part of the unique environment. Work values, for example, are partly influenced by genetic factors (Arvey et al., 1994). This signifies that the organization in which a subject is employed cannot be considered as a pure environmental factor. This problem can be tackled through comparing levels of burnout of MZ twins who work in different environments. Based on earlier results of twin studies on job satisfaction, chronic fatigue and personality characteristics related to burnout, we predicted that burnout would cluster in families mainly as a result of genetic factors. Hence, it was rather unexpected that familial clustering in burnout is due to common environmental factors and not to genetic factors, particularly because a recent published review (Bouchard & McGue, 2003) shows that most lifestyle and personality traits cluster in families because of genetic factors. However, all results of this study support the conclusion that common environmental factors are important in burnout. Two complementary explanations could be offered for these seemingly divergent findings. Overlapping unique environmental factors could underlie the relationship between burnout and the other traits, since unique environmental factors explain half or more of the variance in all these traits. To a lesser extent, this could also be the case for common environmental factors, since familial clustering in both an avoidant coping style and in fatigue has been found to be (partly) due to common environmental factors. Another explanation for the apparent absence of genetic influence on symptoms of burnout could be gene-unique environment interaction. In twin studies the effect of an interaction between genes and unique environment cannot be distinguished from the effect of unique environmental factors alone, since both will lead to differences between MZ twins. There is some support for the hypothesis that gene-environment interaction influences burnout. Burnout scores are more strongly influenced by job stressors in individuals who score high on negative affectivity, a symptom highly comparable with neuroticism, than in individuals who score



low on negative affectivity (Houkes et al., 2003). This signifies that a trait, which is partly influenced by genetic factors, interacts with job stressors, which are possibly unique environmental factors. Although speculative, it can be hypothesized that this might be a result of an interaction between genes leading to negative affectivity and unique environmental factors leading to burnout.

Common environmental factors within the family have rarely been a focus of research on risk factors for burnout. There are a few articles on the effect of family environment on work attitudes. Barling et al. (1998) have investigated the effects of parents' job insecurity on work beliefs and attitudes of male and female undergraduate students. In the best fitting model children who watch their parents experiencing layoffs and insecurity perceive this insecurity and develop negative work beliefs that predict their work-related attitudes (Barling et al., 1998). Loughlin & Barling (2001) describe how contemporary young workers in the US might be influenced by having seen their parents and others around them being 'rightsized' or 'downsized' or otherwise dismissed from their jobs during the 1980s and 1990s. They hypothesize that this new cohort of young workers are less willing to make sacrifices for the sake of their jobs (Loughlin & Barling, 2001). Since our study suggests that familial circumstances, for example high level of education of the parents, can lead to vulnerability for burnout, future research should pay more attention to the influence of the work characteristics and attitudes of the parents (e.g. profession, level of ambition, experiences of dismissal etc.).

The influence of the environment shared by spouses on functioning at work has been studied much more, but is still not well understood (Grzywacz & Marks, 2000). Grzywacz & Marks (2000) found that spouse disagreement, other family criticism/burden and spousal affective support are related with subjective functioning at work. No studies have investigated the effect of having a partner with symptoms of burnout. Regarding the significant correlation in burnout scores between spouses, it might be useful to study couples to find out which circumstances make both of them vulnerable for burnout, e.g. dual earner families with children, care giving needs of parents or having a partner with symptoms of burnout.

To summarize, our major result is that burnout clusters in families as a result of environmental factors shared by family members. This should be a focus of future research.

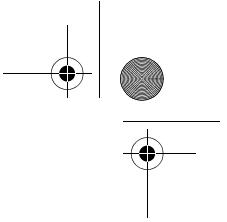
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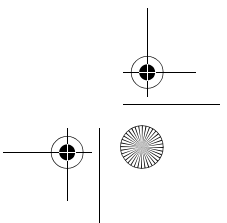
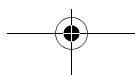
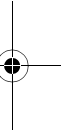
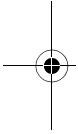
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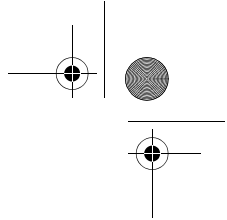
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Familial clustering in burnout

Chapter
6





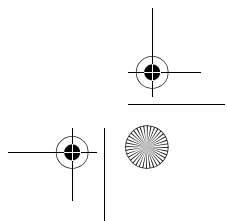
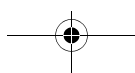
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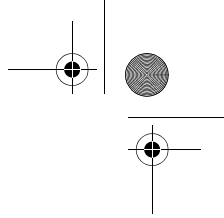
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A twin-family study of the association between employment, burnout and anxious depression

This paper is in press as:

Middeldorp C.M., Cath D.C., Boomsma D.I. (2006). A twin-family study of the association between employment, burnout and anxious depression. Journal of affective disorders, in press.





Abstract

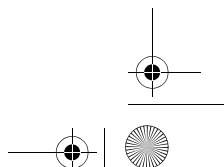
Background Earlier studies have shown that employment and burnout are related to anxiety and depression. This twin-family study aims to investigate to what extent these associations are caused by shared etiological factors.

Methods In a sample of 4309 Dutch twins and 1008 siblings, bivariate genetic analyses of employment and anxious depression and of burnout and anxious depression were carried out using structural equation modeling.

Results Employment and anxious depression were both influenced by genetic and individual-specific environmental factors. The association between employment and anxious depression was small, but significant, estimated at -0.08 . Power was too low to decide whether the covariance was explained by genetic or environmental factors. In burnout, familial clustering was due to genetic factors in men, but to genetic and common environmental factors in women. In both sexes, there was a strong correlation of around 0.40 with anxious depression, which was explained by shared genetic and shared environmental factors.

Limitations The group of unemployed subjects in our sample not only contained subjects who were searching for a job, but also subjects who were out of the labor force.

Conclusions The associations between employment and anxious depression as well as between burnout and anxious depression are due to overlapping genetic and individual-specific environmental factors. Work related circumstances, e.g. financial strain or work-family conflict, might be of importance in burnout and anxious depression. These results support the notion that a genetic vulnerability for depression also increases the risk for exposure to high-risk environments, such as unemployment.



Introduction

There seems to be a negative association between employment on the one hand and anxiety and depression on the other (Blazer et al., 1994; de Graaf et al., 2002b; Klose & Jacobi, 2004; Meertens et al., 2003; Wilhelm et al., 2003). However, burnout, a work related syndrome with symptoms of exhaustion, cynicism and a sense of ineffectiveness at work, is also associated with depression (Maslach et al., 2001). This suggests that being employed might protect against anxiety and depression, but not in the presence of a burnout, since then the risk for depression appears to be increased. This is supported by a longitudinal study on psychological symptoms, in which being unemployed was found to be less harmful than being dissatisfied employed (Graetz, 1993).

There are several models to explain associations between two traits (Neale & Kendler, 1995). The association can be due to an artifact, e.g. overlapping diagnostic criteria. In case of a genuine association, the two conditions might be causally related with three possible directions of causation: 1) A causes B, 2) B causes A or 3) both disorders cause each other, so called reciprocal causation. Another possibility is that the association is caused by etiological factors that increase the risk for both disorders, i.e. overlapping etiologies. Longitudinal studies provide a good means to investigate the causal models. Regarding the negative relation between employment and depression, results of longitudinal studies suggested a model of reciprocal causation, i.e. anxiety or depression can lead to unemployment and vice versa (de Graaf et al., 2002a; Fergusson et al., 1997; Fergusson et al., 2001; Hammarstrom & Janlert, 2002; Pevalin & Goldberg, 2003; Weich & Lewis, 1998). Regarding the association between burnout and depression, there has been a long debate whether overlapping diagnostic criteria underlie this relation. However, several studies have indicated that the concepts, although related to each other, are distinct entities (Glass & Mcknight, 1996; Leiter & Durup, 1994; Schaufeli & Enzmann, 1998). Since most research has focused on the differences between burnout and depression, possible explanations for the association have not been frequently addressed. One longitudinal study failed to show superiority of a model in which burnout led to depression over a model in which depression led to burnout (Mcknight & Glass, 1995). Since both causal paths were not significant, it seemed that burnout and depression develop simultaneously.

The results of these longitudinal studies do not exclude the possibility that overlapping etiological factors explain the association. This can be investigated by twin-family studies (Neale & Kendler, 1995; Rhee et al., 2004). In this study, bivariate genetic epidemiological analyses were performed in a Dutch population of twins and their siblings to investigate whether overlapping etiologies could explain the association between employment status and anxious depression as well as between burnout and anxious depression.

Methods

Subjects

This study is part of an ongoing longitudinal survey study of the Netherlands Twin Register (NTR) that has assessed families with adolescent and adult twins roughly every two years since 1991. Sample selection and response rates are described in detail in Boomsma et al. (2002b). Twin and sibling data were used from the survey in 2000 (Vink et al., 2004). For the majority of the twin pairs, zygosity was determined from questions about physical similarity and confusion of the twins by family members, friends and strangers. Information on zygosity was available from DNA polymorphisms for 726 same sex twin pairs. The agreement between zygosity diagnoses from questionnaire and DNA data was 97%. Twins with unknown zygosity were excluded from the study as well as subjects younger than 18 years or older than 65 years of age. As in our former study on burnout, one sibling per family, the one who was born closest to the twin, was included in the analyses (Middeldorp et al., 2005). The total population included 625 monozygotic male (MZM), 380 dizygotic male (DZM), 1511 monozygotic female (MZF), 806 dizygotic female (DZF) and 987 opposite-sex (DOS) twins as well as 409 brothers and 599 sisters. There were 235 MZM, 126 DZM, 614 MZF, 286 DZF and 296 DOS complete twin pairs. Siblings can form a pair with twin 1 and with twin 2 giving a total of 436 brother pairs, 994 sister pairs and 1130 sibling pairs of opposite-sex.

Questionnaires

Subjects indicated whether they were 1) full-time employed (>32 hours a week), 2) part-time employed, 3) student, 4) unemployed, 5) homemaker, 6) retired, 7) occupational disabled or 8) different, e.g. volunteer. Subjects were divided in three groups: unemployed (categories 4 till 8), part-time employed, full-time employed. Students were coded as missing.

Burnout was measured by a Dutch version of the emotional exhaustion subscale of the Maslach Burnout Inventory – General Survey (Schaufeli et al., 1996). This questionnaire was chosen, because it was also used in a study in the Dutch general population (CBS, 1997). The subscale consists of five items with an answer range between 1-7 (never, a few times a year, monthly, a few times a month, every week, a few times a week, every day). The 5 items can be summarized as 1) emotionally exhausted because of work, 2) feeling empty after work, 3) feeling tired in the morning when confronted with work, 4) completely exhausted because of work, and 5) feeling worn out. The scale provides good internal consistency; Cronbach's alpha was 0.87 in our sample. The variable was logtransformed because of the skewed distribution. By definition, unemployed subjects were coded as missing.

Depression was assessed with the subscale “anxious depression” of the Young Adult Self Report (YASR) (Achenbach, 1990), translated and validated for the Dutch population by Verhulst et al. (1997). For the analysis of the association with burnout, a logtransformation was performed because of the skewed distribution. For the analyses of the association between employment and depression, depression was analyzed as an ordinal trait by creating four categories based on equal numbers of subjects in each group.

Statistical methods

Twin studies provide a means to estimate the influence of genes, common environment and individual-specific environment on individual differences in behavioral and other traits (Boomsma et al., 2002a). These studies make use of the fact that monozygotic (MZ) twin pairs share all (or nearly all) their genes whereas dizygotic (DZ) twin pairs share on average half of their segregating genes. Consequently, if MZ twin pairs are more similar for a trait than DZ twin pairs, this suggests that additive genetic factors (A) influence this trait. If, on the other hand, MZ twin pairs and DZ twin pairs show the same amount of similarity, then common environmental factors, shared by family members (C), probably play a role. The differences within MZ twin pairs are explained by individual-specific environmental factors (E). Siblings, like DZ twin pairs, share on average half of their segregating genes. But twins and siblings may differ in the amount of environment they share. For example, prenatal conditions are different for singletons than for twins and twins grow up together with someone of their own age. Consequently, DZ twin pairs are the perfect controls for MZ twin pairs. However, it can be tested if siblings resemble each other less than DZ twins and additional information on the similarity between siblings increases the power of a study to detect effects of common environment (Posthuma & Boomsma, 2000).

The univariate design can be extended to a multivariate approach in which the correlation between traits is decomposed in a part due to genetic factors shared by these disorders, a part due to shared common environmental factors and a part due to shared individual-specific environmental factors (Neale & Kendler, 1995). This is based on the cross-trait-cross-twin correlation, i.e. the correlation between trait A in twin one and trait B in twin two. If the cross-trait-cross-twin correlation is higher in MZ twins than in DZ twins, overlapping genetic factors possibly explain the correlation between the traits, whereas similar cross-trait-cross-twin correlations in MZ and DZ twins suggest overlapping shared environmental factors.

Before performing the bivariate analyses, twin and twin-sibling correlations were estimated for employment, burnout and anxious depression. Univariate analyses were carried out to test 1) age effects on the three variables and 2) differences between the correlations in the DZ twin pairs and twin-sibling pairs. The results from these analyses were used to specify the two

bivariate models to investigate the association between employment and anxious depression as well as between burnout and anxious depression. In both bivariate analyses, first, the phenotypic correlations were calculated in men and women as well as the twin correlations and the cross-trait-cross-twin correlations in the same-sex and opposite sex twin pairs. Next, it was tested whether the bivariate ACE model described the data well compared to this unconstrained model. In the bivariate ACE model, correlations are calculated between the genetic, common environmental and individual-specific environmental factors. Significant correlations indicate that the same etiological factors influence both traits. Subsequently, the estimates for A, C and E were constrained to be equal in men and women to test sex differences in the amount of influence of A, C and E.

The analyses were performed on raw data using the raw likelihood method implemented in the software program Mx (Neale et al., 1999). The likelihood ratio test was used to test the significance of effects with a threshold p-value of 0.05. For the analysis of the association between employment and depression, a threshold model was used, assuming that the ordinal traits have an underlying normally distributed liability (Falconer & Mackay, 1996).

Chapter 7

Results

Descriptives and univariate analyses

Table 7.1 summarizes mean age, burnout and anxious depression scores and employment status in male and female twins and siblings. Twins and siblings were comparable regarding employment status, burnout and anxious depression scores.

In the univariate analyses, the effect of age was found to be negligible for burnout and anxious depression, but not for employment status. In men and women, the percentage of part-time and full-time employed subjects decreased with age. For example, in the group of women till 40 years of age 52% was working full time, while in the group of women over 40 years of age 19% was working full time. This age-effect was included in the bivariate model.

Table 7.1: Means (SD) for age, anxious depression and burnout scores and percentages of unemployed, part-time employed and full-time employed male and female twins and siblings

	Male twins	Brothers	Female twins	Sisters
Age	29.4 (9.7)	31.2 (9.4)	30.2 (10.0)	31.2 (9.1)
Anxious Depression	4.1 (4.1)	4.0 (3.7)	6.2 (4.8)	6.2 (4.5)
Burnout	9.5 (5.1)	9.7 (5.6)	9.7 (5.6)	9.6 (5.0)
% Unemployed/ part-time/ full-time	6/ 8/ 86	5/ 5/ 90	19/ 33/ 48	17/ 41/ 42

There were no significant differences between the correlations of the DZ twin pairs and the twin-sibling pairs for all three variables indicating no special twin environment, so in the bivariate models the DZ twin pair correlations were constrained to be equal to twin-sibling pair correlations.

Bivariate analysis of anxious depression and employment

The phenotypic correlation between anxious depression and employment was -0.15 for men (Confidence Interval (CI): -0.24 -0.06) and -0.06 for women (CI: -0.11 -0.01). Table 7.2 shows the (cross-) correlations for employment and anxious depression as a function of zygosity. The bivariate ACE model described the data well compared to the unconstrained model ($\chi^2=3.615$ with 4 degrees of freedom, $p = 0.46$). There were no significant sex differences in the estimates of A, C and E ($\chi^2=12.802$ with 7 degrees of freedom, $p=0.08$). The variance in employment status as well as in anxious depression was explained by genetic and individual-specific environmental factors, each explaining around 50% of the variance (Figure 7.1). In the final model, the correlation between employment and anxious depression was estimated at -0.08 for men and women, which was significant ($\chi^2=15.201$ with 3 degrees of freedom, $p = 0.002$). Due to low power, it was not possible to decide whether shared genes or shared individual-specific environmental factors explained the correlation between employment and anxious depression. In other words, either the correlation between the genetic factors or the correlation between the individual-specific environmental factors is needed to explain the observed correlations, but it is not possible to decide which one can be dropped from the model (Figure 7.1).

Employment, burnout and anxious depression

Table 7.2: Twin/sibling and cross-trait-cross-twin/sibling polychoric correlations (CI) for anxious depression (anx dep) and employment (job).

	MZM	DZM/sibsMM	MZF	DZF/sibsFF	DOS/sibsOS
anx dep	.40 (.27-.51)	.13 (.00-.28)	.49 (.42-.56)	.25 (.17-.33)	.21 (.13-.29)
job	.68 (.31-.87)	.38 (.11-.61)	.51 (.39-.60)	.17 (.05-.28)	.13 (-.07-.32)
Cross-trait-cross-twin					.01 (-.10-.12)/ -.14 (-.28-.10)*

MZM: Monozygotic Males, DZM: Dizygotic Males,
 MZF: Monozygotic Females, DZF: Dizygotic Females,
 DOS: Dizygotic twins of Opposite Sex, SibsMM: Brothers,
 SibsFF: Sisters, SibsOS: Sibs of Opposite Sex

*Two correlations are given: 1) the correlation between the employment status of the brother and anxious depression of the sister and 2) the correlation between the employment status of the sister and anxious depression of the brother.

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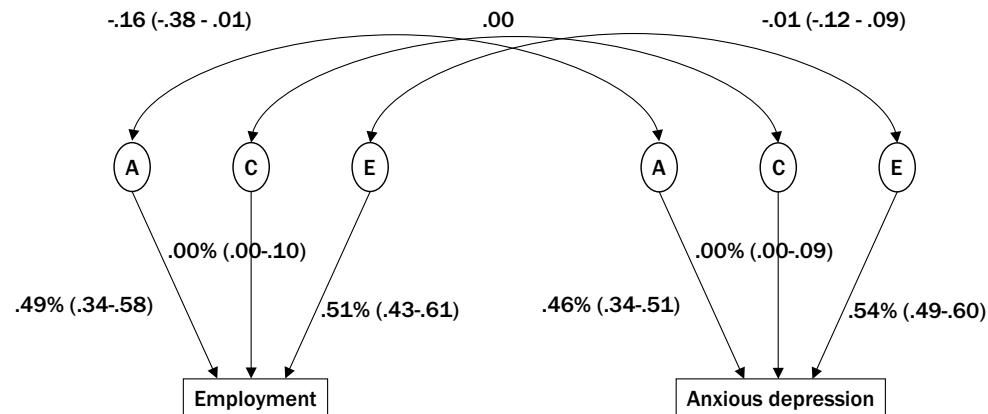


Figure 7.1: Estimates (CI) of the percentages of variance in employment and anxious depression explained by genetic factors (A), common environmental factors (C) and individual-specific environmental factors (E) in men and women. The double headed arrows indicate the correlations (CI) between A, C and E for employment and anxious depression.

Bivariate analysis of depression and burnout

The phenotypic correlation between burnout and anxious depression was 0.42 for men (CI: 0.37 0.47) and 0.36 for women (CI: 0.32 0.39). Table 7.3 shows the (cross-) correlations for the different twin pairs. The bivariate ACE model gave a good fit compared to the unconstrained model ($\chi^2=3.686$ with 4 degrees of freedom, $p = 0.45$). The estimates of A, C and E were significantly different between men and women ($\chi^2=20.086$ with 9 degrees of freedom, $p = 0.02$). In men, both conditions were influenced by genetic and individual-specific environmental factors, explaining around 30% and 70% of the variance

respectively (Figure 7.2). Burnout and anxious depression were strongly correlated (around 0.40). Genes and individual-specific environmental factors influencing both traits explained both half of the association. It should be kept in mind that even if the correlation between risk factors is moderate or high, the contribution to the total phenotypic correlation could be low because only a small amount of variance is explained by these risk factors. Thus, shared common environmental factors explained no covariance between burnout and anxious depression in men, since depression appeared to be hardly influenced by common environment. In women, anxious depression was influenced by genetic factors for 46% and by individual-specific environmental factors for 54%. However, in burnout, apart from genetic and individual-specific environmental factors explaining 13% and 72% of the variance, common environmental factors were also of importance, explaining 15% of the variance. Again, the correlation between the conditions was around 0.40. Shared genes explained 66% of the total phenotypic correlation and individual-specific environmental factors the other 33%.

Table 7.3: Twin/sibling and cross-trait-cross-twin/sibling correlations (CI) for anxious depression (anx dep) and burnout.

	MZM	DZM/sibsMM	MZF	DZF/sibsFF	DOS/sibsOS
anx dep	.39 (.28-.48)	.15 (.03-.26)	.46 (.40-.52)	.21 (.14-.29)	.22 (.15-.29)
burnout	.37 (.21-.51)	.25 (.09-.39)	.27 (.17-.37)	.19 (.07-.29)	.15 (.03-.25)
Cross-twin-cross-trait	.16 (.05-.26)	.10 (.00-.20)	.24 (.18-.30)	.09 (.05-.16)	.20 (.10-.29) / .14 (.05-.22)*

MZM: Monozygotic Males,

MZF: Monozygotic Females,

DOS: Dizygotic twins of Opposite Sex,

SibsFF: Sisters,

DZM: Dizygotic Males,

DZF: Dizygotic Females,

SibsMM: Brothers,

SibsOS: Sibs of Opposite Sex

*Two correlations are given: 1) the correlation between burnout of the brother and anxious depression of the sister and 2) the correlation between burnout of the sister and anxious depression of the brother.

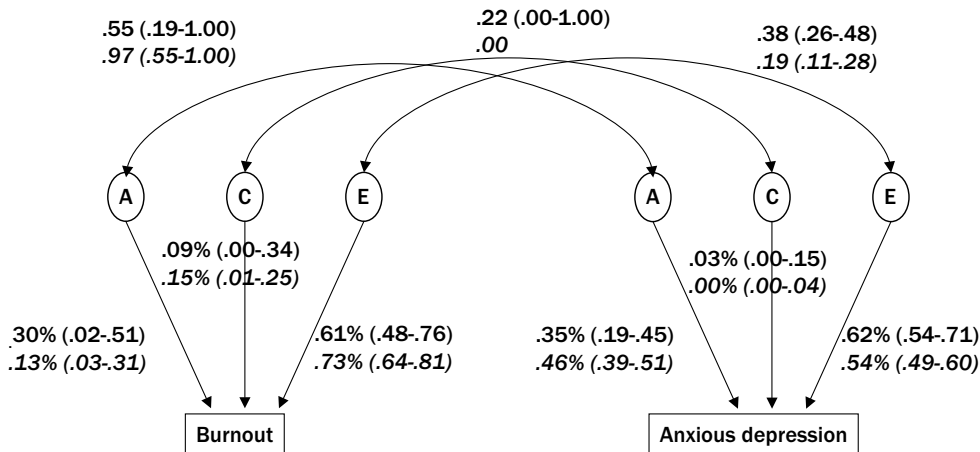


Figure 7.2: Estimates (CI) of the percentages of variance in burnout and anxious depression explained by genetic factors (A), common environmental factors (C) and individual-specific environmental factors (E) in men (upper estimates) and women (lower estimates). The double headed arrows indicate the correlations (CI) between A, C and E for burnout and anxious depression.

Chapter 7

Discussion

The first bivariate analysis showed that employment status and anxious depression are influenced by genetic and individual-specific environmental factors in men and women. The small but significant correlation of -0.08 between employment and depression could be explained by etiological factors, genetic or individual-specific environmental, that influence both traits. In the case of burnout and anxious depression, there were significant differences between men and women. In men, both conditions were influenced by genetic and individual-specific environmental factors. In women, anxious depression was influenced by genetic and individual-specific environmental factors, but in burnout, common environmental factors were of importance in addition to genetic and individual-specific environmental factors. The correlation between burnout and anxious depression of around 0.40 could be explained by genetic and individual-specific environmental factors influencing both traits in men and women. In sum, both the relation between employment and anxious depression as well as between burnout and anxious depression could be due to overlapping etiological factors. It is obvious that employment and anxious depression are considerably less associated with each other than burnout and anxious depression.

Considering previous literature, the finding that burnout is influenced by genetic factors seems to be contradictory to the results of the univariate twin-family analysis of burnout (Middeldorp et al., 2005) which suggested that familial clustering in burnout was entirely due to common environmental

factors explaining 22% of the variance (Middeldorp et al., 2005). These differences can be partly explained by the increase of power in bivariate analyses compared to univariate analyses (Schmitz et al., 1998). Furthermore, the significant cross-trait-cross-twin correlation clearly indicated that the association between burnout and anxious depression was partly due to familial factors and not to individual-specific environmental factors only. Because familial clustering for depression was due to genetic factors only, the association with burnout could not be explained by shared common environmental factors. Considering the results of the univariate and bivariate analyses together, it seems most probable that variation in burnout is influenced by both genetic and common environmental factors, but further research, possibly in larger samples, is necessary to obtain estimates of the influence of these two factors.

The finding that the association with anxious depression is a lot smaller for unemployment than it is for burnout seems to be in agreement with the conclusion that being unemployed is less harmful than being dissatisfied employed (Graetz, 1993). Furthermore, our results are in accordance with the longitudinal studies on unemployment and anxiety/depression that found a causal relationship, implying the possibility of a common etiology (Fergusson et al., 1997; Fergusson et al., 2001; Hammarstrom & Janlert, 2002; Pevalin & Goldberg, 2003). This also holds for burnout and depression, for which the results suggested that these conditions develop simultaneously (Mcknight & Glass, 1995). Apart from agreeing with earlier literature on unemployment and depression as well as on burnout and depression, our results agree with two studies that showed that a genetic vulnerability for major depression also increases the risk for exposure to high-risk environments, in this case unemployment (Kendler et al., 1999; Kendler & Karkowski-Shuman, 1997).

These results imply that employment and circumstances at work are issues that need to be considered in the treatment of depression. Work related conditions like financial strain or work-family conflict might be individual-specific environmental factors influencing both symptoms of burnout as well as depression. Moreover, as a genetic vulnerability for depression could also increase the risk for unemployment, which in turn might worsen the depressive symptoms, it is important to know whether the patient can meet the demands of his job. Further research is necessary to provide more insight into the shared risk factors enabling more detailed recommendations for treatment.

In our study, all subjects who finished education and who were not employed were grouped together. This disregards the possibility that they may form a heterogeneous group. This might explain the relatively small association between employment and depression. However, earlier studies did not show large differences between subjects who were unemployed or who were out of the labour force (Blazer et al., 1994; Klose & Jacobi, 2004; Meertens et al., 2003; Wilhelm et al., 2003).

To conclude, shared genetic and individual-specific environmental factors explain the association between unemployment and anxious depression as well as between burnout and anxious depression. More research is needed to identify specific shared risk factors. Ultimately, this could have implications for the treatment of depression.

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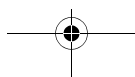
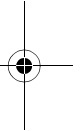
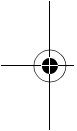
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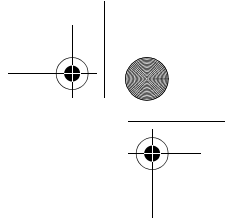


Employment, burnout and anxious depression



Chapter
7





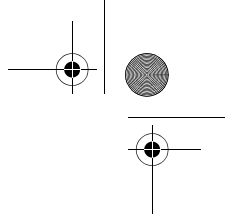
Chapter

8

Twin and genetic effects on life events

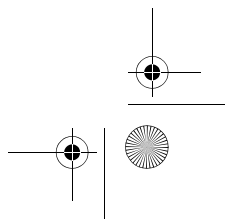
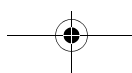
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Abstract

Twin studies that examine the effect of specific environmental risk factors on psychiatric disorders assume that there are no differences in prevalences of these risk factors between twins and singletons. Violation of this assumption signifies that the results from twin studies might not generalize to singletons. Another assumption, not only often underlying twin studies but also epidemiological research, is that life-events are not influenced by familial factors. We tested differences in prevalences of experienced life events in a Dutch sample of 2086 monozygotic twins, 2090 dizygotic twins and 1307 of their siblings. Self-reported data on life events (illness of self, illness of a significant other, spouse / romantic relationship, divorce / break-up of a relationship, death of a significant other, traffic accident, robbery, violent assault, sexual assault) were available from a survey-study. We further investigated whether familial resemblance was present for the exposure to these life events and, if yes, whether this resemblance was due to genetic or common environmental factors. No differences were found in the prevalences of life events between monozygotic twins, dizygotic twins and their siblings. There was evidence for familial aggregation of all life events, except for traffic accidents in women. Results indicated genetic control on the presence of a spouse or involvement in a relationship. Familial resemblance of illness and death of a significant other was mainly due to common environment. For the other life events, it was not possible to distinguish between genetic and common environmental effects.



Introduction

Genetic epidemiological research in psychiatric disorders has suggested that these disorders are likely to be influenced by multiple genes of modest effect as well as by environmental risk factors (Tandon & McGuffin, 2002). Twin studies not only allow the exploration of the question to what extent genes and environment influence these disorders, but are also a good design to study the effects of specific environmental risk factors as well as the interaction or correlation between genes and environment. For example, large population based twin samples can be used as epidemiological samples to investigate environmental risk factors (e.g. Kendler et al. (2001b; 2001a; 2003; 2004)). An interaction between genotype and environment can be studied by comparing the heritability of the disorder in twin pairs in which a) neither twin is exposed to an environmental risk factor, b) one of the twins is exposed to the risk factor, c) both twins are exposed to the risk factor (Boomsma et al., 1999; Boomsma & Martin, 2002; Heath et al., 1998). Purcell (2002) developed several models to investigate gene-environment interaction in a twin design with quantitative measurements of risk factors. Gene-environment correlation can also be incorporated in these models (Purcell, 2002). Alternatively, monozygotic (MZ) twins discordant for the presence of a disorder can be compared on the absence or presence of a certain environment or on the amount of exposure to environmental conditions, which might also provide insight in the risk factors (Kendler & Gardner, 2001).

An important assumption underlying this kind of research is that twins do not differ from singletons regarding their exposure to the environment under study. When this assumption is violated, results of twin studies might not generalize to the general population. Mostly, this seems a reasonable assumption, for example in the case of death or physical illness in the family. However, this might be different for other life events, such as divorce / break-up of a relationship or physical illness of self. Some researchers have suggested that the intimate relationship that exists between twins excludes or discourages outside relationships (Clark & Dickman, 1984; Zazzo, 1976). As a consequence, twins will have a lower marriage rate and more problems in marriage than non-twins (Zazzo, 1976). MZ twins might be especially at risk. At least in childhood, they tend to spend more time together, for instance because they are more likely to share the same room (Pearlman, 1990). So far, the few empirical studies that have addressed this issue, have not confirmed this hypothesis. MZ twins do not report significantly higher levels of intimacy with their co-twin, or significantly lower levels of intimacy with their closest friends when compared to DZ twins (Foy et al., 2001). Twins who report high levels of intimacy with their co-twin do not report significantly lower levels of intimacy with their closest friends (Foy et al., 2001). Finally, MZ twins, DZ twins and

singletons do not seem to differ significantly with respect to marital status, number of years married, whether married before, number of previous marriages and number of years divorced (Pearlman, 1990).

Twins might also differ from singletons regarding physical health. At birth, twins are on average 1000 g lighter than singletons and they are born on average approximately 3 weeks pre-term with a higher frequency of delivery by caesarean section (Alexander & Salihu, 2005). Are twins, due to this difficult start, more prone to diseases? This does not seem to be the case with respect to a wide range of disease characteristics like bone mineral density, osteoarthritis, blood pressure or diabetes mellitus (Andrew et al., 2001; de Geus et al., 2001; Kyvik, 2000).

Most twin and other epidemiological studies of environmental risk factors also assume that the exposure to life-events is random and not influenced by familial factors, either genetic or common environmental factors. If this assumption does not hold and the exposure to a life event is, for example, partly genetically influenced, this signifies that the relationship between a life event and a disorder might be caused by shared genes. The twin design also enables investigating this assumption. Results so far have suggested familial resemblance in the exposure to life events (Bolinskey et al., 2004; Kendler et al., 1993). In life events that partly result from the respondent's own behavior familial resemblance seems to be due to genetic factors (Bolinskey et al., 2004; Kendler et al., 1993).

The aim of the current study is twofold. The first goal is to investigate whether twins differ from singletons regarding their exposure to life events. The prevalence of life events is compared between MZ twins, DZ twins and their siblings, stratified according to sex and age. Since siblings of twins are matched regarding parental social economic status and upbringing, they are the perfect control group. Data on the following life events will be analyzed: divorce / break-up of a relationship, illness of self, illness of a significant other, death of a significant other, traffic accident, robbery, violent assault, sexual assault. As the proportion of subjects who report a divorce can be related to the proportion of subjects who have a spouse or who are involved in a relationship, the number of subjects with a spouse or a romantic relationship was also compared in the three groups. If we do not find differences between MZ twins, DZ twins and singletons, this signifies that twin studies can indeed be used to investigate these life events. In that case, the second goal is to examine in the twins whether the exposure to life events is familial and if yes, whether this familial resemblance is due to shared genes. We begin with a general approach of calculating odds ratios and comparing concordance rates between MZ and DZ twin pairs with a Pearson χ^2 test. Next, life events are analyzed in a threshold model, which provides the opportunity to investigate to what extent familial resemblance is due to genetic and common environmental effects.

Methods

Subjects

This study is part of a longitudinal survey study of the Netherlands Twin Register (NTR) that has assessed families with adolescent and young adult twins roughly every two years since 1991. Sample selection and response rates are described in detail in Boomsma et al. (2002). Data were used from the survey that was sent to twins and their siblings in 2000 (Vink et al., 2004). For the majority of the twin pairs, zygosity was determined from questions about physical similarity and confusion of the twins by family members, friends and strangers. Information on zygosity was available from DNA polymorphisms for 726 same sex twin pairs. The agreement between zygosity diagnoses from questionnaire and DNA data was 97%. Twins with unknown zygosity or subjects younger than 18 years of age were excluded from the study.

The population consisted of 608 MZ male twins, 385 DZ male twins, 1478 MZ female twins, 798 DZ female twins, 907 DZ twins of opposite sex, 517 brothers and 790 sisters, in total 1883 men and 3600 women. For the first part of the study, men and women were stratified according to age into three groups of approximately the same size. Mean ages were around 21 years, 27 years and 42 years (Table 8.1). Less than a quarter of the singleton siblings were in another age group than their twin siblings. For the analyses of familial resemblances in life events, data were analyzed from 1450 complete and 1276 incomplete twin pairs. The group of complete pairs consisted of 222 MZ male, 119 DZ male, 578 MZ female, 261 DZ female and 270 DZ twins of opposite sex. The twins from incomplete pairs came from 486 MZ and 790 DZ pairs.

Instruments

In the demographic section of the 2000 survey subjects were asked if they had a spouse or were involved in a romantic relationship. An adapted version of a Dutch life event scale (Schokverwerkings Inventarisatie Lijst = SchIL) (Van der Velden et al., 1992) asked about the experience of the following life events: death of a spouse, father, mother, child, sibling or significant other, illness of self or a significant other, divorce / break-up of a relationship, traffic accident, violent and sexual assault and robbery. Response categories were "never experienced" "0-6 months ago" "6-12 months ago" "1-5 years ago" and "more than five years ago". In the current study the response categories were reduced to no (never) or yes (all other categories). We did not analyze death of family members, since answers will be similar for twins and siblings from the same family. Death of a spouse or child was not analyzed either, because the prevalences were very low in this relatively young sample.

Statistical methods

Differences between prevalences in life events of MZ twins, DZ twins and singletons were tested with a Pearson χ^2 using SPSS for Windows, Release 11.0. For each life event, Odds Ratio's (OR) and tetrachoric correlations were calculated for MZ and DZ twin pairs to study familial influences. In contrast to OR, tetrachoric correlations were calculated on data from both complete and incomplete twin pairs simultaneously by using the raw data option in Mx (Neale et al., 1999). If familial influences were present, a Pearson χ^2 test was used to compare the proportion of MZ and DZ twin pairs who were concordant exposed, discordant or concordant not exposed to examine whether this familial resemblance could be due to genetic influences. In Mx, a threshold model was used to partition the variance of the underlying liability of experiencing a life event into additive genetic (A), common environmental (C) and unique environmental effects (E). Based on the principle of parsimony, the best fitting model was chosen (Neale & Cardon, 1992). The presence of sex specific genetic effects was tested by constraining the genetic correlation between twins of opposite sex at 0.5. Then, differences in the degree of impact of A, C and E was tested by constraining the estimates for men and women to be equal. Next, A and C were dropped from the model to test their significance by likelihood ratio tests.

Chapter 8

Results

Table 8.1 shows the results for the analyses of the differences in exposure to life events between MZ twins, DZ twins and their siblings, stratified according to sex and age. In women aged around 27 years old, the Pearson χ^2 showed a significant difference between the three groups of MZ twins, DZ twins and sisters regarding the presence of a spouse or involvement in a romantic relationship. Additional analyses, in which the MZ twins were compared to the other two groups and the DZ twins were compared to the singletons, showed that female MZ twins were less likely to have a relationship than their sisters ($p < 0.005$). A p value < 0.05 was found for the comparisons of MZ twins to DZ twins and of DZ twins to their sisters. The significant difference between the three groups of women of around 27 years old with respect to 'serious illness of a significant other' was due to a lower prevalence in female MZ twins as compared to their sisters ($p < 0.01$). Except for these two effects, there are no differences in prevalences of life events between MZ twins, DZ twins and siblings.

The prevalences of reported life events suggested sex differences, which we formally tested. Compared to women, men in the youngest two age groups were more likely to have experienced a robbery ($p < 0.01$ and $p < 0.05$) or a violent assault ($p < 0.001$ and $p < 0.05$), whereas men in the youngest and oldest

age groups were more likely to have experienced a traffic accident ($p < 0.005$ and $p < 0.05$). Women in all age groups reported more sexual assaults ($p < 0.001$ at all ages) than men. Furthermore, women in the oldest age group more often reported a serious illness or death of a significant other ($p < 0.005$ for both life events). Women in the youngest two age groups reported more often to be involved in a romantic relationship ($p < 0.001$ in both age groups).

Next, OR and tetrachoric correlations were calculated for each sex by zygosity group (Table 8.2). In appendix 8A, the number and percentages of concordant exposed, discordant and concordant not exposed twin pairs are given for the five group. All life events appeared to be influenced by familial factors with the exception of traffic accidents in women. Therefore, further analyses on the family resemblance of traffic accidents will be performed in male twins only. In men, OR and correlations could not be calculated for the life events violent and sexual assaults because of the absence of concordant pairs. Consequently, these life events were not included in further analyses. The comparisons of concordance rates between MZM and DZM as well as MZF and DZF pairs using a χ^2 test showed no significant differences. Because we observed significant sex differences in prevalence rates for life events, data from MZF and MZM (or DZF and DZM) twin pairs could not be pooled to test for the differences in concordance rates in larger groups.

Therefore, we turned to model fitting in Mx which made it possible to test for the presence of sex differences in familial resemblances, while using a threshold model with sex-specific thresholds to allow for sex-specific prevalence. We first tested if there was evidence that the genetic correlation between opposite sex twin pairs was different from 0.5. Results showed that the genetic correlation could be constrained to 0.5 for all life events, indicating no qualitative sex differences in genetic influences. The test for quantitative sex differences in the influences of genes and environment showed that the estimates of A, C and E were not significantly different between men and women either. The final series of models tested the AE and CE model against the full ACE (i.e. additive genetic, common environmental and unique environmental influences) model. For involvement in a relationship familial resemblance was best explained by genetic factors.

Chapter 8

Twin and genetic effects on life events

Table 8.1: Total N, mean age and N subjects (%) who experienced a life-event in monozygotic (MZ) twins, dizygotic (DZ) twins and singleton siblings stratified according to age and sex.

	N	Mean age / SD	Spouse	Illness self	Illness significant other	Death significant other	Divorce	Accident	Robbery	Violent assault	Sexual assault
Age 21 yrs											
M	237	21.8 / 1.5	96 (40.7)	21 (9.6)	73 (32.6)	154 (65.8)	48 (21.4)	39 (17.4)	47 (20.9)	19 (8.5)	0 (0.0)
DZ	287	22.1 / 1.5	128 (44.6)	34 (12.5)	87 (32.5)	188 (66.4)	55 (20.1)	51 (18.6)	59 (21.4)	24 (8.8)	0 (0.0)
Sibs	104	21.8 / 1.7	48 (46.2)	18 (18.4)	32 (33.0)	71 (69.6)	18 (18.8)	19 (19.8)	18 (18.4)	11 (11.2)	1 (1.0)
F	510	21.9 / 1.7	312 (61.5)	47 (9.8)	184 (38.0)	328 (66.8)	105 (21.6)	59 (12.2)	68 (14.0)	12 (2.5)	27 (5.6)
DZ	525	22.2 / 1.6	299 (57.4)	53 (10.5)	182 (36.0)	356 (69.8)	139 (27.3)	60 (11.8)	86 (16.9)	23 (4.5)	36 (7.0)
Sibs	165	21.9 / 1.9	105 (63.6)	26 (16.7)	59 (38.3)	108 (67.5)	39 (25.2)	25 (16.1)	23 (14.7)	5 (3.2)	6 (3.8)
Age 27 yrs											
M	199	27.2 / 1.7	122 (61.6)	30 (15.7)	79 (41.1)	136 (69.4)	61 (31.0)	41 (21.2)	40 (20.5)	18 (9.4)	2 (1.0)
DZ	268	27.3 / 1.6	175 (65.8)	47 (19.0)	97 (39.4)	184 (72.7)	83 (32.5)	48 (19.0)	47 (18.6)	17 (6.8)	2 (0.8)
Sibs	161	27.5 / 1.8	102 (65.0)	21 (13.5)	65 (41.9)	101 (64.3)	43 (27.2)	34 (21.5)	34 (21.7)	11 (7.1)	1 (0.6)
F	448	27.8 / 1.8	325 (72.9)*	57 (13.2)	159 (36.5)#	282 (64.1)	147 (33.6)	87 (20.0)	115 (26.2)	21 (4.8)	37 (8.5)
DZ	485	28.0 / 1.9	379 (78.5)*	79 (16.9)	203 (42.7)#	315 (66.5)	156 (32.8)	81 (17.1)	113 (23.8)	23 (4.8)	43 (9.0)
Sibs	267	28.3 / 2.1	224 (84.8)*	41 (16.0)	121 (47.3)#	187 (70.8)	73 (28.0)	40 (15.5)	55 (21.2)	14 (5.4)	32 (12.3)
Age 43 yrs											
M	172	43.9 / 10.1	156 (90.7)	31 (19.0)	78 (48.8)	105 (62.9)	36 (22.2)	36 (22.2)	51 (30.9)	8 (4.9)	2 (1.2)
DZ	203	43.7 / 11.1	171 (84.2)	48 (26.2)	77 (43.3)	110 (59.5)	42 (23.1)	35 (19.2)	53 (29.6)	11 (6.1)	3 (1.7)
Sibs	252	42.1 / 11.4	216 (85.7)	45 (20.0)	95 (42.0)	147 (64.5)	50 (22.3)	49 (22.1)	59 (26.9)	12 (5.5)	4 (1.8)
F	520	44.9 / 10.6	438 (84.6)	104 (22.7)	262 (56.5)	330 (68.8)	133 (28.6)	72 (15.6)	135 (28.6)	27 (5.9)	43 (9.3)
DZ	322	44.3 / 9.8	282 (88.1)	65 (22.6)	142 (50.2)	201 (67.7)	70 (24.3)	50 (17.5)	75 (26.1)	17 (6.0)	24 (8.4)
Sibs	358	41.4 / 9.2	318 (89.1)	67 (20.2)	167 (51.5)	246 (71.9)	87 (26.5)	52 (16.2)	85 (25.7)	9 (2.8)	27 (8.3)

F: Female, M: Male, SD: standard deviation.

* $p < 0.005$ for χ^2 test of differences between MZ, DZ and siblings

$p < 0.05$ for χ^2 test of differences between MZ, DZ and siblings

Table 8.2: Odds ratios (95% confidence interval) for monozygotic and dizygotic complete twin pairs (above bold line) and tetrachotic correlations (95% confidence interval) based on data from complete and incomplete pairs (below bold line)

	Spouse	Illness self	Illness significant other	Death significant other	Divorce	Accident	Robbery	Violent assault	Sexual assault
MZM	8.0 (4.4-14.7)	2.7 (1.1-7.0)	2.4 (1.3-4.3)	3.2 (1.8-5.7)	1.6 (.8-3.3)	5.8 (2.7-12.6)	2.2 (1.0-4.7)	4.8 (1.2-20.3)	*
DZM	2.9 (1.3-6.3)	.8 (-2.4-0)	3.2 (1.4-7.8)	2.5 (1.0-5.8)	1.9 (.6-5.7)	2.3 (.8-7.2)	1.9 (.7-5.4)	*	**
MZF	4.2 (2.8-6.2)	2.8 (1.6-5.0)	2.9 (2.0-4.1)	5.3 (3.6-7.8)	2.7 (1.8-4.1)	1.6 (.8-2.9)	2.3 (1.5-3.6)	8.7 (2.9-26.6)	9.9 (4.6-21.4)
DZF	2.2 (1.2-3.9)	2.7 (1.2-5.9)	2.4 (1.4-4.1)	3.6 (2.0-6.5)	1.1 (.6-2.2)	1.3 (.5-3.4)	2.4 (1.2-4.8)	14.7 (3.0-71.5)	2.4 (.3-20.9)
DOS	2.8 (1.6-4.8)	1.5 (.6-4.0)	2.8 (1.7-4.8)	3.6 (2.1-6.4)	1.6 (.9-3.0)	1.0 (.4-2.2)	1.5 (.7-3.0)	2.7 (.3-25.0)	*
MZM	.68 (.53-80)	.32 (.01-.58)	.33 (12-.52)	.41 (.21-.59)	.16 (-10-.40)	.54 (.31-.72)	.27 (.01-.51)	.40 (-.02-.72)	*
DZM	.38 (.10-.64)	-.10 (-.50-.33)	.43 (13-.67)	.32 (.01-.59)	.25 (-.15-.58)	.27 (-.10-.60)	.21 (-.15-.54)	*	**
MZF	.49 (.37-.60)	.33 (.15-.50)	.39 (26-.54)	.57 (45-.67)	.35 (.21-.48)	.14 (-.06-.33)	.28 (.13-.43)	.52 (22-.74)	.60 (45-.73)
DZF	.27 (.07-.46)	.31 (.05-.54)	.33 (.13-.51)	.45 (25-.62)	.04 (-.19-.26)	.08 (-.22-.37)	.30 (.06-.51)	.62 (.21-.87)	.39 (-.13-.71)
DOS	.37 (.18-.53)	.14 (-.17-.42)	.39 (20-.56)	.45 (26-.61)	.18 (-.05-.39)	-.03 (-.28-.22)	.13 (-.12-.36)	.18 (-.37-.65)	*

MZM: monozygotic male pairs,
 MZF: monozygotic female pairs,
 DOS: dizygotic twin pairs of opposite sex
 *No concordant exposed pairs
 **No exposed subjects

DZM: dizygotic male pairs,
 DZF: dizygotic female pairs,

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Table 8.3: χ^2 for the test of significance of additive genetic (A) and common environmental effects (C). Parameter estimates of the percentage of variance explained by additive genetic, common and unique environmental effects (E) in the best fitting model

	Spouse	Illness self	Illness significant other	Death significant other	Divorce	Accident in men	Robbery
χ^2 drop A*	8.531	1.419	.001	1.637	3.185	1.684	.420
χ^2 drop C*	.740	.049	7.215	6.027	.000	.001	.808
χ^2 drop A and C#	128.255	20.297	73.913	128.989	24.013	20.811	24.060
A/C**	.57 / -	.33 / .27	- / .37	- / .48	.29 / .23	.55 / .47	.30 / .25
E**	.43	.67 / .73	.63	.52	.71 / .77	.45 / .53	.70 / .75

*Critical value of χ^2 : 3.841 at $p=0.05$ with 1 degree of freedom

#Critical value of χ^2 : 5.991 at $p=0.05$ with 2 degrees of freedom

** When it was not possible to decide whether familial resemblance was due to genetic or common environmental effects, the estimates of A and E in the absence of C and the estimate of C and E in the absence of A are given.

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For life events that involved illness and death of a significant other, familial resemblance was best explained by common environment. For the other life events it was not possible to decide whether familial resemblance was due to genetic or common environmental effects. However, as expected, removing both A and C from the model led to a large increase in χ^2 . Table 8.3 shows the differences in χ^2 between the ACE model and the AE, CE and E model after constraining the genetic correlation in the DZ twins of opposite sex to 0.5 and the estimates of men and women to be equal. The lower half of Table 8.3 gives the estimates of A, C and E in the best fitting model. When it was not possible to decide whether familial resemblance was due to genetic or common environmental effects, the estimates of A and E in the absence of C and the estimate of C and E in the absence of A are given.

Discussion

With two exceptions, there are no significant differences between MZ twins, DZ twins and singletons regarding the prevalence of experienced life events, not even for the life events suggested to bear an increased risk for twins, i.e. divorce and serious illness of self. Only in women aged around 27 years, singletons were more likely to have a spouse or be involved in a romantic relationship and

to have someone in their network suffering from a serious illness. Whether these findings are just due to coincidence or reflect real differences needs further exploration.

The overall absence of differences between twins and singletons with respect to relationship and divorce rates are in agreement with earlier literature (Foy et al., 2001; Pearlman, 1990). This indicates that the hypothesis that twins have more problems in relationships with others (Clark & Dickman, 1984; Zazzo, 1976) can be rejected. Moreover, serious illness of self does not seem to be more prevalent in twins. Most studies so far did not find any twin singleton differences at the level of specific diseases either (Andrew et al., 2001; de Geus et al., 2001; Kyvik, 2000). Given the absence of twin singleton differences, a twin population can be used to study environmental risk factors of psychiatric disorders, since these findings can be generalized to the general populations.

OR and tetrachoric correlations suggested familial resemblance for all life-events, except traffic accidents in women. Exposure to a violent or sexual assault was not further analyzed because of the absence of concordant male pairs. Variance components analyses suggested that genetic influences explain 57% of the variation in having a spouse or a relationship. Common environmental effects explain around 30% of the variation in illness and death of a significant other. No distinction could be made between genetic and common environmental effects with respect to the other life events. However, for most events, results pointed more in the direction of genetic than common environmental effects. These findings are in agreement with earlier research. In the Minnesota Twin Registry, the heritability was estimated to be 0.70 for the propensity to marry (Johnson et al., 2004). Furthermore, two studies performed in the Virginia Twin Register indicated that life events that are supposed to partly result from a respondent's own behavior, are probably genetically influenced (Bolinskey et al., 2004; Kendler et al., 1993). This implies that an association between an environmental risk factor and a psychiatric disorder, even in longitudinal research, might be due to genetic influences shared by the risk factor and the disorder. This may be formally tested in bivariate twin models and in models that include gene-environment interaction and correlation (Purcell, 2002), but also needs to be considered in other studies on environmental risk factors.

In the former (Bolinskey et al., 2004; Kendler et al., 1993) and in our own study, the prevalence of some life events was very low, which may have contributed to the problem of distinguishing genetic from common environmental effects. A longitudinal study in which twins are asked on several occasions about experienced life events seems useful to study familial influences on exposure to life events. The rate of reported events will increase when the data collected at several occasions are analyzed simultaneously.

OR and tetrachoric correlations gave the same results regarding the presence of familial influences. Comparisons of concordance rates of life events did not reveal significant differences between MZ and DZ twins suggesting no genetic effects. However, these analyses were performed in men and women separately since the prevalences of some of these experienced life events were significantly different. In the model fitting analyses, thresholds could be estimated separately for each sex, while testing whether the estimates of variance components A, C and E could be constrained to be equal in men and women. Since this was allowed for almost all life events, the power to detect genetic effects was greater in the model fitting analyses than in the comparisons of the concordance rates.

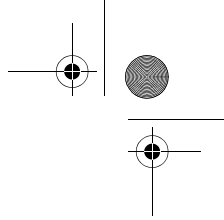
Although it was not a primary aim of our study, we found some clear sex differences on the reported experienced life events. Not surprisingly, men younger than 30 years more often experience an accident, robbery or violent assault and women are more often victim of a sexual assault. Older women more frequently report illness and death of a significant other. An explanation could be that women are more sensitive to the needs of others and more frequently take care of ill people. Women in the two youngest age groups more often have a spouse or are involved in a romantic relationship than men. This is in accordance with marriage rates of men and women in this age group in The Netherlands (CBS, 2000). Women apparently have a relationship with a man who is approximately five years older. An interesting issue to examine in future is whether these differences in exposure to some environmental factors also implies that the impact of these factors on the development of psychiatric disorders is different in men and women.

To summarize, our results suggest that there are no differences in prevalences of exposure to life events between MZ twins, DZ twins and singletons. The exposure to life events was influenced by familial factors. For presence of a spouse, familial resemblance was due to genetic effects. For most other life events, no distinction could be made between genetic and common environmental effects.

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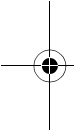
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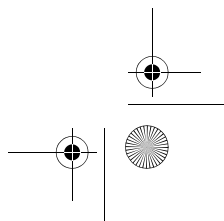
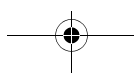
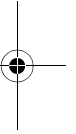


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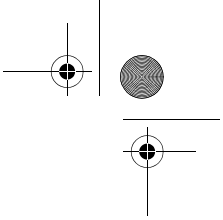
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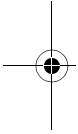
Appendix 8A: N (%) concordant and discordant monozygotic and dizygotic twin pairs for events.

		Spouse	Illness self	Illness significant other	Death significant other	Divorce	Accident	Robbery	Violent assault	Sexual assault
MZM	Con yes	99 (44.6)	8 (4.0)	41 (20.3)	105 (48.6)	15 (7.1)	18 (8.7)	14 (6.7)	3 (1.5)	0 (0.0)
	Disc	57 (25.7)	42 (20.9)	76 (37.6)	72 (33.3)	70 (33.3)	43 (20.8)	59 (28.2)	22 (10.7)	2 (1.0)
DZM	Con no	66 (29.7)	151 (75.1)	85 (42.1)	39 (18.1)	125 (59.5)	146 (70.4)	136 (65.1)	181 (87.9)	203 (99.0)
	Con yes	51 (42.9)	2 (2.0)	20 (20.6)	55 (51.4)	6 (5.8)	6 (5.8)	7 (6.9)	0 (0.0)	0 (0.0)
MZF	Disc	43 (36.1)	28 (28.6)	33 (34.0)	37 (34.6)	30 (28.8)	27 (26.3)	31 (30.4)	11 (10.9)	0 (0.0)
	Con no	25 (21.0)	68 (69.4)	44 (45.4)	15 (14.0)	68 (65.4)	70 (68.0)	64 (62.7)	90 (89.1)	99 (100.0)
DZF	Con yes	334 (57.8)	23 (4.6)	129 (25.0)	275 (51.6)	61 (11.8)	16 (3.1)	43 (8.2)	5 (1.0)	14 (2.7)
	Disc	162 (28.0)	110 (21.8)	189 (36.7)	150 (28.1)	163 (31.5)	124 (24.2)	157 (29.8)	33 (6.5)	51 (9.8)
DOS	Con no	82 (14.2)	372 (73.7)	197 (38.3)	108 (20.3)	294 (56.8)	373 (72.7)	326 (62.0)	470 (92.5)	453 (87.5)
	Con yes	140 (53.6)	12 (5.1)	49 (20.9)	134 (55.4)	18 (7.5)	6 (2.5)	17 (7.1)	3 (1.3)	1 (0.4)
DOS	Disc	90 (34.4)	55 (23.4)	89 (38.1)	73 (30.2)	92 (38.4)	57 (24.1)	67 (27.8)	14 (5.9)	19 (8.0)
	Con no	31 (11.9)	168 (71.5)	96 (41.0)	35 (14.5)	130 (54.2)	174 (73.4)	157 (65.1)	221 (92.9)	217 (91.6)
DOS	Con yes	129 (47.8)	6 (2.4)	50 (20.5)	131 (51.6)	21 (8.3)	8 (3.1)	13 (5.1)	1 (0.4)	0 (0.0)
	Disc	97 (35.9)	55 (22.2)	87 (35.6)	80 (31.5)	87 (34.2)	77 (30.2)	77 (30.4)	25 (10.0)	22 (8.7)
DOS	Con no	44 (16.3)	187 (75.4)	107 (43.9)	43 (16.9)	146 (57.5)	170 (66.7)	163 (64.4)	224 (89.6)	230 (91.3)

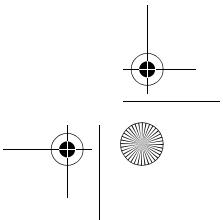
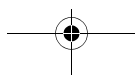
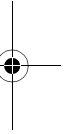
Con: concordant,
 MZM: monozygotic male pairs,
 MZF: monozygotic female pairs,
 DOS: dizygotic twin pairs of opposite sex
 Disc: discordant,
 DZM: dizygotic male pairs,
 DZF: dizygotic female pairs,

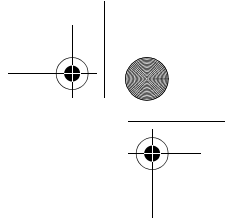


Twin and genetic effects on life events



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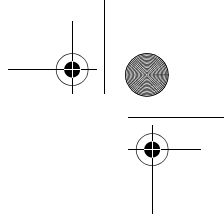
Chapter

9

The interplay of life events and anxious depression, neuroticism and extraversion

This paper is submitted as:

***Middeldorp C.M., Cath D.C., Beem A.L., Willemsen G., Boomsma D.I.
(2005). The interplay of life events and anxious depression, neuroticism
and extraversion.***



Abstract

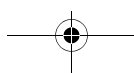
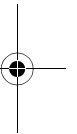
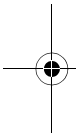
Background More insight into the relation between life events and depression, neuroticism and extraversion can improve depression treatment and research.

Aims This study investigates the underlying mechanisms of associations between life events and depression, neuroticism and extraversion.

Method Information on life events, anxious depression and personality were collected in 5782 twins. To examine causality and gene-environment correlation, data were analyzed longitudinally and with the co-twin control method.

Results Anxious depression was, in general, lower before than after the exposure to life events. Neuroticism and extraversion were hardly influenced by life events. Anxious depression and neuroticism, but not extraversion, also predicted the experience of life events. No evidence was found for gene-environment correlation.

Conclusions These results suggest that life events contribute to anxious depression. In turn, high anxious depression and neuroticism scores also appear to increase the risk for exposure to life events.



Introduction

The association between life events and depression seems to be due in part to the fact that life events increase the risk for depression and in part due to genetic factors which increase the vulnerability for depression and the risk for exposure to life events, i.e. gene-environment correlation (Kendler et al., 1999; Kendler & Karkowski-Shuman, 1997; McGuffin et al., 1988). These genetic factors could be reflected by personality traits related to depression (Kendler et al., 1999), such as high neuroticism or low extraversion (e.g. Middeldorp et al. (2006)). This hypothesis was supported for neuroticism (Kendler et al., 2003; Saudino et al., 1997). Explaining the association between life events and anxious depression is important from a clinical and a research perspective. In the current study, causality and gene-environment correlation were investigated for life events and anxious depression, neuroticism and extraversion in a longitudinal design and with the co-twin control method.

Methods

Subjects

This study is part of a longitudinal survey study of the Netherlands Twin Register (NTR) that has assessed families with adolescent and young adult twins roughly every two years since 1991. Sample selection and response rates are described in detail in Boomsma et al. (2002). For this study, data were used from the 1997, 2000 and 2002 surveys. Each survey was sent to twins and their siblings and, in addition, to spouses of twins in 2000 and 2002 and to parents of twins in 2002. Only twins aged between 18 years and 65 years whose zygosity was known were included in this study. For the majority of the twin pairs, zygosity was determined from questions about physical similarity of the twins and confusion of the twins by family members, friends and strangers. Information on zygosity was available from DNA polymorphisms for 726 same sex twin pairs. The agreement between zygosity diagnoses from questionnaire and DNA data was 97%.

In 1997, 2000 and 2002, neuroticism, extraversion and anxious depression were measured with self-report questionnaires. In 2000 and 2002, exposure to life events was also assessed. Mean ages and scores on neuroticism, extraversion and anxious depression as well as frequencies of experienced life events were comparable for the 2000 and 2002 samples of twins. Therefore, the largest possible sample was made by combining the data that were collected in 2000 and 2002. Data of subjects, who participated in 2000, but not in 2002, were added to the data of subjects who participated in 2002. This led to a sample with cross-sectional data on life events, anxious

depression, neuroticism and extraversion for 1918 male and 3864 female twins. There were 334 complete monozygotic male (MZM) twin pairs, 171 dizygotic male (DZM) twin pairs, 876 monozygotic female (MZF) twin pairs, 414 dizygotic female (DZF) twin pairs and 450 dizygotic twin pairs of opposite sex (DOS). For 1058 male and 2226 female twins, personality and anxious depression data were also available from the survey preceding the survey in which the exposure to life events was assessed.

Instruments

Neuroticism and extraversion were measured with the Amsterdamse Biografische Vragenlijst (ABV) (Wilde, 1970). The ABV neuroticism and extraversion scales were modeled after the Eysenck Personality Questionnaire (Eysenck & Eysenck, 1964). Depression was measured with the anxious depression symptom scale of the Young Adult Self Report (YASR) (Achenbach, 1990; Verhulst et al., 1997). This scale is strongly related to DSM IV major depression (Middeldorp et al., 2006). The neuroticism, extraversion and anxious depression scores were logtransformed following earlier analyses of these data (Boomsma et al., 2000).

In the 2000 and 2002 survey, an adapted version of a Dutch life event scale (the Schokverwerkings Inventarisatie Lijst = SchIL) (Van der Velden et al., 1992) asked about the experience of the following life events: death of a spouse, father, mother, child, sibling or significant other, serious illness or injury of self or a significant other, divorce/break-up of a relationship, traffic accident, violent and sexual assault and robbery. Response categories were "never experienced" "0-6 months ago" "6-12 months ago" "1-5 years ago" and "more than five years ago". In the current study the response categories "0-6 months ago" and "6-12 months ago" were combined to "last year". The reliability of the life events scale was investigated in the total sample of subjects that participated in both the 2000 and 2002 survey. This sample consisted of 4225 twins, siblings and spouses of twins. For each life event, a maximum of 15.1% of the subjects gave inconsistent answers, i.e. they reported a life event in 2000, but not in 2002 or they did not report a life event in 2000, but reported in 2002 to have experienced this life event more than five years ago. Inconsistencies in life event report might be the result of mood congruence recall bias, i.e. "some material, by virtue of its affectively valenced content, is more likely to be stored and/or recalled when one is in a particular mood" (Blaney, 1986), which can lead to exaggeration of effect size estimates. This was tested in two ways. Firstly, for the subjects whose life event report was inconsistent, their depression score at the time that they reported a life event was compared to their depression score at the time that they did not report a life event. If mood congruence bias is of importance, subjects are expected to score higher on depression at the time that they report the life event. These tests were performed separately for the subjects who reported a life event in

2000 but not in 2002 and for the subjects who reported in 2002 to have experienced a life event more than five years ago, but had not reported this life event in 2000. This yielded no significant results (threshold p-value of 0.05). Secondly, the group of subjects with consistent life event reports was compared to the subjects with inconsistent reports regarding the depression scores measured at the time that the last group did not report the event. If mood congruence bias is of importance, the depression score is expected to be lower in the group of subjects with the inconsistent reports. For divorce, a significant difference ($p < 0.01$) in the depression score of 2002 was found for subjects who reported a divorce/break up in 2000 but not in 2002 compared to subjects who reported this event twice. However, the depression score in 2000 was not significantly different between subjects who reported a divorce more than five years ago in 2002, while they had not reported this event in 2000 compared to the subjects who reported the divorce twice. For death of a significant other, the results were the other way around. The depression score in 2000 was significantly different ($p < 0.01$) between subjects who reported this event in 2002 but not in 2000 compared to subjects who reported this event twice. The depression score in 2002 was not significantly different for subjects who reported this event in 2000, but not in 2002. Thus, there was hardly any evidence for mood congruence recall bias.

A recent analysis of the life event data demonstrated that familial clustering in death of a family member and death or serious illness/injury of significant other was explained by common environmental factors (Middeldorp et al., 2005b). As a consequence, gene-environment correlation cannot be present for the relation of these life events with anxious depression, neuroticism or extraversion. Therefore, the life events included in the present analyses consisted of serious illness or injury of self, divorce/break-up, traffic accident, robbery, violent assault and sexual assault.

Statistical methods

The longitudinal data were analyzed in two ways. To investigate the influence of life events paired t-tests were performed to compare the anxious depression, neuroticism and extraversion scores before and after the experience of a life event last year. In turn, the influence of these traits on the exposure to life events was also examined. Exposed and unexposed subjects were compared on their anxious depression, neuroticism and extraversion scores measured before life event exposure. This was tested with a Student's t-test.

Significant results can indicate a causal relationship, but do not exclude the possibility of gene-environment correlation. Therefore, the co-twin control method (Cederlof et al., 1977) was used to investigate gene-environment correlation for life events and anxious depression, neuroticism and extraversion. In this design, the relative risk to have a disorder in the presence of a putative risk factor is calculated in a group of monozygotic (MZ) twins

discordant for exposure to the risk factor, a group of dizygotic (DZ) twins discordant for exposure to the risk factor and in a population consisting of unrelated subjects. If the relation between the risk factor and the disorder is causal and gene-environment correlation is absent, the relative risks will be the same in the three groups. If, on the other hand, the correlation between the risk factor and the disorder is due to genes that lead both to a higher risk for the disorder and to a higher risk of exposure to the risk factor, the relative risk will be higher in the total population than in the discordant dizygotic twins, whose relative risk will in turn be higher than the relative risk in the discordant monozygotic twins. Moreover, when gene-environment correlation entirely explains the relation between the risk factor and the disorder, the relative risk in MZ twins will be unity. This is because the unexposed member of MZ twins has the same genetic vulnerability to get the disorder as the twin that is exposed to the risk factor. Since DZ twins share on average half of their genes, the unexposed twin will share some of the genetic vulnerability to the disorder with the twin exposed to the risk factor. Unrelated subjects will show the highest relative risk.

As in this study anxious depression, neuroticism and extraversion were measured as continuous variables, relative risks could not be calculated and we had to compare the three groups in another way. Following the same logic as for the relative risks, in the presence of gene-environment correlation, two results are expected when continuous variables are compared between MZ twins discordant for exposure to a risk factor, DZ twins discordant for the exposure to a risk factor and a population of unrelated subjects, either exposed or non-exposed. First, it is expected that the differences between the exposed and non-exposed subjects are larger in the total population than in the discordant DZ population, while the discordant MZ twins do not differ from each other. Second, it is expected that the larger differences are not due to differences in scores between the exposed subjects, but to differences in scores between the non-exposed subjects in the three groups. Non-exposed subjects from the total population will score lower than the DZ discordant non-exposed subjects who in turn will score lower than the MZ discordant non-exposed subjects. Both expectations were tested in our study. Differences in depression, neuroticism and extraversion scores between the exposed and non-exposed subjects were tested with a paired t-test in the groups of MZ and DZ discordant twin pairs and with a Student's t-test in the population of unrelated subjects. Next, it was investigated whether the scores of non-exposed subjects in the group of unrelated subjects was lower than the scores of non-exposed subjects in the group of discordant DZ twins and whether the latter was lower than the scores of the non-exposed subjects in the group of discordant MZ twins.

Results

Longitudinal analysis

Table 9.1 shows mean age, anxious depression, neuroticism and extraversion scores. As expected, women score higher than men on anxious depression and neuroticism. Anxious depression, neuroticism and extraversion scores before and after exposure to a life event were compared to investigate the influence of life events (table 9.2). Sexual assault was not separately investigated, as only three subjects were exposed and had scores on both occasions. Anxious depression scores were significantly increased after exposure for all life events, except robbery and violent assaults. Neuroticism and extraversion scores showed no considerable change before and after exposure.

Table 9.1: Mean (SD) age, mean (SD) depression, neuroticism and extraversion scores measured at the time of the life event questionnaire

	Men (N=1918)	Women (N=3864)
Age	30.8 (9.7)	31.7 (9.9)
Anxious Depression	5.0 (4.9)	7.6 (5.9)
Neuroticism	42.6 (23.8)	52.3 (25.7)
Extraversion	63.1 (16.3)	60.1 (16.8)

Table 9.2: Anxious depression, neuroticism and extraversion scores (SD) before measurement of the life events (T1) and at the time of the measurement of the life events (T2). Two tests were performed: 1) within group differences were analyzed for the scores of T1 and T2. This signifies in the case of an event that anxious depression, neuroticism and extraversion scores before and after exposure were compared, and 2) between group differences were analyzed for the scores at T1, thus before exposure, comparing the group who did not experience an event (first three rows) with the groups that did experience an event.

		T1	T2
No events (N=1149)	Anxious depression	18.9 (9.7)	19.4 (9.9) ^{1*}
	Neuroticism	18.2 (2.7)	18.2 (2.8)
	Extraversion	20.3 (1.6)	20.2 (1.7) ^{1***}
Any event (N=539)	Anxious depression	21.3 (10.2) ^{2***}	22.5 (10.2) ^{1***}
	Neuroticism	18.9 (2.8) ^{2***}	19.0 (2.9)
	Extraversion	20.5 (1.6)	20.4 (1.7) ^{1*}
Illness / injury self (N=107)	Anxious depression	21.9 (10.4) ^{2***}	23.9 (10.8) ^{1**}
	Neuroticism	19.4 (2.6) ^{2**}	19.7 (2.8)
	Extraversion	20.2 (1.7)	20.0 (2.0)

Life events and depression, neuroticism and extraversion

Table 9.2: Anxious depression, neuroticism and extraversion scores (SD) before measurement of the life events (T1) and at the time of the measurement of the life events (T2). Two tests were performed: 1) within group differences were analyzed for the scores of T1 and T2. This signifies in the case of an event that anxious depression, neuroticism and extraversion scores before and after exposure were compared, and 2) between group differences were analyzed for the scores at T1, thus before exposure, comparing the group who did not experience an event (first three rows) with the groups that did experience an event. (Continued)

		T1	T2
Divorce/break-up (N=139)	Anxious depression	22.6 (9.8) ^{2***}	24.8 (9.3) ^{1**}
	Neuroticism	19.2 (2.9) ^{2***}	19.3 (2.9)
	Extraversion	20.7 (1.4) ^{2*}	20.7 (1.3)
Accident (N=91)	Anxious depression	19.4 (10.3)	20.8 (9.5) ^{1*}
	Neuroticism	18.6 (2.8)	18.5 (2.8)
	Extraversion	20.4 (1.9)	20.4 (1.7)
Robbery (N=236)	Anxious depression	21.0 (10.1) ^{2**}	21.5 (10.2)
	Neuroticism	18.8 (2.7) ^{2**}	18.9 (2.8)
	Extraversion	20.5 (1.5) ^{2*}	20.4 (1.7) ^{1*}
Violent assault (N=28)	Anxious depression	22.2 (8.2)	21.1 (9.7)
	Neuroticism	18.1 (3.3)	18.9 (3.2)
	Extraversion	20.6 (2.2)	20.7 (2.1)

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

¹Within group differences

²Between group differences

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Next, we investigated whether anxious depression, neuroticism or extraversion might influence the risk to the experience of life events. Subjects who reported a life event in the last year were compared with subjects who reported no life event in the last year on their anxious depression, neuroticism and extraversion scores two years before the assessment of life events (table 2). For all life events, but traffic accident and violent assault, subjects who were to experience a life event scored significantly higher on anxious depression and neuroticism than subjects who were not going to experience a life event. Subjects that reported a violent assault showed the highest anxious depression scores before exposure of all events, but this did not reach significance because of the low frequency (N=28). This pattern was not seen for neuroticism. Again, differences for extraversion were small and in general non-significant.

Gene-environment correlation

Discordant twin pairs were defined as a pair in which one twin had never experienced a life event, while the other had experienced a life event at least once. Only same sex twin pairs were included in this analysis. The sample of unrelated individuals consisted of twins of a same sex twin pair of whom the co-twin had not participated or twins who were randomly selected from a same sex twin pair concordant for exposure to life events.

In these three groups, differences in anxious depression, neuroticism and extraversion scores were tested between subjects who did not experience any event and subjects who were exposed to any life event during last year, the last 5 years or ever (Table 9.3). The differences between exposed and non-exposed subjects were sometimes larger in the discordant DZ twin pairs and in the unrelated subjects than in the discordant MZ twin pairs, but the expected pattern of non-exposed subjects scoring highest in the discordant MZ twin pairs, lowest in the unrelated subjects and in-between in the discordant DZ twin pairs was not seen. These analyses were repeated for the life events separately (Table 9.4). Violent and sexual assault were not included in the analyses of the specific life events, since less than 20 discordant dizygotic pairs could be identified. The expected pattern was not seen for any of these events.

Discussion

Our results indicate that having experienced a serious illness of self, divorce or traffic accident increase symptoms of anxious depression. Neuroticism and anxious depression, on the other hand, increase the risk for exposure to serious illness of self, divorce and robbery. This could also account for the life event violent assault, but the group of exposed subjects was too small to draw this conclusion. Gene-environment correlation for life events and anxious depression, neuroticism and extraversion appears to be absent. This signifies that the relation between life events and anxious depression seems to be explained by reciprocal causation. Neuroticism might also be causally related to life events, but life events do not cause neuroticism. There does not seem to be an association between life events and extraversion. Therefore, the relation between low extraversion and depression is not due to a higher risk for life events in introverted subjects as was suggested earlier (Middeldorp et al., 2006).

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Table 9.3: Mean (SD) anxious depression, neuroticism and extraversion scores of subjects who were never exposed to any life event (le) and subjects who were exposed to a life events last year (below first bold line), in the last 5 years (below second bold line) or ever (below third bold line) in discordant monozygotic (MZ) twin pairs, discordant dizygotic (DZ) twin pairs and unrelated subjects.

	Discordant MZ			Discordant DZ			Unrelated subjects		
	Never le (N=107)	Last year le (N=107)	Δ	Never le (N=55)	Last year le (N=55)	Δ	Never le (N=993)	Last year le (N=498)	Δ
Anxious depression	19.2 (11.0)	22.5 (9.7)	3.3**	19.3 (9.1)	22.0 (9.6)	2.7	19.8 (10.1)	23.1 (9.8)	3.3***
Neuroticism	18.4 (3.0)	18.7 (3.0)	.3	18.0 (2.7)	18.8 (2.7)	.8	18.5 (2.7)	19.2 (2.8)	.7***
Extraversion	20.3 (1.7)	20.5 (1.6)	.2	20.4 (1.4)	20.2 (1.9)	-.2	20.2 (1.7)	20.5 (1.6)	.3**
	Never le (N=269)	Last 5 years le (N=269)	Δ	Never le (N=143)	Last 5 years le (N=143)	Δ	Never le (N=993)	Last 5 years le (N=1102)	Δ
Anxious depression	20.3 (9.7)	21.6 (9.5)	1.3	19.5 (9.6)	22.1 (8.7)	2.6**	19.8 (10.1)	22.4 (9.9)	2.6***
Neuroticism	18.4 (2.9)	18.6 (2.8)	.2	18.4 (2.7)	18.8 (2.5)	.4	18.5 (2.7)	19.1 (2.7)	.6***
Extraversion	20.3 (1.7)	20.4 (1.6)	.1	20.6 (1.4)	20.4 (1.7)	-.2	20.2 (1.7)	20.5 (1.6)	.3***
	Never le (N=372)	Ever le (N=372)	Δ	Never le (N=201)	Ever le (N=201)	Δ	Never le (N=993)	Ever le (N=1540)	Δ
Anxious Depression	20.2 (9.9)	20.9 (9.6)	.7	19.2 (9.7)	21.1 (9.7)	1.9*	19.8 (10.1)	21.9 (10.1)	2.1***
Neuroticism	18.4 (2.9)	18.6 (2.8)	.2	18.3 (2.8)	18.6 (2.6)	.3	18.5 (2.7)	19.0 (2.8)	.5***
Extraversion	20.2 (1.7)	20.3 (1.7)	.1	20.5 (1.5)	20.4 (1.6)	-.1	20.2 (1.7)	20.5 (1.6)	.3***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 9.4: Mean (SD) depression, neuroticism and extraversion scores of subjects who were never exposed to any life event and subjects who were exposed to serious illness/ injury self, divorce/break-up, accident, robbery in discordant monozygotic (MZ) twin pairs, discordant dizygotic (DZ) twin pairs and unrelated subjects.

	Discordant MZ			Discordant DZ			Unrelated subjects			
	Never	Ever	Δ	Never	Ever	Δ	Never	Ever	Δ	
Illness / injury self	Anxious depression	20.1 (10.4)	22.5 (10.7)	2.4	17.6 (10.7)	21.8 (10.8)	4.2	19.8 (10.1)	22.7 (10.2)	2.9***
	Neuroticism	18.3 (3.1)	18.9 (3.0)	.6*	18.3 (2.7)	19.3 (2.8)	1.0	18.5 (2.7)	19.3 (2.8)	.8***
	Extraversion	20.2 (1.6)	20.0 (1.9)	-.2	20.6 (1.4)	20.1 (1.8)	-.5	20.2 (1.7)	20.3 (1.7)	.1
Divorce	Anxious depression	19.7 (10.2)	21.6 (10.0)	1.9	19.4 (9.7)	22.3 (9.9)	2.9*	19.8 (10.1)	23.4 (9.8)	3.6***
	Neuroticism	18.5 (2.8)	18.9 (2.7)	.4	18.1 (2.9)	18.8 (2.5)	.7	18.5 (2.7)	19.2 (2.8)	.7***
	Extraversion	20.3 (1.8)	20.3 (1.7)	.0	20.7 (1.4)	20.5 (1.8)	-.2	20.2 (1.7)	20.6 (1.5)	.4***
Accident	Anxious depression	19.7 (9.8)	21.5 (9.9)	1.8	18.8 (9.6)	20.4 (9.9)	1.6	19.8 (10.1)	21.8 (9.9)	2.0***
	Neuroticism	18.0 (2.7)	18.7 (2.9)	.7*	18.7 (2.8)	18.7 (2.5)	.0	18.5 (2.7)	18.9 (2.8)	.4***
	Extraversion	20.1 (1.7)	20.2 (1.7)	.1	20.4 (1.6)	20.3 (1.6)	-.1	20.2 (1.7)	20.6 (1.5)	.4***
Robbery	Anxious depression	19.4 (9.5)	21.3 (8.9)	1.9*	18.5 (9.4)	21.5 (8.8)	3.0*	19.8 (10.1)	21.8 (10.0)	2.0***
	Neuroticism	18.4 (2.8)	18.5 (2.7)	.1	18.1 (2.7)	18.4 (2.5)	.3	18.5 (2.7)	18.9 (2.7)	.4***
	Extraversion	20.1 (1.9)	20.3 (1.8)	.2	20.5 (1.5)	20.1 (1.7)	-.4	20.2 (1.7)	20.4 (1.7)	.2*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Comparisons with other studies

The results of our longitudinal analyses are in agreement with earlier studies. It has repeatedly been found that life events precede the onset of depression (for a review see Paykel (2003)). The absence of an effect of life events on neuroticism and extraversion was also suggested by other research (Vaidya et al., 2002). Furthermore, results of several investigations have indicated that depression and neuroticism, in contrast to extraversion, predict the occurrence of negative life events (Fergusson & Horwood, 1987; Hammen, 2003; Magnus et al., 1993; Patton et al., 2003; Poulton & Andrews, 1992; van Os et al., 2001).

To our knowledge, there has been only one study that used the co-twin control design with discordant twin pairs to investigate the relation between life events and depression (Romanov et al., 2003). Their results were in agreement with ours (Romanov et al., 2003). Other studies have also addressed the question of gene-environment correlation, but in different ways. One family study also found no evidence for a common factor influencing both depression and life events (Farmer et al., 2000), but a number of other studies concluded that gene-environment correlation is present for life events and depression or neuroticism (Kendler et al., 1999; Kendler et al., 2003; Kendler & Karkowski-Shuman, 1997; McGuffin et al., 1988; Saudino et al., 1997). There are several differences between these studies and our study that could explain the divergent results regarding gene-environment correlation. In our study, anxious depression is analyzed as a continuous variable and not as a dichotomous trait. Non-depressed family members of depressed subjects probably have higher scores on a self-report depression questionnaire than non-depressed family members of control subjects. According to our results, non-depressed family members of depressed subjects may report more life events than non-depressed family members of control subjects, not as a consequence of their genetic liability for depression, but as a consequence of their higher depression scores. This effect will be strongest in MZ twins. Kendler et al. (1999) compared the odds ratio for onset of major depression in the month of a stressful life event between the total population of twins, dizygotic twin pairs and monozygotic twin pairs. They found that the odds ratio was higher in all subjects than in dizygotic pairs, whose odds ratio was higher than in monozygotic pairs. The difference with our study is that they did not select the discordant pairs, but analyzed all twin pairs. Therefore, the lower odds ratio in the MZ twins could be due to the concordant pairs instead of to the discordant pairs. In that case, their findings might be a coincidence since for the concordant pairs the same odds ratios are expected as for the population of unrelated subjects. Finally, the relatively low age of our sample compared to the other studies might also be the reason for the divergent results, especially when comparing our results to a study in older twins (Saudino et al., 1997).

Strengths and weaknesses

To our knowledge, this is the first study in which the relation between life events on the one hand and anxious depression, neuroticism and extraversion on the other, have been investigated both from a genetic as well as from a longitudinal perspective. This provided the opportunity to distinguish between causal effects and gene-environment correlation and to answer the question whether the relation between personality and depression is mediated by life events.

A weakness of the study was that life events were assessed with a questionnaire and not with an interview. Interviews may be more reliable than questionnaires (Paykel, 1983). However, it would have been difficult to reach such a large twin sample with interviews. Furthermore, recall bias, for which we were most concerned, did not seem to play a role. In our questionnaire, only acute life events were assessed. Probably, chronic stress, caused by for example financial difficulties or marriage problems, is also related to anxious depression, neuroticism and extraversion.

In the analyses of differences in anxious depression, neuroticism and extraversion scores between exposed and non-exposed subjects in the sample of unrelated individuals, sex differences were not considered. This might have influenced the results, since women score higher on anxious depression and neuroticism. Therefore, the analyses were repeated with a selected sample in which the number of men and women exposed to a life event was the same as the number of men and women who were not exposed and with the same female/male ratio as in the groups of discordant twins (2.4). Results were similar as in the other analyses.

The sample was relatively young. It is possible that some vulnerability genes have not been expressed yet, but will be expressed at a later age. Therefore, results might be different when the analyses are repeated when the subjects are older.

Implications

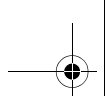
The results of this study have important implications for clinicians as well as researchers. In the treatment of depressive patients, attention should be paid to behavior that could lead to the experience of life events. They could, for example, be at risk for a divorce since spouses might experience difficulties in living with a depressed patient. Involvement of the spouse in the treatment and, if necessary, personal support for the spouse might prevent him or her from divorcing the patient before the depression is in remission. Another issue in treatment could be unhealthy lifestyles as they might lead to a higher risk for a serious illness. The exact mechanisms that lead to depressed patients being more prone to life events should be subject of future investigation.

Moffitt et al. (2005) recently pointed out that an essential step before investigating gene-environment interaction is the exclusion of gene-environment correlation. Gene-environment interaction reflects genetic control of sensitivity to the environment, i.e the effect of an environmental risk factor depends on the genetic make-up of an individual (Kendler & Eaves, 1986). In an analysis modeling a potential change in heritability in subjects exposed and non-exposed to a certain environment, a significant gene-environment interaction effect can even be due to gene-environment correlation if this is not included in the model (Purcell, 2002). Moreover, in a study on the interaction of the effect of a specific gene and the exposure to an environmental factor, gene-environment interaction might actually be gene-gene interaction if gene-environment correlation is present (Moffitt et al., 2005). Our study indicated that gene-environment correlation is not of importance in the relation between life events and depression and therefore needs not to be considered in an analysis of the interaction between the effect of genes and life-events in the development of depression.

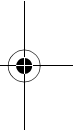
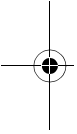
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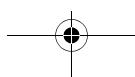
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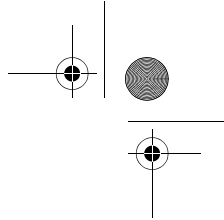


Life events and depression, neuroticism and extraversion



Chapter
9

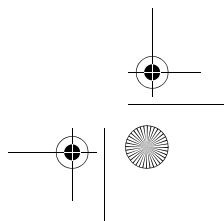
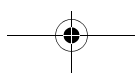
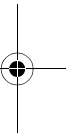
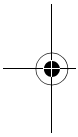


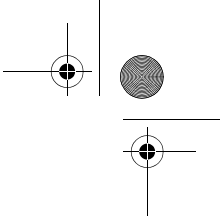


Chapter

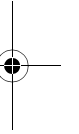
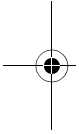
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Summary and General Discussion

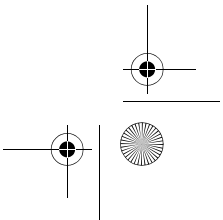
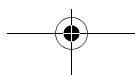




Summary and general discussion



Chapter
10



This chapter discusses the implications of the results of the studies described in this thesis.

First, a summary is given of the results of the previous chapters.

Summary

As a prelude to the subsequent analyses, chapter two addressed the co-morbidity between anxiety and depression, by reviewing empirical evidence regarding mechanisms that might underlie the frequent co-morbidity within anxiety disorders, and between anxiety disorders and depression. The theory of Gray & McNaughton (2000) was taken as a frame of reference. Gray & McNaughton (2000) hypothesized that the anxiety disorders as well as depression are distinct entities with the co-morbidity explained by 1) recursive interconnections linking the brain regions involved in fear, anxiety and panic and 2) heritable personality traits such as neuroticism underlying anxiety as well as depression. Their theory can be translated into the co-morbidity models of Klein and Riso (1993) and Neale and Kendler (1995). These models describe causes for co-morbidity in general, which can be formally tested in longitudinal or twin-family designs. Co-morbidity due to recursive interconnections linking brain regions can be viewed as one disorder being an epiphenomenon of the other, i.e. multiformity. Co-morbidity due to neuroticism being a heritable risk factor for anxiety as well as depression can be interpreted as co-morbidity due to a partly shared genetic etiology. Twin and family studies investigating these models for anxiety, depression and neuroticism were reviewed. To compare the outcomes systematically, genetic and environmental correlations between disorders were calculated for 23 twin studies and the results of 12 family studies were summarized according to the method of Klein & Riso (1993). Twin studies showed that co-morbidity within anxiety disorders and between anxiety disorders and depression is explained by a shared genetic vulnerability for both disorders. Genetic factors influencing neuroticism seemed to overlap with vulnerability genes for anxiety and depression. Some family studies supported this conclusion, but most family studies suggested that co-morbidity is due to one disorder being an epiphenomenon of the other. These discrepancies between the twin and family studies could be due to differences in methodology. All twin and some of the family studies used biometrical model fitting, whereas most family studies compared prevalence rates of disorders in family members of affected probands. Two simulation studies testing the validity of the Klein and Riso predictions and the Neale and Kendler model fitting approach revealed that the latter method was more valid to discriminate the correct co-morbidity model (Rhee et al., 2003; Rhee et al., 2004). The predictions of Klein & Riso (1993) did not seem to be valid under some circumstances (Rhee et al., 2003). However, all studies using biometrical

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model fitting only tested the model of shared etiology. Rhee et al. (2004) demonstrated that this model might also fit when another model, e.g. multiformity, describes the data even better. Nevertheless, considering the fact that the model of shared etiology fits the data in 23 twin and three family studies, the theory of Gray and McNaughton (2000) is supported that anxiety disorders and depression are distinct entities with at least part of the co-morbidity explained by shared genetic risk factors reflected in the personality trait neuroticism. Further research should reveal whether recursive interconnections linking brain regions are also of importance in the frequent co-morbidity.

Chapter three continued with the co-morbidity issue, by describing two studies performed to investigate the association between neuroticism, extraversion and sensation seeking, on the one hand, and anxious and depressive psychopathology, on the other. In both studies, co-morbidity between depression and other psychopathology was explicitly taken into account. In study I, data from 7969 twins and siblings of the Netherlands Twin Register were analyzed. Correlations were estimated within and between self-report measures of the three personality dimensions, anxiety and depression. Furthermore, to take co-morbidity into account, subjects were divided into cases and controls on the measures of anxiety and depression, with the 95th percentile used as a cut-off score. Next, the mean scores of the “pure cases” and the “co-morbid cases” were compared with the means of the control subjects. In study II, analyses were performed on DSM IV diagnoses of major depression, dysthymia, social phobia, generalized anxiety disorder and panic disorder. These data were obtained for a selected sample of 1240 individuals. Per diagnosis, personality scores were compared between affected and unaffected subjects, correcting for co-morbidity by including all disorders in the model. Additionally, personality scores were compared between subjects with zero, one, two or three or more diagnoses. Study I showed that high neuroticism and low extraversion were related to anxiety as well as depression. Sensation seeking was related to neither of them. These results were replicated when the personality scores of the “pure” and “co-morbid cases” were compared with control subjects. In study II, high neuroticism was related to all disorders, except dysthymia. Low extraversion was related to social phobia and panic. High neuroticism and low extraversion were both related to the number of disorders. No associations were found with sensation seeking. Thus, high neuroticism and low extraversion appear to be related to anxiety and depression, also when co-morbidity is taken into account. Remarkably, sensation seeking seems an independent personality dimension, which is not associated with anxious and/or depressive psychopathology.

In chapter four data from Australian (N=2287) and Dutch (N=1185) dizygotic twins and siblings, who were selected for a linkage study and participated in clinical interviews to obtain lifetime DSM IV diagnoses, were

used to investigate familial influences and their dependence on sex for panic disorder and/or agoraphobia, social phobia, generalized anxiety disorder and major depression. A correction for ascertainment bias was carried out by including the selection variables in the analyses (Little & Rubin, 1987). In a liability model, tetrachoric correlations were estimated in male, female and opposite-sex sibling pairs. For each diagnosis, the sibling correlations could be constrained to be equal across the Australian and Dutch samples. Next, sex differences in the correlations were tested. For each diagnosis, the sibling correlations were similar for brothers and sisters. With the exception of panic disorder and/or agoraphobia, the same sex correlations could be constrained to be equal to the correlations of the opposite-sex sibling pairs. For major depression, social phobia and generalized anxiety disorder, the correlations were estimated to be about 0.20. For panic disorder and/or agoraphobia, the correlation was 0.23 in brother and sister pairs, but absent in opposite-sex sibling pairs. To conclude, upper heritability estimates, based on twice the correlations in the sibling pairs, vary between 36% (major depression) and 50% (social phobia). Furthermore, different genetic risk factors appear to contribute to the vulnerability for panic disorder and/or agoraphobia in men and women. No other sex differences were found.

Chapter five investigated the association between the serotonin transporter gene polymorphism (5-HTTLPR) and quantitative measures of neuroticism, anxiety and depression. Chapter three had clearly shown an association between these measures and DSM IV anxiety disorders and depression. Genetic epidemiological analyses of the neuroticism, anxiety and depression scores had already indicated heritabilities of 40%-50% (Boomsma et al., 2000). Lesch et al. (1996) were the first to report an association between 5-HTTLPR and anxiety-related personality traits; subjects with the short variant of the gene scored significantly higher on these traits than subjects with only the long variant. Since then, the association between 5-HTTLPR and anxiety-related personality traits or depressive psychopathology has been investigated in numerous studies, but with conflicting results. In a large study retaining 100% power to detect a genetic effect accounting for just 0.5% of phenotypic variance no significant association between 5-HTTLPR and neuroticism or major depression was found (Willis-Owen et al., 2005). However, population stratification, which can lead to both type I and type II errors, was not considered in their analyses. Therefore, we carried out a family based association analyses of 5-HTTLPR and neuroticism, anxiety and depression. In 466 families from the Netherlands Twin Register, 254 fathers, 305 mothers, 501 male and 744 female offspring were genotyped for 5-HTTLPR. These families were selected from the Netherlands Twin Register to include sibling pairs scoring extremely high or low on a composite score of neuroticism, anxiety and depression. The subjects had participated between one and five times in a survey study measuring neuroticism, anxiety or depression. The

Summary and general discussion

association between the ss, sl and ll variants of 5-HTTLPR, and these traits was investigated, modeling an additive effect of the s-allele with sex included as a fixed effect. Both within family association and total association were tested in QTD for the five measures of the three traits and for the mean scores of the traits for each subject over the five occasions. Only 3 of the 36 association tests showed a significant effect of 5-HTTLPR ($p < 0.05$). Neuroticism and anxiety measured in 1991 showed a significant negative regression coefficient for the s allele, whereas neuroticism measured in 2000 showed a significant positive regression coefficient for the s allele. The overall results clearly suggest no association between 5-HTTLPR and anxiety-related traits. They also show how associations can be found by coincidence. Had we chosen to report the results of the 1991 survey, we would have drawn the conclusion that there is a significant association between 5HTTLPR and anxiety-related traits.

As a preparation for a study on the association between burnout and employment on the one hand and anxiety and depression on the other, we investigated in chapter six whether burnout clusters within families and, if yes, whether this is due to genetic influences or to environmental factors shared by family members. Finally, we tried to identify specific risk factors for burnout. Earlier research on risk factors for burnout had mainly focused on circumstances at work and personal characteristics and had not addressed the issue of familial clustering. In 2707 twins, 736 of their siblings and 575 of their spouses from a population based twin-family sample, burnout was measured using a self-report questionnaire. Correlations in burnout scores were calculated in monozygotic (MZ) and dizygotic (DZ) male and female twin pairs and in brothers, sisters and sibling pairs of the opposite sex. Next, differences in correlations between MZ, DZ and sibling pairs were tested as well as differences in correlations between brothers and sisters and between same-sex and opposite- sex pairs. Moreover, correlations between twins and their spouses were derived conditional on the length of the relationship. In the final model, correlations of the MZ and DZ twin pairs and sibling pairs were significantly different from zero, but not significantly different from each other. No sex differences in the correlations were found either. The sibling correlation was estimated at 0.22. The correlation between spouses was also significant. This was mainly due to the group with a relationship longer than 5 years in which the correlation was 0.24. From the investigated specific risk factors, only a high level of education in the parents was associated with higher burnout scores. Age did not have a considerable effect on burnout. To conclude, there appears to be familial clustering for burnout, which is due to environmental factors shared by family members, explaining 22% of the variance. Genetic factors do not seem to be of importance. The significant correlation between spouses supports the conclusion that common environment plays a role in burnout. A high level of parental education could be one of the familial risk factors.

Chapter seven aimed to find out whether the association between burnout and anxious depression as well as between employment and anxious depression could be caused by shared etiological factors. Both conditions have repeatedly been found to be related to anxiety or depression, but the causes of these relations were still unclear. In a sample of 4309 Dutch twins and 1008 of their siblings, bivariate genetic analyses of employment and anxious depression and of burnout and anxious depression were carried out using structural equation modeling. These analyses revealed that employment and anxious depression were both influenced by genetic and unique environmental factors. The association between employment and anxious depression was small, but significant, estimated at -0.08 . Statistical power was too low to decide whether the covariance was explained by genetic or unique environmental factors. In burnout, familial clustering was due to genetic factors in men, while in women genetic and common environmental factors explained familial resemblance. In both sexes, there was a strong correlation of around 0.40 with anxious depression, which was explained by shared genetic and shared unique environmental factors. Thus, the associations between employment and anxious depression as well as between burnout and anxious depression seemed to be due to overlapping genetic and unique environmental factors. Work related circumstances, e.g. financial strain or work-family conflict, might be of importance in burnout and anxious depression. Furthermore, these results could support the notion that a genetic vulnerability for depression can also increase the risk for exposure to high-risk environments such as unemployment, i.e. gene-environment correlation.

Before performing a study on the relation between life events and depression, **chapter eight** tested two assumptions often made in studies investigating the effect of life events on psychiatric disorders. Twin studies assume that there are no differences in prevalences of the experience of life events between twins and singletons. Violation of this assumption signifies that the results from twin studies might not generalize to singletons. Twin studies as well as other epidemiological designs investigating the association between environmental risk factors and psychiatric disorders also often assume that the exposure to life-events is random and not influenced by familial factors, either genetic or common environmental factors. If this assumption does not hold and the exposure to a life event is, for example, partly genetically influenced, this signifies that the relation between the life event and the disorder might not be causal. Instead, genes influencing the vulnerability for a disorder might also increase the risk for exposure to a life event. To test these assumptions, we first investigated differences in prevalences of experienced life events in a Dutch sample of 2086 MZ twins, 2090 DZ twins and 1307 of their siblings. Since siblings of twins are matched regarding parental social economic status and upbringing, they are the perfect control group. Self-reported data on life events (serious illness or injury of self, serious illness or injury of a significant other,

Summary and general discussion

being married or involved in a romantic relationship, divorce / break-up of a relationship, death of a significant other, traffic accident, robbery, violent assault, sexual assault) were available from the Netherlands Twin Register survey studies. Second, we investigated whether familial resemblance was present for the exposure to these life events and, if yes, whether this resemblance was due to genetic or common environmental factors. No differences were found in the prevalences of life events between MZ twins, DZ twins and their non-twin siblings. There was evidence for familial aggregation of all life events, except for traffic accidents in women. Results indicated genetic control on the presence of a spouse or involvement in a relationship. Familial resemblance of illness and death of a significant other was mainly due to common environment. For the other life events, it was not possible to decide whether familial clustering was due to genetic and common environmental effects.

Chapter nine investigated the relation between life events and anxious depression. Since chapter three concluded that anxious depression was related to neuroticism and extraversion in, these personality traits were also considered in the analysis. In addition to establishing whether or not an association exists between these measures and life events, the aim was to get more insight into the mechanism underlying a possible association. Is this due to causality or are there genes that influence both depression and increase the risk to experience a life event, so called gene-environment correlation. Cross-sectional data on life events, anxious depression and personality were collected with self-report questionnaires for 1918 male and 3864 female twins. For 1058 male and 2226 female twins, personality data were also available from the survey previous to the survey in which the exposure to life events was assessed. Life events were measured on two occasions. Inconsistencies in answers did not appear to be due to recall bias. The life events serious illness of self, divorce, traffic accident, robbery, violent assault and sexual assault were investigated. Sexual assault was not included in the analyses of the specific life events, as the prevalence was too low. Paired t-tests of anxious depression scores before and after the exposure to a life event showed that the life events serious illness of self, divorce and traffic accident increase symptoms of anxious depression. Robbery and violent assault do not have that effect. Neuroticism and extraversion scores are hardly influenced by life events exposure. Next, to investigate whether depression, neuroticism or extraversion might be causally related to the experience of life events, depression, neuroticism and extraversion scores two years before the life event report were compared between subjects that had reported a life event last year and subjects who had reported no events last year. Higher neuroticism and anxious depression scores preceded the life events serious illness of self, divorce and robbery. Higher scores on anxious depression, but not on neuroticism, also seemed to precede violent assault, but the prevalence of this life event was too

low to draw this conclusion. With the co-twin control method, gene-environment correlation was investigated. In the presence of gene-environment correlation, e.g. for life events and depression, MZ twins discordant for life events show no difference in depression scores. DZ twins discordant for life events do show a difference in depression scores, but this difference is smaller than in a population of unrelated subjects. These differences in scores are due to differences in the scores of non-exposed subjects. The non-exposed subjects of the discordant MZ twin pairs score higher than the non-exposed subjects of the discordant DZ twin pairs, who in turn score higher than the non-exposed subjects in the total population. This pattern of results was not seen for anxious depression, neuroticism or extraversion. These results suggest a reciprocal causal relation between most of the life events under study and anxious depression. High neuroticism scores in general preceded life events. There was no association between life events and extraversion. Gene-environment correlation appeared to be absent for the investigated life events and anxious depression, neuroticism and extraversion.

General Discussion

A few small explanations

Kendler (2005b) stated that “What we can best hope for is lots of small explanations, from a variety of explanatory perspectives, each addressing part of the complex etiological processes leading to disorders. It will be particularly challenging to understand how these many different small explanations all fit together.” The goal of this thesis was to add some “small explanations” to the current knowledge on anxiety and depression from a genetic perspective.

The first part (chapter two to five) aimed to get more insight in the genetic background of anxiety and depression. Using the paradigm of advanced genetic epidemiology (Kendler, 2005a), it was examined whether genetic risk factors are shared for anxiety and depression and if yes, whether a genetic vulnerability for anxiety or depression can be expressed as a personality trait. Furthermore, sex differences in genetic architecture for anxiety and depression were investigated. Finally, employing the paradigm of gene finding methods (Kendler, 2005a) a family association analysis was carried out with 5-HTTLPR and anxiety, depression and neuroticism. Chapter two showed that anxiety and depression are distinct entities, but with a partly shared genetic background, probably expressed in the personality trait neuroticism. Chapter three confirmed that anxiety as well as depression is related to neuroticism. Moreover, extraversion appeared to be negatively related to these symptoms. Sensation seeking was not associated with anxiety and depression at all. Chapter four supported the findings of earlier studies that major depression, generalized anxiety disorder, social phobia and panic disorder and/or

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agoraphobia are for 30%-40% heritable. Sex differences in genetic architecture of anxiety and depression are probably limited. With the exception of panic disorder and/or agoraphobia, the genes that influence anxiety or depression appeared to be the same for men and women. This signifies for gene finding studies that neuroticism and extraversion might be appropriate endophenotypes for research aiming to identify genes underlying the vulnerability for anxiety and depression and that it is not strictly necessary to take sex differences into account. Next, the association between 5-HTTLPR polymorphism and self-report measures neuroticism, anxiety and depression was investigated in a large sample of parents and siblings. Overall, there did not appear to be a significant association. Together with a recent study in a large sample of unrelated subjects (Willis-Owen et al., 2005), this study strongly suggests that the short form of 5-HTTLPR is not associated with higher scores on neuroticism, anxiety and depression measures which are associated with DSM IV anxiety and depression .

The second part of the thesis investigated specific risk factors that are mostly considered to be purely environmental. More knowledge on the mechanisms underlying exposure to certain risk factors can enable genetic research to better model the combined effect of genes and other risk factors on anxiety and depression. Again using the paradigm of advanced genetic epidemiology (Kendler, 2005a), we examined whether familial factors can increase the risk for exposure to specific environments. Moreover, the issue of gene-environment correlation was addressed, i.e. does a genetic vulnerability for anxiety or depression also increase the risk for exposure to high-risk environments? Our results indicated that the occurrence of risk factors is fairly random in the population, but familial factors are also of importance. For employment status, genetic factors seem to cause resemblance in family members. For burnout both genetic and common environmental factors might explain familial clustering. In the case of life-events, it was not possible to decide whether genetic or common environmental factors were of importance. Bivariate genetic epidemiological analyses suggested that the associations between employment and depression and between burnout and depression are due to shared genetic and shared unique environmental factors. Regarding the association with life events gene-environment correlation seems to be absent, but high scores on depression or neuroticism lead to a higher risk for life events. Life events, on the other hand, also increase depression scores. These results indicate the complexity that can exist in a relation between a risk factor and a disorder. Further research is needed to unravel more precisely the mechanisms of the associations. Still, these issues need to be considered in the treatment of depression as well. It is necessary to discuss what the circumstances at work are like for a patient, since stressful conditions might play a role in the development of burnout as well as depression. Moreover, as a genetic vulnerability for depression may also increase the risk for

unemployment, it is important to know whether the patient can meet the demands of his job. Problems in this area should be a focus of treatment. The same holds for the higher risk to experience life events in depressed subjects, especially since these life events might worsen the depression. If possible, measures should be taken to prevent life events, such as meetings with the spouse of a depressed patient to discuss the risk of a divorce.

The bits of knowledge that are still missing

The conclusions of the previous chapters raise several new research questions and identify bits of knowledge that are still missing. These will be discussed in the following section together with recommendations for future studies.

Chapter six and seven describe, to our knowledge, the first twin-family studies on respectively burnout and the associations between burnout and anxious depression as well between employment and anxious depression. It is obvious that further investigations are necessary to shed more light on these issues. The results were somewhat contradictory regarding the influence of genetic and common environmental factors on burnout. This could be partly due to an increased power to detect small effects in the bivariate analysis. Another reason could be the different order of the steps taken in the model fitting procedure. In chapter six, the correlations between the MZ and DZ male pairs were first constrained to be equal before this correlation was constrained to the correlation in the brothers. However, first constraining the correlation of the dizygotic male twin pairs to the pairs of brothers, leads to slightly different results as shown in Table five in chapter seven. While the model fitting procedure as described in chapter six did not show any genetic influences, the presence of genetic effects was suggested in the other chapter. In chapter six, the significant spouse correlations support the finding of common environmental factors, but in chapter seven the significantly higher MZ than DZ cross-twin-cross-trait correlations for burnout and anxious depression support the influence of genetic factors. Additional data on burnout in the parents of the twins and siblings might provide the opportunity to resolve this issue by including the effect of cultural transmission from parents to offspring as well as environment shared by twins and siblings in the model (Truett et al., 1994).

The association between employment status and anxious depression also needs to be further investigated. The negative association between employment and depression had already been repeatedly found. Therefore, we decided that, the small, but significant, correlation of -0.08 found in our study fitted into the general picture. An explanation for such a low correlation could be that all unemployed subjects were considered as one group. Possibly, unemployment is more harmful when it is involuntarily than when it is a well-contemplated choice. In the former case, financial consequences might, for example, be more severe. Our group of unemployed subjects was too small to further examine this question (see Appendix A). Another reason for the low

Summary and general discussion

correlation might be that, as is also suggested by our results, being employed might protect against depression in the right circumstances, but might provoke a depression in stressful conditions. To summarize, more extensive data collection, especially regarding employment status and work conditions, is necessary. This needs to be done in a longitudinal or twin-family design to be able to investigate the underlying mechanisms of associations.

What do our results mean for future research focusing on the genes underlying the vulnerability for anxiety and depression? Chapter two has shown that the DSM IV anxiety disorders and major depression are distinct entities with a partly shared genetic background. Therefore, there are probably two strategies that can be followed in gene finding studies. It can either be useful to focus on the differences by defining narrow phenotypes or to focus on what these disorders have in common. An example of the first strategy is a study in which four factors were defined in subjects with a history of at least 2 depressive episodes (Korszun et al., 2004). These factors were “mood symptoms and psychomotor retardation”, “anxiety”, psychomotor agitation, guilt and suicidality” and “appetite gain and hypersomnia”. Sibling correlations were significant for three of the symptom dimensions, suggesting a genetic etiology. These factors might be more appropriate phenotypes than DSM IV depression in a gene finding study, as there are several combinations of symptoms possible to get a diagnosis.

An example of the second strategy is to focus on continuous traits that are related to all these phenotypes, e.g. high neuroticism, low extraversion or high scores on self-report questionnaires for anxiety or depression. As a lot more information is used in analyses of quantitative measures versus dichotomous variables, power to detect a small effect of a gene is increased (Williams & Blangero, 2004).

As it is well known that anxiety and depression are multifactorially determined, multiple risk factors should be considered together. This stresses the continuing importance of research on other risk factors than genetic ones. Focus of these studies needs to shift from finding associations to finding out what mechanisms underlie these associations. Is there a causal relation and, if yes, is this effect additive to or interactive with genetic effects? Or does gene-environment correlation play a role? The study on the interaction between the number of experienced life events and the effect of the short variant of 5-HTTLRP demonstrates that modeling genetic and environmental factors together can be a promising strategy (Caspi et al., 2003), although studies trying to replicate this finding do not all find a significant interaction effect (Eley et al., 2004; Gillespie et al., 2005; Kendler et al., 2005; Surtees et al., 2005). The association between employment status, stressful circumstances at work and depression is interesting for further investigation. The advantage of research on employment status and work related factors is that they might explain more variation in depression on a population level than life events,

since it affects more subjects' lives. Relatively rare life events, like sexual assault, can have a large effect on the individual, but explain little variance in depression on a population level.

Future research in the Netherlands Twin-Family Study on Anxious Depression

It is repeatedly mentioned in this thesis that the Netherlands twin-family study on anxious depression was designed to perform a linkage study aimed to find genes underlying the vulnerability for anxiety and depression. Just as this thesis was going to press, additional marker data had become available, giving a grand total of 1541 sibling pairs in which at least 250 markers were genotyped. Genotyping was performed in Marshfield (USA) and Leiden University Medical Center. In the near future, a multivariate genome-wide linkage study will be carried out on these marker data for neuroticism and extraversion. This is another design to investigate multiple risk factors, in this case genetic, simultaneously. Furthermore, genes involved in the serotonin system in the brain will remain a focus of attention. The population analyzed in chapter five, will be genotyped for a total of 12 polymorphisms in the genes coding for the serotonin receptors (e.g.1A, 1D, 2A, 2D) and BDNF in the department of molecular epidemiology in the Leiden University Medical Center. Rat studies have shown that BDNF stimulates function and growth of neurons producing serotonin in the brain, while the expression of BDNF is also regulated by serotonin (for a review of the function of BDNF see Angelucci et al. (2005)). A study in adults with childhood onset mood disorder, mostly major depression, found an association with BDNF (Strauss et al., 2004). Another promising candidate is the gene encoding for Tryptophan Hydroxylase type 2, the rate limiting enzyme in the synthesis of serotonin, expressed in the brain only (Zhang et al., 2004). Recently, several studies found evidence for association with major depression (Harvey et al., 2004; Zhang et al., 2005; Zill et al., 2004), but one study was not able to replicate the association found by Zhang et al. (Garriock et al., 2005). We aim to find a method to genotype subjects for TPH2. The relation between these polymorphisms and neuroticism, extraversion and the self-report measures of anxiety and depression will be analysed simultaneously in a family based association analysis.

The effect of environmental risk factors will be considered in these linkage and association analyses. Interaction between genes and risk factors, like the exposure to life events, being single and urbanicity, will be investigated. Gene-environment correlation will be included in these analyses where necessary.

Summary and general discussion

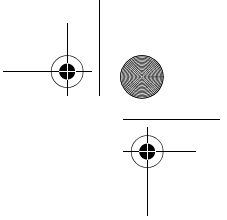
The frequent co-morbidity between anxiety and depression will be taken into account if necessary. Moreover, the co-morbidity models as discussed in chapter two will be tested. These results can provide information regarding which phenotypes can be analyzed simultaneously in a linkage or association analysis.

Finally, if one or more genes have been found to influence, for example, neuroticism, the next step is to investigate whether this gene is associated with a certain cluster of symptoms. Ultimately, the small explanations deriving from this research in combination with the findings from other fields like neuro-imaging and neurophysiology, hopefully lead to a more detailed description of the mechanisms underlying anxiety and depression.

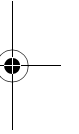
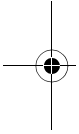
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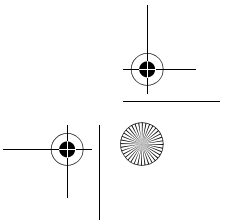
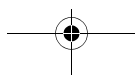
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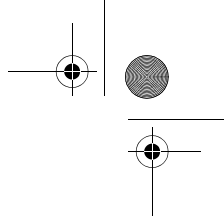


Summary and general discussion

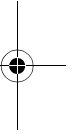
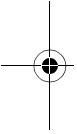


Chapter
10

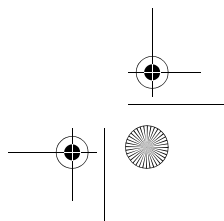
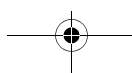




Samenvatting



**De rol van genetische factoren en ernstige
gebeurtenissen in het ontstaan van angst en
depressie**



Inleiding

Na een periode waarin de oorzaak van psychiatrische aandoeningen veelal werd gezocht in omgevingsfactoren zoals een ongunstig opvoedingsklimaat, is er tegenwoordig weer veel aandacht voor de rol van biologische factoren in het ontstaan van deze ziekten. Zo is inmiddels duidelijk geworden dat angst en depressie, het onderwerp van dit proefschrift, voor zeker 30% tot 40% erfelijk zijn. Deze erfelijkheidsschattingen, die dus geen 100% zijn, betekenen automatisch dat omgevingsfactoren ook van belang zijn. Tweelingonderzoek heeft aangetoond dat het hierbij niet gaat om omgevingsfactoren die worden gedeeld door familieleden, maar juist om de omstandigheden waaraan het ene familielid wel en het andere familielid niet wordt blootgesteld. Stressfactoren zoals werkloosheid of het meemaken van ernstige gebeurtenissen zijn bijvoorbeeld geassocieerd met deze klachten.

Ondanks deze kennis over de risicofactoren is nog niet duidelijk wat de exacte mechanismen zijn die leiden tot het ontstaan van angst en depressie. Hiervoor zijn verschillende oorzaken waarvan er slechts een aantal worden besproken. Eén van de struikelblokken is de complexiteit van het brein. Verschillende hersengebieden staan met elkaar in contact en zo wordt de activiteit in het ene gebied beïnvloed door activiteit in het andere gebied. Dit heeft bijvoorbeeld als gevolg dat het feit dat antidepressiva de hoeveelheid serotonine verhogen geenszins betekent dat de oorzaak van een depressie ook in het serotoninesysteem zal liggen. Het is heel goed mogelijk dat de oorzaak ligt in een ander systeem dat wordt beïnvloed door het serotoninesysteem. Een andere complicerende factor is dat psychiatrische aandoeningen multifactorieel bepaald zijn. Dat wil zeggen dat meerdere genen en omgevingsfactoren een rol spelen, waarbij waarschijnlijk geen enkele risicofactor afzonderlijk voldoende is om een aandoening te veroorzaken. Verder is het de vraag in hoeverre bepaalde omgevingsfactoren gelijkmatig in de bevolking voorkomen. Er zijn aanwijzingen dat sommige risicofactoren vaker voorkomen bij een bepaalde genetische achtergrond, zogenaamde gen-omgevingscorrelatie. Deze correlatie kan ontstaan op het moment dat de omgeving van een kind afhankelijk is van het genotype van zijn ouders. Kinderen die bijvoorbeeld het risico erven om depressief te worden, hebben ook meer kans dat ze opgroeien in een suboptimale omgeving vanwege een depressieve ouder. Gen-omgevingscorrelatie kan ook ontstaan doordat de omgeving waarin een individu zich bevindt afhankelijk is van zijn genotype, bijvoorbeeld door een hogere kans op het meemaken van ernstige negatieve gebeurtenissen. Tenslotte wordt het onderzoek naar oorzaken van psychiatrische stoornissen bemoeilijkt door de veel voorkomende comorbiditeit; dat wil zeggen dat twee aandoeningen zoals bijvoorbeeld een angststoornis en depressie vaker samen voorkomen dan op grond van toeval zou worden verwacht. Dit zou een resultaat kunnen zijn van het gebruikte

classificatiesysteem, de “Diagnostic and Statistical Manual of mental disorders, 4th edition” (DSM IV), waarbij clusters symptomen ten onrechte aan twee syndromen worden toegeschreven, terwijl het eigenlijk om één stoornis gaat. Maar andere verklaringen zijn eveneens mogelijk. Zo zou de comorbiditeit onder andere het gevolg kunnen zijn van risicofactoren die de kans op beide stoornissen verhogen.

Gegeven deze complicerende factoren kunnen we “het beste hopen op vele kleine verklaringen vanuit verschillende perspectieven, die ieder een deel van de complexe etiologische processen beschrijven die leiden tot psychiatrische aandoeningen.” (vrij vertaald van Kendler 2005, *American Journal of Psychiatry*, blz 435). Het doel van dit proefschrift was om vanuit een genetisch epidemiologisch perspectief een paar “kleine verklaringen” te vinden voor het ontstaan van angst en depressie.

Hierbij is veelal gebruik gemaakt van tweelingonderzoek. In het klassieke tweelingdesign wordt de mate van erfelijkheid van verschillen tussen mensen voor een bepaalde eigenschap onderzocht door de mate van gelijkenis tussen eeneiige tweelingen te vergelijken met de mate van gelijkenis tussen twee-eiige tweelingen. Deze mate van gelijkenis wordt statistisch uitgedrukt in een correlatie. Eeneiige tweelingen zijn genetisch identiek, terwijl bij twee-eiige tweelingen gemiddeld 50% van hun segregerende genen gelijk zijn. Als de correlatie in eeneiige tweelingen hoger is dan die in twee-eiige tweelingen duidt dit er dus op dat de betreffende eigenschap (deels) erfelijk is. Als de correlatie in eeneiige tweelingen gelijk is aan de correlatie in twee-eiige tweelingen is dat een aanwijzing dat de omgeving die gedeeld wordt door leden uit hetzelfde gezin van belang is. Verschillen tussen eeneiige tweelingen worden verklaard door omgevingsfactoren waaraan de ene tweeling wel wordt blootgesteld en de andere tweeling niet, de zogenaamde *individu-specifieke* omgevingsfactoren. Broers en zussen delen, net als twee-eiige tweelingen, gemiddeld 50% van hun genetisch materiaal. Maar zij delen mogelijk minder omgeving met elkaar dan tweelingen. Zo groeien zowel eeneiige als twee-eiige tweelingen tegelijkertijd op in dezelfde baarmoeder en hebben zij altijd een broertje of zusje van dezelfde leeftijd in de nabijheid. Zodoende zijn twee-eiige tweelingen de perfecte groep om met eeneiige tweelingen te vergelijken. Het toevoegen van broers en zussen aan de studipopulatie heeft echter als voordeel dat het statistisch gezien beter mogelijk is om vast te stellen of er effecten zijn van de gedeelde familieomgeving. Bovendien kan worden getoetst of tweelingen inderdaad meer omgeving met elkaar delen dan eenlingen uit hetzelfde gezin. Daarom zijn in dit proefschrift broers en zussen van tweelingen vaak ook betrokken bij het onderzoek. In tweelingonderzoek kan ook worden bepaald of er verschillen zijn tussen mannen en vrouwen met betrekking tot deze risicofactoren. Hierbij wordt onderscheid gemaakt tussen kwantitatieve en kwalitatieve verschillen. Er is sprake van kwantitatieve verschillen als de mate waarin variatie bij mannen wordt beïnvloed door bijvoorbeeld genetische



factoren verschilt van de mate waarin variatie bij vrouwen daardoor wordt beïnvloed. Dit kan eenvoudig worden onderzocht door te kijken of de erfelijkheidsschatting voor mannen significant verschilt van de erfelijkheidsschatting voor vrouwen. Er is sprake van kwalitatieve verschillen als andere genen van invloed zijn op variatie bij mannen en vrouwen. Dit kan worden bepaald door de correlatie van broer-zus paren te vergelijken met de correlaties van broer-broer of zus-zus paren. Dit kunnen dan uiteraard ook tweeeiige tweelingparen zijn. Als de correlatie in broer-zus paren lager is in verhouding tot de correlaties in broer-broer en zus-zus paren, wijst dit erop dat er andere factoren van belang zijn in mannen dan in vrouwen.

Behalve dat met tweelingonderzoek kan worden gekeken of en in welke mate een eigenschap erfelijk is, kan ook worden onderzocht wat de oorzaak is dat twee stoornissen vaak samen voorkomen. Als het bijvoorbeeld zo is dat het hebben van een familielid met een angststoornis het risico verhoogt dat iemand zelf een depressie krijgt, met of zonder co-morbide angststoornis, kan dit erop wijzen dat angst en depressie voor een deel dezelfde risicofactoren hebben. In het geval dat het risico van depressie hoger is bij eeneiige tweelingen van wie de co-twin angstig is dan bij tweeeiige tweelingen, zijn er mogelijk genen die zowel het risico van angst als van depressie verhogen. Is dit risico bij één- en tweeeiige tweelingen gelijk, dan zou het kunnen dat er gedeelde omgevingsfactoren zijn die het risico van beide stoornissen verhogen. Verder kan met tweelingfamilie-onderzoek ook worden vastgesteld of bepaalde eigenschappen samenhangen met een verhoogd risico van bepaalde omgevingsfactoren. Een andere mogelijkheid is om in families te kijken of een bepaalde variant van een gen vaker voorkomt bij mensen met angst of depressie. In dat geval speelt dat gen dus mogelijk een rol bij het ontstaan van de klachten. Van deze verschillende methoden is in dit proefschrift gebruik gemaakt om meer te weten te komen over de ontstaanswijze van angst en depressie. Hoofdstuk 2 tot en met 5 richten zich hierbij met name op het onderzoek naar het effect van genen. In hoofdstuk 6 tot en met 9 wordt vooral gekeken naar omgevingsfactoren en hun eventuele samenhang met genetische effecten.

Chapter 1

Samenvatting

Genetische factoren

Hoofdstuk 2 geeft een systematisch overzicht van de uitkomsten van tweeling- en familie-onderzoek naar de oorzaken voor de co-morbiditeit van angst en depressie. Behalve dat co-morbiditeit een gevolg kan zijn van overlappende etiologische factoren, zoals hierboven beschreven, kan het ook veroorzaakt worden doordat het hebben van aandoening A het risico verhoogt op het hebben van aandoening B. Dit laatste wordt multifomiteit genoemd. Het

verschil tussen co-morbiditeit ten gevolge van overlappende etiologische factoren en multiformiteit is dat bij overlappende etiologische factoren het risico van ziekte A samenhangt met het risico van ziekte B. Met andere woorden: als de risicofactor aanwezig is, is het risico van beide aandoeningen verhoogd. Het is dan afhankelijk van andere risicofactoren welke van de twee aandoeningen ontstaat of dat ze allebei ontstaan. In het geval van multiformiteit is het zo dat ziekte A aanwezig moet zijn voordat het risico van ziekte B is verhoogd. De risicofactoren voor ziekte A verhogen dus op zichzelf niet het risico van ziekte B. Het hebben van ziekte A is echter wel een risicofactor voor het ontwikkelen van ziekte B. Een andere oorzaak voor co-morbiditeit is dat er sprake is van drie aandoeningen: ziekte A, ziekte B en ziekte AB, de co-morbide conditie. Tenslotte is het ook nog mogelijk dat angst en depressie verschillende uitingsvormen van één aandoening zijn. Met behulp van tweeling- en familie-onderzoek kan worden onderscheiden welke van deze verschillende mechanismen een rol spelen. Uit het systematische overzicht van deze studies naar de co-morbiditeit van angst en depressie blijkt dat angst en depressie wel verschillende aandoeningen zijn, maar dat de risicofactoren waarschijnlijk deels overlappen. Zo lijkt het erop dat bepaalde genen zowel het risico van angst als het risico van depressie verhogen. Mogelijk uit deze risicofactor zich in de, voor ongeveer 50% erfelijke, persoonlijkheidstrek neuroticisme. Verder zijn er, in mindere mate, individu-specifieke omgevingsfactoren die het risico van beide stoornissen verhogen. Het is echter niet uitgesloten dat multiformiteit ook een deel van de co-morbiditeit verklaard. Een model waarin behalve angst en depressie ook neuroticisme is opgenomen, zou duidelijk kunnen maken of multiformiteit inderdaad van belang is.

Hoofdstuk 3 kijkt naar de samenhang tussen persoonlijkheidstrekken en angst en depressie. De volgende persoonlijkheidstrekken zijn onderzocht: neuroticisme, extraversie en sensatie zoeken. Neuroticisme is een maat voor emotionele instabiliteit. Extraversie geeft aan in hoeverre iemand sociaal, levendig en impulsief is. Sensatie zoeken hangt samen met de behoefte aan afwisseling en nieuwe impulsen. Er zijn verschillende hypothesen over de samenhang tussen deze persoonlijkheidstrekken en angst en depressie. Volgens Eysenck zijn hoge neuroticisme en lage extraversie scores geassocieerd met angst en depressie. Het tripartite model zegt echter dat hoge neuroticisme scores inderdaad zijn geassocieerd met angst en depressie, maar dat lage scores op extraversie alleen samenhangen met depressie. Angst zou volgens dit model worden gekenmerkt door meer autonome symptomen zoals hartkloppingen etc. Sensatie zoeken zou niet geassocieerd zijn met angst of depressie. Eerder onderzoek naar de samenhang tussen de verschillende persoonlijkheidstrekken en angst en depressie liet tegenstrijdige resultaten zien. Dit zou kunnen worden veroorzaakt doordat er bij de analyses niet altijd rekening werd gehouden met de co-morbiditeit tussen angst en depressie. In de twee onderzoeken die worden beschreven in hoofdstuk 3 wordt dit wel gedaan.

Eenzijds is de samenhang geanalyseerd tussen deze persoonlijkheidstrekken en angst en depressie, gemeten door middel van zelfbeoordelingvragenlijsten. Hierbij hadden we de beschikking over gegevens van 7969 tweelingen en hun broers en zussen die meedoen aan het longitudinale onderzoek van het Nederlands Tweeling Register (NTR). Anderzijds is de samenhang geanalyseerd tussen deze persoonlijkheidstrekken en diagnoses van angststoornissen en depressie gesteld volgens de criteria van de DSM IV. Hierbij is gebruik gemaakt van een gestandaardiseerd telefonisch interview dat is afgenomen bij 1256 tweelingen en hun broers en zussen. Door in beide studies de gegevens over zowel angst als depressie in één keer in de analyses te betrekken hielden we rekening met de co-morbiditeit voor angst en depressie. Uit beide studies bleek duidelijk dat hoge neuroticisme scores geassocieerd zijn met angst en depressie, evenals lage extraversie scores het zij in mindere mate. Deze resultaten bevestigen het model van Eysenck. Sensatie zoeken was met geen van beide geassocieerd. Bovendien werd duidelijk dat er een lineair verband bestaat tussen het aantal diagnoses van angst of depressie en de mate van neuroticisme en extraversie. Dat wil zeggen: iemand met twee aandoeningen scoort twee keer zo hoog op neuroticisme en twee keer zo laag op extraversie als iemand met één aandoening. Deze resultaten sluiten aan bij de hypothese dat meerdere genen betrokken zijn bij het ontstaan van angst en depressie. Deze genen komen mogelijk tot uiting in de persoonlijkheidstrekken neuroticisme en extraversie.

Hoofdstuk 4 beschrijft een onderzoek naar de mate waarin DSM IV angststoornissen en depressie familiair zijn. Ook is in dit onderzoek gekeken of er kwantitatieve en/of kwalitatieve verschillen zijn in deze familiale risicofactoren tussen mannen en vrouwen. Het ging hierbij om de diagnoses paniekstoornis en/of agorafobie, sociale fobie, gegeneraliseerde angststoornis en depressie. Agorafobie is de angst om in ruimtes of drukke menigtes te verblijven waaruit men niet zo makkelijk kan ontsnappen, de zogenaamde straatvrees. Sociale fobie is de angst om in een situatie te zijn met andere mensen uit angst voor afkeuring. Voorbeelden hiervan zijn angst voor het houden van een presentatie, eten in een restaurant, naar een verjaardagsfeestje gaan enz. Bij een gegeneraliseerde angststoornis is er sprake van overmatig piekeren / zorgen maken over alledaagse zaken. De populatie bestond uit 2287 Australische en 1185 Nederlandse twee-eiige tweelingen en broers en zussen. Zij waren geselecteerd uit het Australische en Nederlandse tweelingregister in het kader van een onderzoek naar de genetica van angst en depressie. De twee populaties waren vergelijkbaar en konden dus voor de analyses worden gecombineerd. De broer-broer, zus-zus en broer-zus correlaties lagen in het algemeen rond de 0.20. Hieruit volgt een maximale erfelijkheidsschatting van 40%, wat overeenkomt met eerdere onderzoeken. Er

werden geen sekse verschillen gevonden wat betreft de erfelijkheid, behalve voor de diagnose paniekstoornis en/of agorafobie. Hierbij bleken andere genen een rol te spelen bij mannen dan bij vrouwen.

In *hoofdstuk 5* is gekeken of er verband bestaat tussen een variant van het serotonine transporter gen en neuroticisme, angst en depressie, gemeten met zelfbeoordelingvragenlijsten. In hoofdstuk 3 was aangetoond dat de scores op deze vragenlijsten samenhangen met DSM IV diagnoses. Eerder onderzoek had al aangetoond dat variatie in deze scores ook erfelijk is. Een bepaald deel van het serotonine transporter gen, namelijk de promotor, varieert in lengte tussen individuen. In 1996 is gevonden dat individuen met een korte variant hoger scoren op neuroticisme en harm avoidance, een aan neuroticisme gerelateerde persoonlijkheidstrekk. Inmiddels zijn er tegenstrijdige resultaten van meer dan 20 studies die dit eveneens hebben onderzocht. In het kort komt het erop neer dat van die ruim 20 studies de ene helft het effect ook vond en de andere helft niet. Uiteindelijk is geconcludeerd dat alleen goed uitgevoerde studies in grote populaties uitkomst konden bieden. Wij hadden de beschikking over DNA van 254 vaders, 305 moeders en 501 mannelijke en 744 vrouwelijke kinderen afkomstig uit 466 families. Deze proefpersonen hadden zeker één keer, maar meestal vaker, deelgenomen aan ons onderzoek, waarbij hen sinds 1991 vijf maal dezelfde vragenlijsten werden voorgelegd over neuroticisme, angst en depressie. Het effect van de korte variant van het serotonine transporter gen is onderzocht voor iedere vragenlijst op ieder tijdstip afzonderlijk en voor de gemiddelde scores op de verschillende tijdstippen. Ook zijn er analyses uitgevoerd waarbij rekening is gehouden met de familiestructuur. Dit heeft als voordeel dat er wordt gecontroleerd voor variabelen zoals etnische achtergrond waardoor zowel vals positieve als vals negatieve bevindingen ten gevolge hiervan worden vermeden. Uiteindelijk waren drie van de 36 tests significant, waarbij twee significante resultaten suggereerden dat de lange variant geassocieerd was neuroticisme en angst en één significant resultaat suggereerde dat de korte variant was geassocieerd met neuroticisme. Drieëndertig van de 36 tests lieten dus geen significant resultaat zien. Deze resultaten geven aan dat de korte variant van het serotonine transporter gen niet direct geassocieerd is met neuroticisme, angst of depressie.

Ernstige gebeurtenissen

In *hoofdstuk 6* is onderzocht in hoeverre familiale factoren van invloed zijn op het ontstaan van klachten van burnout. Burnout is een aan werk gerelateerd syndroom bestaande uit klachten van emotionele uitputting, verminderde betrokkenheid bij het werk / cynisme en een gevoel van falen. Emotionele uitputting is het belangrijkste symptoom. Dit symptoom was al eerder onderzocht in de Nederlandse bevolking door het Centraal Bureau van Statistiek (CBS). Zodoende was besloten om dezelfde vragenlijst op te nemen

in ons onderzoek. De invloed van familiale factoren op burnout was nog niet eerder onderzocht. De burnoutvragenlijst was ingevuld door 2707 één- en twee-eiige tweelingen, 736 broers of zussen van deze tweelingen en 575 partners van deze tweelingen. De correlatie tussen eeneiige tweelingparen was gelijk aan die van twee-eiige tweelingparen of broer-broer / zus-zus paren. Deze correlatie was 0.20. Dit was voor mannen en vrouwen gelijk. Dit duidt erop dat de familiariteit bij mannen en vrouwen wordt veroorzaakt door omgevingsfactoren die worden gedeeld door familieleden. Ook de correlatie tussen broer-zus (tweeling) paren was 0.20. Dit geeft aan dat dezelfde factoren in de gedeelde omgeving een rol spelen bij mannen en vrouwen. Verder was de echtpaarcorrelatie ook significant groter dan 0. Dit werd voornamelijk veroorzaakt door echtparen die langer dan vijf jaar bij elkaar waren. Dan was de correlatie 0.24. Dit is een extra aanwijzing dat gedeelde omgevingsfactoren van belang zijn bij het ontstaan van klachten van burnout. Genetische factoren lijken dus geen rol te spelen. Eén van de gedeelde omgevingsfactoren die van belang zou kunnen zijn is een hoog opleidingsniveau van de ouders.

Hoofdstuk 7 beschrijft vervolgens een studie naar de samenhang tussen burnout en depressie en tussen het hebben van een baan en depressie. Eerder onderzoek had aangetoond dat het hebben van een baan beschermt tegen een depressie. Echter, als iemand een baan heeft, maar daarbij ook klachten heeft van burnout, is het risico van een depressie ook vergroot. Mogelijk is het hebben van een baan alleen gunstig als er geen sprake is van burnout. In dit onderzoek hebben we gekeken of de samenhang tussen enerzijds het hebben van een baan en depressie en anderzijds burnout en depressie zou kunnen worden veroorzaakt door risicofactoren die op beide van invloed zouden kunnen zijn. Hierbij is gebruik gemaakt van gegevens over 4309 één- en twee-eiige tweelingen en 1008 broers en zussen van deze tweelingen. Er was een zwak statistisch significant verband tussen het hebben van een baan en depressie (correlatie -0.08). Zowel depressie als het al dan niet hebben van werk werd voor ongeveer 50% door genen en voor ongeveer 50% door individu-specifieke omgevingsfactoren bepaald. De samenhang tussen werk en depressie leek te worden veroorzaakt door gedeelde risicofactoren. Met de beschikbare data was echter niet definitief vast te stellen of deze gedeelde risicofactoren genetisch zijn of dat het juist individuspecifieke omgevingsfactoren betreft. Het verband tussen burnout en depressie was veel sterker (correlatie 0.40). Bij mannen waren zowel burnout als depressie erfelijk bepaald en waren verder individu-specifieke omgevingsfactoren van belang. Bij vrouwen gold dit ook voor depressie. Burnout werd bij vrouwen behalve door genen en individu-specifieke omgevingsfactoren ook door omgevingsfactoren gedeeld door familieleden beïnvloed. De samenhang tussen burnout en depressie leek zowel bij mannen als bij vrouwen te worden veroorzaakt door gedeelde risicofactoren, te weten genen en individu-specifieke omgevingsfactoren.

In *hoofdstuk 8* zijn ter voorbereiding van hoofdstuk 9 data van 2086 eeneiige tweelingen, 2090 twee-eiige tweelingen en 1307 broer en zussen van tweelingen geanalyseerd met betrekking tot ernstige negatieve gebeurtenissen. Als eerste is onderzocht of het zijn van een één- of twee-eiige tweeling het risico van het meemaken van een ernstige gebeurtenis vergroot of verkleind. In het verleden is bijvoorbeeld gesuggereerd dat tweelingen meer moeite zouden hebben om in het latere leven relaties aan te gaan, omdat zij als kind vooral met elkaar omgaan. Dientengevolge zouden zij vaker een echtscheiding meemaken. In dat geval zou onderzoek naar ernstige gebeurtenissen bij tweelingen niet kunnen worden gegeneraliseerd naar de algemene populatie. Ten tweede is onderzocht of ernstige gebeurtenissen familiair zijn en of deze eventuele familiariteit toe te schrijven is aan de gedeelde familieomgeving of aan genen. De volgende ernstige gebeurtenissen zijn geanalyseerd: ernstige ziekte of verwonding van jezelf, ernstige ziekte of verwonding van een dierbare, overlijden van een dierbare, echtscheiding / verbreking duurzame relatie, slachtoffer zijn van een verkeersongeval, diefstal, geweldsmisdrijf of seksueel misdrijf. In de analyses is ook het hebben van een duurzame relatie meegenomen, omdat alleen mensen met een relatie een echtscheiding kunnen meemaken. Er zijn geen significante verschillen gevonden tussen eeneiige tweelingen, twee-eiige tweelingen en hun broers en zussen wat betreft het percentage dat een duurzame relatie heeft of een ernstige gebeurtenis heeft meegemaakt. Alle ernstige gebeurtenissen waren familiair met uitzondering van verkeersongevallen bij vrouwen. De familiariteit van het hebben van een duurzame relatie kon worden toegeschreven aan genetische factoren. Bij ziekte of overlijden van een dierbare ander was de familiariteit het gevolg van de gedeelde familieomgeving. Voor de andere ernstige gebeurtenissen kon niet worden bepaald of genen of gedeelde familieomgeving er toe leiden dat individuen uit hetzelfde gezin op elkaar lijken wat betreft de ernstige gebeurtenissen die zij meemaken.

Hoofdstuk 9 onderzocht de samenhang en eventuele oorzaken hiervoor tussen het meemaken van ernstige gebeurtenissen en depressie, neuroticisme en extraversie. Deze persoonlijkheidstrekken zijn meegenomen in de analyses, omdat in hoofdstuk 3 was gebleken dat zij samenhangen met depressie. Om te beoordelen of er mogelijk sprake is van een causaal verband zijn bij 1058 mannelijke en 2226 vrouwelijke tweelingen de scores van depressie, neuroticisme en extraversie, gemeten voorafgaand aan de blootstelling aan de ernstige gebeurtenissen, vergeleken met de scores na de blootstelling. Ook is met deze gegevens geanalyseerd of individuen waarvan bekend is dat ze later zijn blootgesteld aan een ernstige gebeurtenis anders scoren dan individuen waarvan bekend is dat ze in de twee jaar daarna geen ernstige gebeurtenis hebben meegemaakt. Als bij deze analyses significante verschillen worden gevonden sluit dit echter niet uit dat zowel de ernstige gebeurtenissen als de depressie, neuroticisme of extraversie scores worden beïnvloed door dezelfde

etiologische factoren, bijvoorbeeld genen. Dan spreek je van gen-omgevingscorrelatie. Dit is onderzocht met behulp van de co-twin controle methode waarbij eeniige en twee-eiige tweelingen waarvan slechts één van de twee een ernstige gebeurtenis heeft meegemaakt zijn geselecteerd uit een sample van 1918 mannelijke en 3864 vrouwelijke tweelingen. Door op basis van toeval uit de overige tweelingen er één te selecteren werd een populatie gecreëerd van niet aan elkaar gerelateerde individuen. Als er sprake is van gen-omgevingscorrelatie zijn de scores voor depressie, neuroticisme en extraversie bij de eeniige tweelingen waarvan er slechts één een ernstige gebeurtenis heeft meegemaakt aan elkaar gelijk, aangezien zij dezelfde genetische kwetsbaarheid hebben voor deze trekken. Deze scores verschillen bij de twee-eiige tweelingen waarvan er slechts één een ernstige gebeurtenis heeft meegemaakt, maar dit verschil is kleiner dan in de populatie van niet aan elkaar gerelateerde individuen, omdat twee-eiige tweelingen 50% van hun genen met elkaar delen. Onze vergelijkingen van de scores voor en na een ernstige gebeurtenis lieten zien dat blootstelling aan een ernstige gebeurtenis in het algemeen de depressieve klachten verergert. Neuroticisme en extraversie scores veranderden nauwelijks door blootstelling aan ernstige gebeurtenissen. Aan de andere kant was het ook zo dat individuen die later werden blootgesteld aan ernstige gebeurtenissen van tevoren al hoger scoorden op neuroticisme en depressie. Er waren geen aanwijzingen voor gen-omgevingscorrelatie, want de verschillen in de scores voor depressie, neuroticisme en extraversie tussen de individuen die geen life event hadden meegemaakt en de individuen die dat wel hadden meegemaakt waren gelijk in de eeniige en twee-eiige tweelingen waarvan er slechts één een ernstige gebeurtenis had meegemaakt en in de groep niet aan elkaar gerelateerde individuen. Deze resultaten wijzen op een reciproque causale relatie tussen ernstige gebeurtenissen en depressie. Verhoogde scores op neuroticisme lijken te leiden tot een verhoogde kans op blootstelling aan ernstige gebeurtenissen. Extraversie is in zijn geheel niet geassocieerd met ernstige gebeurtenissen.

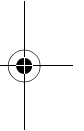
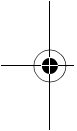
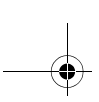
“Een paar kleine verklaringen”

Chapter 1

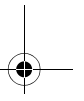
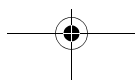
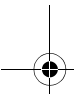
Wat zijn nu de “kleine verklaringen” die dit proefschrift heeft opgeleverd ten aanzien van de ontstaanswijze van angst en depressie? Hoofdstuk 2 tot en met 5 hadden als doel om meer inzicht te verkrijgen in de genetische achtergrond van angst en depressie. Uit deze onderzoeken kan worden geconcludeerd dat angst en depressie weliswaar verschillende aandoeningen zijn, maar dat de genetische risicofactoren waarschijnlijk deels overlappen. Deze genetische risicofactoren komen mogelijk tot uiting in de persoonlijkheidstrekken neuroticisme en, in mindere mate, extraversie. In het algemeen zijn de genetische risicofactoren voor mannen en vrouwen hetzelfde. Alleen voor paniekstoornis lijkt het erop dat andere genen bij mannen en vrouwen tot deze klachten leiden. Onderzoek dat erop gericht is om specifieke genen voor angst

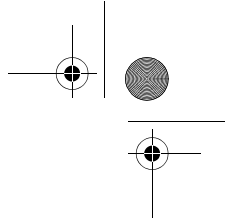
en depressie te identificeren zou daarom kunnen beginnen met de persoonlijkheidstrekken neuroticisme en extraversie. Deze persoonlijkheidstrekken hebben als voordeel dat ze makkelijker in meer individuen te meten zijn. Onze eigen analyses naar de samenhang van de korte variant van het serotonine transporter gen en neuroticisme, angst en depressie lieten geen significante associaties zien. Dit pleit sterk tegen een hoofdeffect van deze gen variant in deze klachten. Het tweede deel van dit proefschrift ging over specifieke risicofactoren voor angst en depressie, zoals burnout, werkloosheid en het meemaken van ernstige gebeurtenissen. Het bleek dat burnout en werkloosheid inderdaad samenhangen met depressie en dat deze samenhang mogelijk verklaard kan worden door genen en omgevingsfactoren die zowel tot burnout of werkloosheid als tot depressie leiden. Dit betekent dat het bij de behandeling van depressie belangrijk is om ook aandacht te besteden aan de werkstatus van een patiënt en aan de eventuele omstandigheden op het werk. Met betrekking tot de ernstige gebeurtenissen leek het niet zo te zijn dat dezelfde genen die het risico van depressie verhogen ook de kans op de blootstelling aan ernstige gebeurtenissen verhogen. Er was dus geen sprake van gen-omgevingscorrelatie. Wel gaven de resultaten aan dat hogere depressie of neuroticisme scores samenhangen met een hogere kans op de blootstelling aan ernstige gebeurtenissen welke op hun beurt de depressie weer verergeren. Wat betreft de behandeling van depressie lijkt het daarom zinvol is om aandacht te schenken aan het gedrag van patiënten dat mogelijk zou kunnen leiden tot een ernstige gebeurtenis zoals bijvoorbeeld een echtscheiding of gezondheidsproblemen. Mogelijk dat extra aandacht voor de partner tijdens de behandeling een echtscheiding kan voorkomen. Ook zou voorlichting van patiënten over de mogelijkheid dat een ernstige gebeurtenis een depressie kan uitlokken tot gevolg kunnen hebben dat zij eerder hulp zoeken, zodat de depressie in een eerder stadium kan worden behandeld.

Het onderzoek naar angst en depressie zal in de komende jaren worden voortgezet met behulp van de gegevens van het Nederlands Tweeling Register. Evenals in dit proefschrift zullen hierbij zowel genetische als omgevingsfactoren onderwerp van studie blijven. Wel zal in de toekomst meer onderzoek worden gedaan waarin het effect van specifieke genen en het effect van een specifieke omgevingsfactor tegelijk worden opgenomen, bijvoorbeeld als een interactie-effect. Hopelijk leidt dit in de toekomst, in combinatie met resultaten van andere onderzoeksgebieden zoals de neuro-imaging, tot de vele kleine verklaringen die nodig zijn om de ontstaanswijze van angst en depressie te beschrijven.



**Chapter
1**

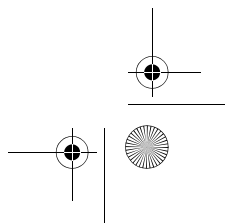
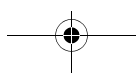
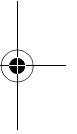
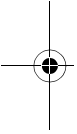




Appendix



Additional information on the sample



Appendix A

This thesis used survey and interview data collected in the framework of the Dutch twin-family study of health-related behavior. This is a large-scale longitudinal questionnaire study in twins and their family members from the Netherlands Twin Register. Each survey was sent to the twins and additional family members, namely parents in 1991 and 1993, parents and siblings in 1995, siblings in 1997, sibling and spouses in 2000 and parents, siblings and spouses in 2002.

Data collection is described in detail in the following PhD theses:

“The genetics of health-related behaviors. A study of adolescent twins and their parents.” by J.R. Koopmans (1997). The initial recruitment of twin families through city councils in The Netherlands and the first three waves of data collection, performed in 1991, 1993 and 1995, are described.

“Mediating factors in the association between anxious depression and cardiovascular disease risk” by M. van den Berg (2002). The fourth wave of survey data collection, performed in 1997 and the data collection for the Netherlands twin-family study of anxious depression (NETSAD) are described.

“A twin-family study of smoking behavior” by J.M. Vink (2004). The fifth wave of survey data collection performed in 2000 is described including a detailed overview of response rates and characteristics of non-responders.

“Resolving cause and effect in the association between exercise participation and psychological well-being” by J.H. Stubbe (in preparation). The sixth wave of data collection performed in 2002 will be summarized in this thesis.

In the current thesis, each chapter contains a section describing the sample used for the analysis. In this appendix some additional information on the participants is given.

In chapter 3, on the relation between personality and anxious and depressive psychopathology, data collected in 1991, 1993 and 1997 in twins and siblings were combined to make the largest possible sample. If subjects had participated more than once, their scores over the occasions were averaged. Table A1 shows how many subjects had participated one, two or three times.

Table A1: Number of men and women who participated one, two or three times in the 1991, 1993 and 1997 survey.

	Men	Women
1	2067	2561
2	1051	1344
3	375	571
Total	3493	4476

Appendix
A

For each survey, a genetic factor score expressing an individual's vulnerability for anxious depression was calculated for all subjects who had filled out the neuroticism, anxiety, somatic anxiety and depression scales. In total, there were 3414 men and 4422 women. The factor scores were used to select families with extreme discordant and concordant sibling pairs for a linkage study aiming to find genes underlying the liability for anxiety or depression. The twins and siblings from these families were approached to participate in a clinical interview. This interview was administered in 1257 subjects. Seventeen twins and siblings participated in the interview, although their genetic factor score was unavailable. They were family members of an extreme scoring sibling pair. One of the 1257 interviewed subjects was mother of twins and her data were excluded from the analyses. From the remaining 1256 subjects, data regarding a diagnosis of major depression were unavailable for 2 men, as the answers on the questions were not saved during the interview. The diagnosis of generalized anxiety disorder was also missing for 2 men and 3 women, as these subjects could not tell how long their period of worry had lasted. Data of these 5 subjects regarding the other diagnoses were used in the analyses.

In chapter 4, on the genetic analyses of the CIDI data, information from the Australian Twin Register was combined with data from the Dutch sample. Analyses were carried out on the data from dizygotic twins, siblings, and, in the Australian sample, adult offspring of twins, who have a score on the selection variable and at least one additional full sibling with a score on the selection variable. Half siblings, twin pairs with unknown zygosity, and subjects without additional siblings are excluded. Monozygotic twins were included if there was a sibling available with a score on the selection variable. This resulted in a total population for the analyses of 11291 Australian and 5836 Dutch subjects with scores on the selection variables; 2287 Australian and 1185 Dutch subjects had participated in the CIDI interview. From the 2287 Australian subjects, five did not have information regarding panic disorder and/or agoraphobia, generalized anxiety disorder and social phobia. The Dutch sample included the two subjects without information on major depression diagnosis and the five subjects without information on generalized anxiety.

In chapter 5, on 5-HTTLPR and neuroticism, depression and anxiety, genotype information was available for 466 families selected from the Netherlands Twin Register. Of these families, 254 fathers, 305 mothers, 501 male and 744 female offspring, all aged between 16 and 65 years, were genotyped for 5-HTTLPR. Within-family association and total association tests between 5-HTTLPR and neuroticism, anxiety and depression were carried out with QTDT. In a within-family association test, only informative individuals are used, i.e. phenotyped offspring with at least one heterozygous parent or with a sibling differing in genotype. Table A2 shows the total number of genotyped and

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phenotyped subjects (including parents), which were used for the total association test, and the number of informative siblings which were used for the within family association test.

Table A2: the total number of genotyped and phenotyped twins, siblings and parents, used for the total association test, and the number of informative twins and siblings used for the within family association test

	N total	N informative twins and siblings
Neu 1991	680	184
Neu 1993	986	275
Neu 1997	1019	560
Neu 2000	833	457
Neu 2002	1160	438
Anx 1991	683	184
Anx 1993	985	280
Anx 1997	1019	563
Anx 2000	856	466
Anx 2002	1182	445
Dep 1991	332	184
Dep 1993	521	274
Dep 1995	1024	563
Dep 2000	852	467
Dep 2002	1171	442
Mean neu	1558	653
Mean anx	1721	656
Mean dep	1717	654

In chapters 6 and 7, data on employment, burnout and depression were used, that were collected in 2000. Table A3 gives detailed information on the employment status of the total population of twins, siblings and spouses aged between 18 years old and 65 years old.

Table A3: Employment status for the total population between 18 years and 65 years old that participated in the 2000 survey.

	Total population	Males	Females
Employment >32 hours a week	3088 (49%)	1649 (70%)	1439 (36%)
Employment 12-32 hours a week	1035 (16%)	100 (4%)	935 (24%)
Employment < 12 hours	148 (2%)	18 (1%)	130 (3%)
Employed, hours unknown	184 (3%)	71 (3%)	113 (3%)
Students	1078 (17%)	404 (17%)	674 (17%)
Unemployed	67 (1%)	23 (1%)	44 (1%)
Early retired	46 (1%)	29 (1%)	17 (0%)
Housekeeping	425 (7%)	5 (0%)	420 (11%)
Occupational disabled	121 (2%)	23 (1%)	98 (2%)
Otherwise	46 (1%)	11 (0%)	35 (1%)
Missing	71 (1%)	32 (1%)	39 (1%)

In chapter 8, data on life events were used that were collected in 2000. Prevalence rates of the different life events for men and women for different age groups are given in that chapter. In chapter 9, data on life events collected in 2000 and 2002 were combined to make the largest possible sample. There were 4225 twins, siblings and spouses who participated in both the 2000 and 2002 survey. Their data were used to check the reliability of the life event scale. For each life event, a maximum of 15.1% of the subjects gave inconsistent answers, i.e. they reported a life event in 2000, but not in 2002 or they did not report a life event in 2000, but reported in 2002 to have experienced this life event more than five years ago. Inconsistencies in life event report might be the result of mood congruence recall bias, i.e. "some material, by virtue of its affectively valenced content, is more likely to be stored and/or recalled when one is in a particular mood" (Blaney, 1986), which can lead to exaggeration of effect size estimates. This was tested in two ways. First, for the subjects whose life event report was inconsistent, their anxious depression score at the time that they reported a life event was compared to their anxious depression score at the time that they did not report a life event. If mood congruence bias is of importance, subjects are expected to score higher on anxious depression at the time that they report the life event. These tests were performed separately for the subjects who reported a life event in 2000 but not in 2002 and for the

Appendix A

subjects who reported in 2002 to have experienced a life event more than five years ago, but had not reported this life event in 2000. This yielded no significant results (threshold p-value of 0.05) (Table A4).

Table A4: Logtransformed anxious depression scores in 2000 and 2002 in subjects who reported a life in 2000, but not in 2002 (above bold line) and in subjects who reported a life event in 2002 to have happened more than five years ago, but did not report this life event in 2000.

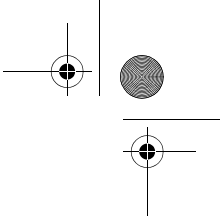
	N	Anxious Depression 2000	Anxious Depression 2002	p
Death significant other	404	19.9 (9.4)	20.3 (9.7)	Ns
Illness / injury self	204	21.7 (10.1)	22.1 (9.8)	Ns
Illness / injury significant other	410	21.2 (9.6)	21.2 (10.4)	Ns
Divorce	317	21.9 (9.3)	21.0 (10.1)	Ns (p=0.052)
Accident	183	21.4 (10.3)	21.9 (10.4)	Ns
Robbery	266	20.3 (9.4)	20.9 (9.2)	Ns
Violent assault	74	21.4 (10.9)	22.0 (10.0)	Ns
Sexual assault	51	23.0 (10.2)	23.8 (10.0)	Ns
Death significant other	135	17.5 (9.7)	18.2 (9.8)	Ns
Illness / injury self	89	20.8 (9.0)	21.3 (9.7)	Ns
Illness / injury significant other	137	19.0 (10.4)	20.1 (9.8)	Ns
Divorce	112	19.9 (9.6)	20.5 (9.8)	Ns
Accident	135	20.5 (9.1)	20.2 (9.7)	Ns
Robbery	116	21.9 (9.1)	21.4 (9.9)	Ns
Violent assault	66	22.4 (9.5)	21.5 (10.5)	Ns
Sexual assault	73	23.9 (9.5)	24.4 (10.0)	Ns

Second, the group of subjects with consistent life event reports was compared to the subjects with inconsistent reports regarding the anxious depression scores measured at the time that the last group did not report the event (Table A5). If mood congruence bias is of importance, the anxious depression scores are expected to be lower in the group of subjects with the inconsistent reports. For divorce, a significant difference ($p < 0.01$) in anxious depression scores was found for subjects who reported a divorce/break up in 2000 but not in 2002 compared to subjects who reported this event twice.

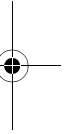
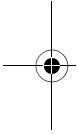
However, anxious depression scores were not significantly different between subjects who reported a divorce more than five years ago in 2002, while they had not reported this event in 2000 compared to the subjects who reported the divorce twice. For death of a significant other, the results were the other way around. Anxious depression scores were significantly different between subjects who reported this event in 2002 but not in 2000 compared to subjects who reported this event twice. Scores were not significantly different for subjects who reported this event in 2000, but not in 2002. Thus, there was hardly any evidence for mood congruence recall bias.

Table A5: Anxious depression scores in 2002 (above bold line) and in 2000 (below bold line) in subjects with consistent life event reports and subjects with inconsistent reports at the time that the latter group did not report the event.

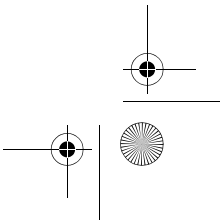
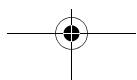
	N	Anxious depression in subjects with consistent reports	N	Anxious Depression in subjects with inconsistent reports	p
Death significant other	1963	20.8 (10.2)	409	20.1 (9.8)	ns
Illness / injury self	322	22.4 (10.0)	204	22.1 (9.8)	ns
Illness / injury significant other	980	21.6 (9.8)	416	21.2 (10.3)	ns
Divorce	606	22.8 (9.8)	318	21.0 (10.1)	<0.01
Accident	435	20.6 (10.0)	184	22.0 (10.4)	ns
Robbery	549	21.3 (9.8)	267	21.0 (9.3)	ns
Violent assault	106	23.5 (10.2)	74	22.0 (10.0)	ns
Sexual assault	143	25.5 (9.5)	52	23.7 (9.9)	ns
Death significant other	724	20.3 (10.1)	135	17.7 (9.6)	<0.01
Illness / injury self	165	21.7 (9.1)	90	20.9 (9.0)	ns
Illness / injury significant other	295	20.2 (9.5)	154	19.0 (10.5)	ns
Divorce	286	21.5 (9.3)	112	19.8 (9.7)	Ns
Accident	263	19.8 (9.8)	137	20.7 (9.2)	ns
Robbery	242	21.2 (9.6)	117	22.0 (9.1)	ns
Violent assault	57	24.9 (9.0)	66	22.4 (9.5)	ns
Sexual assault	128	25.1 (9.7)	76	23.7 (9.4)	ns



Appendix A



Appendix
A



Appendix

B

Additional information on the measurement instruments

The second part of this appendix is based on:

Middeldorp C.M., Cath D.C., Boomsma D.I. (2006). Het Composite International Diagnostic Interview (CIDI), lifetime versie 2.1: suggesties voor correcties in de secties paniekstoornis en gegeneraliseerde angststoornis (The Composite International Diagnostic Interview (CIDI), lifetime version 2.1: suggestions for corrections of the panic and generalized anxiety disorder section). Nederlands Tijdschrift voor psychologie (in press).

Appendix B

This appendix provides a concise summary of the assessment instruments, which have been used in my thesis:

- Zuckerman sensation seeking scale (Feij & Zuilen, 1984; Zuckerman, 1971).
- Amsterdamse Biografische Vragenlijst (ABV): the subscales neuroticism, extraversion and somatic anxiety (Wilde, 1970).
- Spielberger State Trait Anxiety Inventory - Trait version (STAI) (Spielberger et al., 1970; Van der Ploeg et al., 1979).
- Young Adult Self Report (YASR): the subscale anxious/depression (Achenbach, 1990; Verhulst et al., 1997).
- Beck Depression Inventory, 13-item version (Beck et al., 1974).
- Composite International Diagnostic Interview (CIDI): Demographics (Sections A); Social Phobia, Agoraphobia, Panic Disorder and Generalized Anxiety Disorder (D33 and further); Depression and Dysthymia (E); Mania Screen and Bipolar Affective Disorder (F) and Obsessive-Compulsive Disorder (K1-22) (World Health Organization, 1992a).
- Maslach Burnout Inventory - General Survey: the subscale emotional exhaustion (Schaufeli et al., 1996).
- Schokverwerkings Inventarisatie Lijst = SchIL, which is a Dutch life event scale (Van der Velden et al., 1992).

For most of these instruments, the scores were constructed according to the manual. However, for the YASR and the CIDI, scoring was adapted.

Young Adult Self Report

Scores on the anxious depression subscale can be obtained in two ways. First, the scores on the following items can be summed, divided by the number of items a subject has answered and then multiplied by 16 (the maximum number of items) (Verhulst et al., 1997).

- I feel lonely
- I cry a lot
- I deliberately try to hurt or kill myself (*not included in survey 6*)
- I am afraid I might think or do something bad
- I feel that I have to be perfect
- I feel that no one loves me
- I feel that others are out to get me (*not included in survey 6*)
- I feel worthless or inferior
- I am nervous or tense
- I am too fearful or anxious
- I feel too guilty
- I am self-conscious or easily embarrassed
- I am suspicious (*not included in survey 6*)
- I think about killing myself (*not included in survey 6*)

I am unhappy, sad, or depressed

I worry a lot

Second, the following items can be summed, divided by the number of items a subject has answered and then multiplied by 17 (the maximum number of items) (Achenbach, 1990):

I feel lonely

I feel confused or in a fog

I cry a lot

I worry about my future

I am afraid I might think or do something bad

I feel that I have to be perfect

I feel that no one loves me

I feel worthless or inferior

I am nervous or tense

I lack self confidence (*not included in survey 1 and 3*)

I am too fearful or anxious

I feel too guilty

I am self-conscious or easily embarrassed

I am unhappy, sad or depressed

I worry a lot

I am too concerned about how I look

I worry about my relations with the opposite sex

When the anxious depression scale was included in the first survey, the Dutch version of the Youth Self Report was still in the experimental phase and later versions were somewhat different than the first ones.

In chapter 3 and 7, the first Dutch definition was used. Because survey 2002 included only the items according to the American manual (see above), the calculation of the scores on the anxious depression scale needed to be adapted. It appeared that, since a lot of subjects responded negatively to the questions missing in 2002, the mean scores decreased when, in an effort to get comparable anxious depression scores, the sum of the remaining 12 items was divided by the number of items a subject had answered (maximum 12) and then multiplied by 16. Therefore, it was decided to use the second definition for the analyses in chapter 5 and 9. However, the item "I lack self-confidence" was not included in the 1991 and 1995. To get comparable anxious depression scores for all waves, this item was excluded from the scale. Thus, the scores of the other 16 items were summed, divided by the total number of items a subject had responded and multiplied by 16. The correlation between the scores based on 16 and on 17 items was .99 for the 1997, 2000 and 2002 survey. The correlations between the scores based on the first and second

Appendix B

definition were between .96 and .97 for the 1991, 1995, 1997 and 2000 survey. Apparently, they all measure more or less the same construct, but the absolute scores differ.

CIDI

The Composite International Diagnostic Interview (CIDI) (World Health Organization, 1992a) and the syntax, which contains the diagnostic algorithm to make the diagnosis after the interview, both delivered by the Dutch CIDI training center, appeared to contain three errors. The syntax needed to be corrected for the diagnosis of generalized anxiety disorder at two points. Furthermore, there appeared to be an error in the part of the CIDI interview asking about the criteria for a panic disorder. The corrections and the consequences for the prevalence rates are described below.

Panic disorder

Criterion A: repeated panic attacks with four or more physical symptoms

The instruction after question D57 when the remaining questions about panic disorder can be skipped is wrong. According to the interview, the following question on panic disorder can be skipped if a subject reports less than *five* symptoms. However, according to the Diagnostic and statistical manual of mental disorders, 4th edition (DSM IV) (American Psychiatric Association, 1994), only *four* physical symptoms are required to be considered for the diagnosis.

The background of this mistake can be found in the differences between the International statistical classification of diseases and related health problems (ICD 10) (World Health Organization, 1992b) criteria and the DSM IV criteria for panic disorder. According to the DSM IV, a subject is required to have four of 13 physical symptoms. According to the ICD 10, a subject is required to have four of 14 physical symptoms, including at least one of the following: heart palpitations or rapid heartbeat, sweating, trembling or dry mouth. In the Dutch version of the CIDI, these four symptoms are the first to ask. This leads to a problem, as the symptom "dry mouth" is not included in the DSM IV criteria. As a consequence, respondents who positively answer the first four questions do not fulfill the DSM IV criterion. For this reason, it is required that a subject has five physical symptoms. But then, subjects who do report to have four symptoms, but not a dry mouth, during an attack, do not get to answer the following questions on panic disorder.

Figure B1 shows the consequences for the prevalence rates for panic disorder. According to Means-Christensen et al. (2003), the respondents who fulfill the positive criteria, but not the negative criteria, are considered to have the disorder. In sum, 21% of the respondents with four or more symptoms, i.e. 26 of the 125 subjects, do not get to answer all questions. Of the respondents with four DSM IV symptoms and the ICD 10 symptom, 49% get the diagnosis. This signifies that from the 26 respondents with missing information, around 13 would have got the diagnosis. Thus 70 subjects, i.e. 5.6% of the total population, instead of 57 subjects, i.e. 4.5%, would have been diagnosed with panic disorder. This is an increase of 24%. As the symptoms of panic disorder probably lie on the same continuum (Kendler et al., 2001) as the full blown syndrome, the subjects with the missing information, but with four physical symptoms, were considered as having a panic disorder in our analyses in chapter 4.

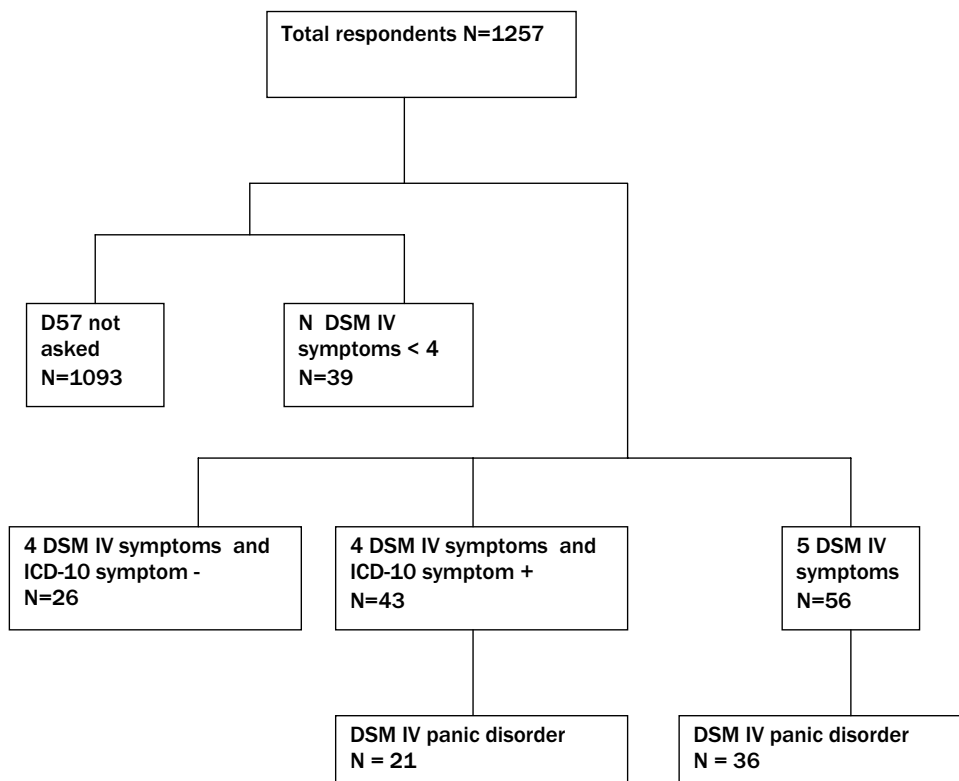


Figure B1

Appendix B

Generalized Anxiety Disorder

Criterion F: the disorder is not only present during a mood episode.

Respondents who only fulfill the criteria for a generalized anxiety disorder during a depressive episode should be coded '3' which signifies that a subject fulfills the positive criteria, but not the negative criteria. By an error in the syntax, only the respondents with a history of both major depression as well as dysthymia get code 3, when they report to have the symptoms of generalized anxiety disorder only during these mood disorders. In our population, 72 respondents fulfilled the positive criteria for GAD. Ten of these subjects received code 3 with the original syntax, as they only had complaints during a mood disorder. After the syntax was corrected, 31 subjects received code 3 because of this reason, i.e. the number of subjects fulfilling the positive as well as the negative criteria decreased with 29%

Original version of the syntax

CRITERION F

DO IF (D63 = 0 AND D63B = 0).

COMPUTE GAD4F = 0.

ELSE IF (D66 = 5 AND (((E1 = 1 AND E2 = 1) OR E25 NE 5 OR E26 LT 26 OR E26 = 991 OR E26 = 992 OR E26 = 993 OR (E28 = 1 OR D69_AGO LT E27_AGO)) OR (E34 = 1 OR E34A = 1 OR E52 = 1 OR (E54 = 1 OR D69_AGO LT E53_AGO))))).

COMPUTE GAD4F = 5.

ELSE IF (D66 = 2 AND (((E1 = 1 AND E2 = 1) OR E25 NE 5 OR E26 LT 26 OR E26 = 991 OR E26 = 992 OR E26 = 993 OR (E28 = 1 OR D69_AGO LT E27_AGO)) OR (E34 = 1 OR E34A = 1 OR E52 = 1 OR (E54 = 1 OR D69_AGO LT E53_AGO))))).

COMPUTE GAD4F = 3.

ELSE IF ((D63B = 1 OR (D63C GT 0 AND D63C LT 6) OR D64D = 1 OR NGADSXA = 0 OR NGADSXB LT 4) OR D66 NE 5 OR E28 = 5 OR E54 = 5).

COMPUTE GAD4F = 1.

ELSE.

COMPUTE GAD4F = 0.

END IF.

The corrected version of the syntax

CRITERION F

DO IF (D63 = 0 AND D63B = 0).

COMPUTE GAD4F = 0.

ELSE IF (D66 = 5 AND (((E1 = 1 AND E2 = 1) OR E25 NE 5 OR E26 LT 26 OR E26 = 991 OR E26 = 992 OR E26 = 993 OR (E28 = 1 OR D69_AGO LT E27_AGO)) AND (E34 = 1 OR E34A = 1 OR E52 = 1 OR (E54 = 1 OR D69_AGO LT E53_AGO))))).

COMPUTE GAD4F = 5.

ELSE IF (D66 = 2 AND (((E1 = 1 AND E2 = 1) OR E25 NE 5 OR E26 LT 26 OR E26 = 991 OR E26 = 992 OR E26 = 993 OR (E28 = 1 OR D69_AGO LT E27_AGO)) AND (E34 = 1 OR E34A = 1 OR E52 = 1 OR (E54 = 1 OR D69_AGO LT E53_AGO))))).

COMPUTE GAD4F = 3.

ELSE IF ((D63B = 1 OR (D63C GT 0 AND D63C LT 6) OR D64D = 1 OR NGADSXA = 0 OR NGADSXB LT 4) OR D66 NE 5 OR E28 = 5 OR E54 = 5).

COMPUTE GAD4F = 1.

ELSE.

COMPUTE GAD4F = 0.

END IF.

Criterion A: excessive anxiety and worry during at least 6 months.

Since 2000, a corrected version of this part of the syntax is available internationally. However, this correction has been known in the Netherlands since 2004 only. For the sake of completeness, the correction will be described here. In the CIDI, a respondent is asked in two different ways whether he or she ever had a period of excessive anxiety and worry during at least six months. First, it is asked whether respondents ever had a period of six months in which they felt tens, worried or anxious over daily problems. Second, it is asked whether there has ever been a period of at least 6 months in which they worried more than most people would in the same situation. In the original syntax, only respondents who answered positively on the second question were considered for a diagnosis. As a lot of subjects had already responded positively on the first question, the correction of the syntax led to a considerable increase of the number of diagnoses. In our population, at first, only 1.0% fulfilled the positive criteria. After correction, 5.7% fulfilled the positive criteria.

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Original version of the syntax

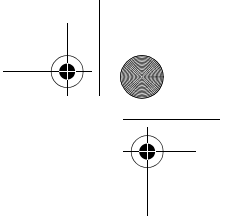
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 COMPUTE D30002 = 0.
 ELSE IF (D63B = 1 OR D63C LT 6 OR D64D = 1 OR NGADSXA = 0 OR NGADSXB
 LT 4).
 COMPUTE D30002 = 1.
 ELSE IF ((D63 = 5 OR D63B = 5) AND (GAD4A = 1 OR GAD4B = 1 OR GAD4C =
 1 OR GAD4D = 1 OR GAD4E = 1)).
 COMPUTE D30002 = 1.
 ELSE IF (GAD4A = 5 AND GAD4B = 5 AND GAD4C = 5 AND GAD4D = 5 AND
 GAD4E = 5 AND GAD4F = 5).
 COMPUTE D30002 = 5.
 ELSE IF (GAD4A = 5 AND GAD4B = 5 AND GAD4C = 5 AND GAD4D = 5 AND
 GAD4E = 5 AND GAD4F NE 5).
 COMPUTE D30002 = 3.
 ELSE.
 COMPUTE D30002 = 0.
 END IF.

Corrected version of the syntax

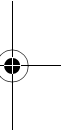
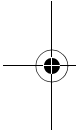
DIAGNOSIS OF 300.02 GENERALIZED ANXIETY DISORDER.
 DO IF (D63 = 0 AND D63B = 0).
 COMPUTE D30002 = 0.
 ELSE IF (D63B = 1 OR (D63C GT 0 AND D63C LT 6) OR D64D = 1 OR
 NGADSXA = 0 OR NGADSXB LT 4).
 COMPUTE D30002 = 1.
 ELSE IF ((D63 = 5 OR D63B = 5) AND (GAD4A = 1 OR GAD4B = 1 OR GAD4C =
 1 OR GAD4D = 1 OR GAD4E = 1)).
 COMPUTE D30002 = 1.
 ELSE IF (GAD4A = 5 AND GAD4B = 5 AND GAD4C = 5 AND GAD4D = 5 AND
 GAD4E = 5 AND GAD4F = 5).
 COMPUTE D30002 = 5.
 ELSE IF (GAD4A = 5 AND GAD4B = 5 AND GAD4C = 5 AND GAD4D = 5 AND
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 COMPUTE D30002 = 3.
 ELSE.
 COMPUTE D30002 = 0.
 END IF.

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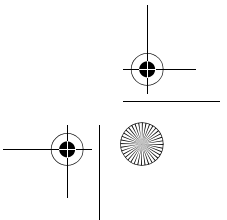
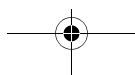
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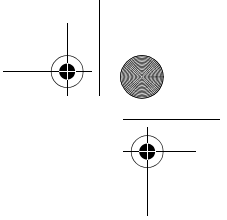


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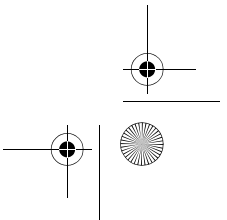
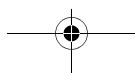
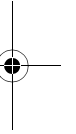
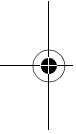


Appendix B





Dankwoord



Dankwoord

Deze bladzijdes zijn voor de mensen zonder wie dit boekje er niet zou zijn geweest, er heel anders zou hebben uitgezien of met veel minder plezier tot stand zou zijn gekomen.

Eerst de vele mensen zonder wie dit boekje er niet zou zijn geweest. Ik wil alle tweelingen en hun familieleden die de vragenlijsten hebben ingevuld, aan het interview hebben deelgenomen en hun DNA hebben afgestaan van harte bedanken. Ook ben ik zeer veel dank verschuldigd aan degene die deze data hebben verzameld: Judith Koopmans (lijst 1 tot en met 3), Jacqueline Vink (lijst 5), Janine Stubbe (lijst 6) en in het bijzonder Mireille van de Berg (lijst 4, CIDI en DNA). Verder wil ik Conor Dolan bedanken voor het uitvoeren van de selectie van het NETSAD sample en Leo Beem, Gonneke Willemsen en Eco de Geus voor het opschonen van alle vragenlijst data, waardoor ik er meteen mee aan de slag kon. Tenslotte gaat mijn dank uit naar Nico Lakenberg, Eka Suchiman en Eline Slagboom voor de genotypering van het serotonine transporter gen en naar Jouke Jan Hottenga voor het beheren van de genotype database.

Dan de mensen zonder wie dit boekje er heel anders zou hebben uitgezien. Mijn promotoren Dorret Boomsma, Richard van Dyck en mijn copromotor Danielle Cath hebben hierbij vanzelfsprekend de belangrijkste rol gespeeld. Dorret, net als vele promovendi voor mij, wil ik je bedanken voor het waardevolle en bijzonder snelle commentaar op artikelen. Verder vond ik het altijd geruststellend dat jij je zelden zorgen maakte over onverwachte resultaten van analyses of afwijzingen van artikelen. Op momenten dat ik dacht dat de zaken er nu toch echt volkomen hopeloos voorstonden, vroeg jij onverstoorbaar wat mijn ideeën waren over "hoe nu verder". En uiteindelijk is ook gebleken dat, zoals jij een keer zei, er geen data zijn die niet te analyseren zijn. Richard, jij was degene die heeft voorgesteld dat ik onderzoek zou gaan doen in de genetica. Daarvoor alleen al ben ik je dankbaar. Nadat het onderzoek eenmaal op gang was gekomen, ben je meer op de achtergrond getreden. Dat neemt niet weg dat je soms nog wel raak commentaar leverde over bijvoorbeeld de leesbaarheid van een artikel of de relevantie van bepaalde resultaten. Danielle, het echte werk is begonnen bij jou thuis achter de computer met het schrijven van de AGIKO subsidie-aanvraag. Zonder jouw hulp was die subsidie er niet gekomen. Ook daarna bij het schrijven van artikelen heb ik veel aan je commentaar gehad. Jij wees me steeds weer op het belang van een goede opbouw van een artikel en heldere formuleringen.

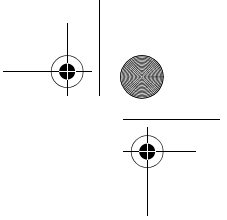
I would like to thank Nick Martin and Andrew Birley for the collaboration that resulted in chapter four. I had a magnificent time in Brisbane. I am not only grateful that I could make use of your data, but also for your helpful comments regarding the analyses of the combined samples. Furthermore, I would like to thank Ken Kendler and Nick Martin for their interest in my thesis. It is a great honor that you are members of the reading committee. Ook de andere leden

van de leescommissie / opponenten wil ik bedanken voor hun interesse in mijn proefschrift: Aartjan Beekman, Leo Beem, Hans den Boer, Peter Heutink en Brenda Penninx.

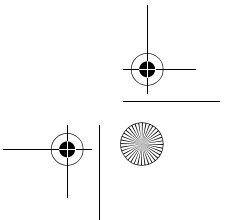
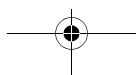
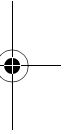
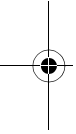
En tenslotte de mensen zonder wie dit boekje met veel minder plezier tot stand zou zijn gekomen. Omdat ik op twee afdelingen werkte en dus twee keer zoveel collega's had, kon ik al mijn frustraties en succesjes ook twee keer zo vaak delen. Voor zo'n kletskaus als ik is dat de ideale situatie. Allereerst biologische psychologie waar ik de afgelopen drie jaar de meeste tijd heb gependeed. Een geweldige afdeling! Het secretariaat onder de bezielende leiding van Natascha staat altijd voor je klaar. Dan de traditionele vrijdagmiddagborrel waar onder het genot van een drankje de toekomst van het onderzoek, Nederland en de rest van de wereld wordt besproken. Ik heb ervan genoten. Speciale dank gaat uit naar mijn collega aio's: Annebeth, Chantal, Daniel, Dirk, Eske, Frederiek, Irene, Janine, Lannie, Marieke, Marijn, Marleen, Nina, Rosa en Tinca. Ik zal de aio-etentjes missen. Tenslotte wil ik mijn kamergenoot Jacqueline bedanken. We hebben veel meer gedeeld dat alleen een kamer.

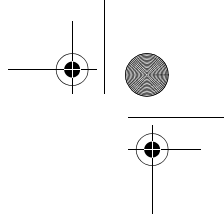
Ook de collega's van de psychiatrie ben ik veel dank verschuldigd. De flexibiliteit van de opleiding in GGZ Buitenamstel heeft het mogelijk gemaakt dat ik dit onderzoek kon doen en dat ik hier ook mee verder kan gaan. Deze flexibiliteit heeft tot een toenemend aantal AGIKO's en aanverwanten geleid. De etentjes met de AGIKO-intervisie groep waren en blijven zeer waardevol. Arne, Daniel, Eric, Gerben, Marijke, Neeltje, Odile, Peter, Ritsaert en Saskia, jullie hebben allemaal zo je eigen kijk op het onderzoekswereldje en dat maakt de discussies levendig en interessant. Marijke van Toolen en andere medewerkers van de bibliotheek van de Valeriuskliniek wil ik bedanken voor het onvermoeibaar opsturen van artikelen.

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Curriculum Vitae

Christel Maria Middeldorp werd op 4 november 1973 te Breda geboren. Haar hele jeugd woonde zij in Hoeven (NB). Na in 1992 het atheneum te hebben afgerond aan het Thomas More College in Oudenbosch, werd zij gelukkig direct ingeloot voor de studie geneeskunde, welke zij volgde aan de Erasmus Universiteit Rotterdam. Gedurende deze studie liep zij stage op de autisme kliniek van het Child Study Center van de Yale University. Dit was de eerste ervaring met onderzoek. Haar eerste artikel schreef zij naar aanleiding van een keuze co-schap op de afdeling kinderneurologie van het Sophia Kinderziekenhuis. In 1999 behaalde zij haar artsenbul. Vervolgens werkte zij gedurende 9 maanden op de afdeling neurologie van Ziekenhuis Amstelveen. Sinds maart 2000 werkt zij bij GGZ Buitenamstel, waar zij sinds juli 2001 in opleiding is tot psychiater. Vanaf oktober 2002 doet zij onderzoek op de afdeling biologische psychologie van de Vrije Universiteit in samenwerking met GGZ Buitenamstel. De komende jaren zal zij op beide afdelingen blijven werken.

