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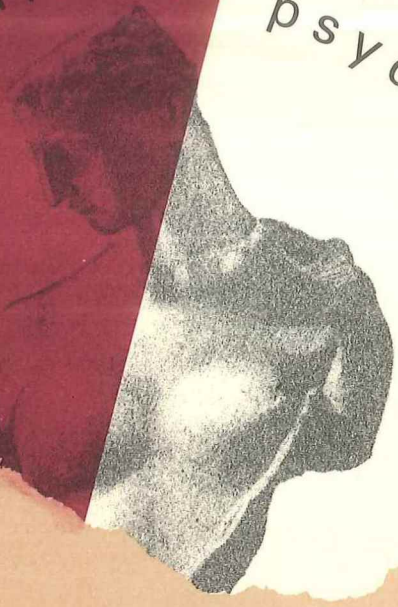

The Genetics of Electrophysiological Indices of Brain Activity

An EEG study in adolescent twins

Toos van Beijsterveldt

UNIVERSITEIT VAN AMSTERDAM

THE GENETICS OF ELECTROPHYSIOLOGICAL INDICES OF BRAIN ACTIVITY

AN EEG STUDY IN ADOLESCENT TWINS

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Contents

1

General Introduction

Little is known about the genetic and environmental determinants of individual differences in central nervous system function (CNS) and its development. The purpose of this thesis is to investigate these two influences on the individual differences of several indices of neural functioning during late adolescence. Genetic influences on the development of the brain were suggested by Thatcher et al. (1987). By using measures of the electrical activity of the brain, Thatcher et al. (1987) studied cerebral development in a large group of children varying in age from two months to early adulthood. They found evidence of discrete spurts in the growth of the functional connections in the brain during childhood, which appeared in specific anatomical locations at specific postnatal periods. The findings lead to the following statement:

'*...the strength and the specificity of the pattern in the data strongly favor the ontogenetic hypothesis of human cortical development in which there is a genetically programmed unfolding of specific corticocortical connections at relatively specific postnatal ages'* (pp. 1113).

The design of the study of Thatcher et al. did not allow them to test the relative contributions of genetic and environmental factors to the development of the brain. To specify the genetic contribution to individual differences in a particular trait, a design that includes subjects with varying familial relationships (for example, parents and offspring or siblings or twins) is necessary. Behavior genetic (or quantitative genetic) methods can be employed to measure the contribution of genetic factors to individual differences in complex traits, such as the indices of neural functioning. Unlike most psychophysiological research, quantitative genetics is not concerned with the variance due to specific experimental manipulations or mean differences between various subject populations, but with the determinants of individual differences for a particular trait.

The genetic architecture of both structural and functional characteristics of the CNS is especially difficult to study in man. Not only does the CNS genetics face the usual problems in human genetics (long generation time, impossibility of experimental crosses), but the CNS, unlike blood enzymes, can not be directly observed. Recording of electrical activity of the brain from the scalp, however, may be an important approach to assess CNS functioning and may lead to the mechanism underlying

genetic effects on behavior in humans. These indices can be obtained completely noninvasive.
Several studies investigated the genetics of CNS functioning by measuring parameters of brain activity in twin pairs (reviewed in the second chapter of this thesis). Although most twin studies were characterized by a small sample size, overall it can be concluded that most brain activity parameters are genetically determined to a large extent. None of the studies looked at differences in genetic architecture between males and females, applied model fitting to their data, or looked for genetic differences in topography and none of the studies obtained data related to developmental issues of the human CNS. We decided, therefore, to do an additional study to establish genetic and environmental influences on several different indices (EEG power, P300, and EEG coherence) in a large twin sample.
The neural indices that will be presented in this thesis have been obtained in a longitudinal design, which included 213 twin pairs, divided in an equal number of male and female monozygotic (MZ) and dizygotic (DZ) twin pairs and opposite sex twin pairs, all aged 16 on the first measurement occasion and 17.5 on the second measurement occasion.
A short description of the neural indices used in this thesis (EEG power, P300 amplitude, and EEG coherence) follows below. A rationale to use these neural indices is that they are sensitive to age-related effects, and thus genetic influences on developmental changes in the brain may be measured (Courchesne, 1978; Matoušek & Petersén, 1973). Also, these neural indices of the CNS functioning are associated with variation in normal and abnormal behavior.

EEG/ERP parameters

EEG power
As a first indicator of the CNS functioning, background EEG has been measured. The EEG is a recording of electrical activity of the brain, which is measured by electrodes placed at various positions on the scalp. The resulting EEG signal consists of a broad range of frequencies. With the help of spectral analysis the EEG signal can be decomposed into its frequency components, which can be clustered together into broad frequency bands (delta (1.5-3.5 Hz), theta (4-7.5 Hz), alpha (8-12.5 Hz), and beta (13-25 Hz)). The amount of activity in each frequency band describes the EEG. During wakefulness all frequencies are present, but alpha and beta frequencies dominate. Alpha frequency predominates over the posterior regions of the head during wakefulness, generally with higher voltage over the occipital areas. Alpha is best observed with closed eyes and under conditions of physical relaxation and relative mental inactivity. Beta refers to the range with the higher frequencies that is obtained during states of higher arousal, and is found chiefly over the frontal and

central regions. The normal adult waking EEG contains but a small amount of delta and theta frequencies, these two frequency bands play an important role in states of drowsiness and sleep (Niedermeyer, 1993).
The relative contribution of frequency bands to total EEG varies strongly with age and brain area (Matoušek & Petersén, 1973; John et al., 1980; Matthis et al., 1980; Hudspeth and Pribram, 1992; Gasser et al., 1988). With increasing age, slow EEG activity is gradually substituted by fast frequencies. These changes do not occur in equal steps throughout the years (Gasser et al., 1988; Hudspeth & Pribram 1992) and developmental patterns differ with topography (Gasser et al., 1988; Katada et al., 1980; Matoušek & Petersén, 1973). The age-related changes in children are more pronounced in posterior regions, and for adolescents in anterior brain areas. Maturation of the brain extends into middle and late adulthood (Fisher & Rose, 1994), from the age of fifteen especially the frontal lobes maturate (Buchsbaum et al., 1992; Hudspeth & Pribram, 1992; Thatcher et al., 1987).
EEG is used as an indicator of brain functioning and organization. Although, until now no clear relationship has been found between EEG pattern and psychological properties. Still, EEG is empirically associated with a wide range of psychopathological behavior, such as dyslexia (Duffy & McAnulty, 1990), learning disabilities (John et al., 1980), psychopathology (Buchsbaum, 1993), and vulnerability for alcoholism (Propping et al., 1981).

P300

An event related potential (or ERP) is a change in the electrophysiological activity of the brain in response to a stimulus, and is obtained by averaging the EEG time locked to the stimulus. The resulting ERP wave form consists of a pattern of waves, which can be described by their latency (occurrence in time), polarity (positive or negative) and scalp distribution. The P300 is one component of the ERP and is a large positive going potential that peaks between the 300-600 ms after stimulus onset with parieto-central maximum scalp distribution. The P300 is called an endogenous component because it is not influenced directly by the physical parameters of the stimulus; the variance of its amplitudes and latency is primarily determined by the psychological processes evoked by the stimulus. The simplest paradigm to obtain a P300 is an 'oddball' task: the subject has to attend to a series of frequently occurring trials (nontargets) and to detect the infrequent stimuli (targets). In general, P300 is characterized by the amplitude and latency and is believed to reflect memory updating operations during information processing (Donchin et al., 1986). Other studies showed the variation in P300 amplitude to be related to the amount of information provided by a given stimulus (Johnson, 1988; Ruchkin et al., 1990). Latency of P300 latency has been associated with the speed of information processing (Donchin et al., 1986).

During development, the P300 amplitude and latency show age-related changes in morphology and topography. Standard (nontargets) and rare stimuli (targets) elicit a P300 component with decreasing latency and amplitude as children grow up and do not reach mature values until puberty or young adulthood (Courchesne, 1978). In studies which included subjects from age 16 year in their sample (Wijker et al., 1989; Segawolitz & Barnes, 1993) no noticeable age-related changes occurred.
Because the P300 is thought to reflect cognitive processing, it is often used in studies in which abnormal behavior is associated with cognitive dysfunction, such as, in relation to autism (Courchesne, 1987), and in relation to schizophrenia (Friedman et al., 1986). P300 characteristics also have been studied in relation to alcoholism (for a review see Polich et al., 1994)

EEG coherence
The third index of neural functioning, studied in a genetic framework, is EEG coherence. Besides the EEG activity, investigated in different brain areas, the brain activity shared between brain areas can be estimated. By estimating the cross-correlation of EEG signals recorded from different brain areas, the coherence can be measured. EEG coherence is an index that may reflect the degree of functional organization of different brain areas. In a large cross-sectional study Thatcher et al. (1987) measured EEG coherence in a large group of children, ranging in age from two months to seventeen years. They found that specific functional connections within the left and right human hemispheres develop at different rates and at different postnatal onset times. The coherence model of Thatcher is based upon the theoretical network model of Nunez (1981). In this model, besides short corticocortical tracts, longer corticocortical connections are suggested. These kinds of connections may be the fundament of the shared brain activity between two brain areas.
Compared to age-related changes of EEG power, coherence is subject to changes during maturation (Schmidt et al., 1992; Marosi et al., 1992; Gasser et al., 1987). With increasing age EEG coherence may increase as a consequence of myelination and synapto-genesis, which produce more efficient interconnections between different regions. However, coherence may decrease due to increased cortical differentiation. Like the EEG power, prominent changes of the EEG coherence in the frontal areas may occur from age sixteen.
Also, EEG coherence has been associated with variation in normal and abnormal behavior. For example, the EEG coherence has been associated with intelligence, a negative correlation with intelligence was found by Thatcher et al. (1983), and EEG coherence has been associated with various forms of psychopathology, for example, schizophrenia (Hoffman, 1991) and Alzheimer disease (Dunkin et al., 1994).

Quantitative genetics and the twin method

This section offers a general introduction to quantitative genetic approaches to individual differences and the twin method. Quantitative genetics can be employed to estimate the contribution of genes and environment to the interindividual differences in a particular phenotype[1]. Traits that show the classical segregation ratios described by Mendel, are probably influenced by a single gene and called Mendelian. In the EEG some rare variants that show Mendelian inheritance (Vogel, 1970) were found. However, most complex behaviors and characteristics of the EEG are explained by more than one gene. It is assumed that the normal alpha activity of the background EEG is explained by polygenes (Vogel, 1970). The essence of quantitative genetics is that Mendel's law of discrete inheritance also applies to normally distributed complex characteristics (Plomin et al., 1990). The idea to extend the Mendelian theory of inheritance of qualitative traits to the genetic determination of complex continuous quantitative traits was proposed by Fisher (1918). Fisher assumed that the combined effects of alleles across loci could sum up, each with a small effect, to produce several observable different phenotypes in the population. According to Mendelian laws a trait influenced by one gene would lead to a binomial distribution in the population; for traits influenced by many genes the observed distribution leads to a normal curve in the population. Thus, the fundamental point of quantitative genetics is that polygenetic differences among individuals can lead to phenotypic differences. The inheritance of quantitative traits follows the same laws of transmission and leads to a predictable genetic correlation among individuals. Quantitative genetic theory also recognizes that environmental influences can contribute to observed variance among individuals and observed covariance among relatives.

In humans, a decomposition of phenotypic variance into genetic and environmental variances is possible with data from genetically related subjects. A basic model often used in quantitative genetics is the twin design. The twin method compares the resemblance for identical (monozygotic, MZ) twin pairs with fraternal (dizygotic, DZ) twin pairs for a particular trait to obtain an estimate of its heritability. MZ twins are genetically identical to each other. Any true differences, free of measurement error, between identical twins are attributable to their nonshared environment

[1] Explanation of some terms used in this section. Phenotype refers to the observed characteristic/traits. Locus is the site of a gene on a chromosome. Alleles are alternative forms of a gene that occupy the same locus on a chromosome. The genotype is the chromosomal complement of alleles for an individual. The additive genetic value of a gene is the sum of the average effects of the individuals alleles. Dominance effects refer to the extent to which genotypes differ from the additive genetic value. A system in which multiple loci are involved in the expression of a single trait is called polygenetic. A system with polygenetic and environmental influences is called multifactorial.

(Molenaar et al., 1993). Fraternal twins share, on average, 50% of their genetic material. If heredity affects a trait, the phenotypical resemblance should be roughly two times larger for identical twins. If the degree of resemblance of traits is the same in identical as in fraternal twins, the shared environment determines that trait. The twin method assumes that MZ and DZ twin pairs share their family environment to the same extent. To express the similarity between twin pairs doubling the differences between identical and fraternal correlations has been used (Falconer, 1981). Several drawbacks of this method were listed by Eaves et al. (1989): it does not test any explicit model for individual differences, it only works with twins and will not generalize to more complex data sets, and it does not consider nongenetic transmission. Additionally, the classical approach of correlations ignores information available in variances and covariances, which is important in the genetic analysis of sex and generation differences.

Nowadays model fitting procedures are increasingly used to analyze data from twin studies (Boomsma & Molenaar, 1986; Heath et al., 1989; Neale & Cardon, 1992). The major advantages of the model fitting approach include: models make the assumptions explicit; it allows to conduct tests of significance of alternative hypotheses; and it enables to simultaneously analyze data from several different familial relationships; it provides appropriate estimates of quantitative genetic parameters and can be generalized to multivariate phenotypes (Martin & Eaves et al., 1977; Boomsma & Molenaar, 1986) and to time dependent observations (Boomsma & Molenaar, 1987).

In the model fitting approach the total variance is decomposed into variance due to genetic and environmental effects. The total genetic effect on a phenotype can be divided into one due to the additive effect of alleles at multiple loci, one due to dominance effect, and one due to epistatic interactions between loci. Epistatic effects would lead to very low correlations between any type of relatives except MZ twins but have not been tested. The total environmental effect into can be divided into one due to environmental influences shared by twins reared in the same family (shared, common or between-family environmental effects), and into one due to environmental effects which make family members differ from one another (random, specific, or within-family environmental effects). The observed phenotypes are assumed to be linear functions of the underlying additive genetic variance, dominance variance, shared environmental variance, and random environmental variance. This genetic model can be represented by the following equations:

$$P1 = eE1 + cC1 + aA1 + dD1$$
$$P2 = eE2 + cC2 + aA2 + dD2$$

with:

P is the observed behavior (phenotype).
A is the latent additive genetic factor.
C is the latent shared environmental factor.
D is the latent genetic dominance.
E is the latent nonshared environmental factor.
a, c, d, and *e* are loadings of P on respectively A, C, D, and E.
Subscript 1 refers to the first twin and subscript 2 refers to the second twin.
It is assumed that A, C, and E do not correlate or interact.

The narrow-sense heritability (h^2) is calculated as the relative contribution of additive genetic variance to the total phenotypic variance (Vp), $h^2= a^2/Vp$, where $Vp=a^2+c^2+d^2+e^2$ and the variance of the latent variables A (Va), C (Vc), D (Vd), and E (Ve) are standardized (Va=Vc=Vd=Ve=1). The broad-sense heritability (h_B^2) is the proportion of phenotypic differences due to all sources of genetic variance, regardless of whether the genes operate in an additive or nonadditive manner.
Although the shared environmental (C) and the dominance (D) factors both can contribute to Vp, with only twin data it is not possible to test both factors at the same time. In the model fitting of twin data the genotypes and environments are not measured directly, but their influence is inferred through their effects on the covariances of relatives. Genetic and environmental influences predict similarities between relatives. Because MZ twins have the same genes and shared environmental influences as the co-twin (C), the covariance of a MZ twin may be expressed in the following equation:
COV(*mz*)=Va +Vc or Cov(*mz*)= Va +Vd
On average, DZ twins have 50% of their genes in common, and it is assumed that they share family environmental influences to the same extent as MZ do, thus their covariance is expressed as:
COV(*dz*)=.5Va + Vc or Cov(*dz*)=.5Va + .25Vd
In a design with MZ and DZ twin pairs, the observed variance and covariance of the twin pairs are compared with the expected values from a genetic model. The model fitting function is defined as a function of the differences between the expected statistics and the observed statistics, and optimization is concerned with finding values for the unknown *a, c, e*, and *d* parameters that minimize these differences. The best result is when the discrepancies between the observed and expected statistics are minimal. To judge the fit of the model a chi-square test is often used. When the model does not fit, the chi-square will be large and the model will be rejected. All model fitting reported in this thesis was done with Mx, a software package for structural equation modeling, which was developed by Mike Neale (1994).

Applying quantitative genetics to the present twin study

Model fitting in the papers of this thesis has used to obtain insight in genetic determination of EEG/ERP parameters, while simultaneously accounting for sex differences and brain location. The study has been conducted in a large group of twins. Since quantitative genetics deals with decomposition of variance in the population, a larger number of subjects are necessary, than when working with first-order statistics. A longitudinal design was used to study the change in genetic contribution over time.
Structural differences in the anatomy of the brain of males and females are suggested, such as the difference in size and morphology of the corpus callosum between males and females (Steinmetz et al., 1995), and differences in sylvian fissura morphology (Witelson& Kigar, 1992). Functional differences have also been suggested, for example sex differences in hemisphere specialization of function (McGlone, 1980). Some sex differences manifested themselves in the P300 (Segawolitz & Barnes, 1993), EEG power (Matoušek & Petersén, 1973; Harmony et al., 1990; Benninger et al., 1984; Matsuura et al., 1985) and EEG coherence (Marosi et al, 1993, Flor-Henry et al., 1987; Rappelsberger & Petsche, 1988). Therefore, sex differences in genetic architecture and environmental experiences have been tested in this thesis. Two kinds of sex differences may be distinguished (Eaves et al., 1978): 1) Sex differences in the magnitude of genetic and environmental influences, but the genetic and environmental influences themselves are the same, 2) The genetic (and environmental) influences that are expressed in one sex are not expressed in the other sex. A model including same-sex male and female twin pairs allows for test of differences in magnitude of parameters. DZ opposite-sex twin pairs are crucial to test whether the same genetic (or environmental) factors influence the traits in males as in females. If genetic (or environmental) influences differ in kind for males and females, the DZ opposite-sex correlation will be less than the average of the two same-sex zygosity correlations (Reynolds & Hewitt, 1995).
The EEG/ERP parameters have been measured in 14 brain locations, therefore it was possible to test whether the heritability was the same in different parts of the brain. The various brain areas seem to differ in anatomy, for example, in the prefrontal cortex, cortical connections are more extensive and appear to be organized in a way fundamentally different from those in the posterior cortex (Gevins & Illes, 1991). The frontal brain area is also thought to participate in other functions than the posterior brain areas. The frontal area is involved in a variety of functions, such as planning and sequencing of behaviors and the occipital, posterior brain areas are concerned with visual and visuo-spatial functions. In the ontogeny, the prefrontal cortex is the last one to mature. One may ask if the heritability estimates are the same for EEG/ERP parameters, involved in the relatively new brain areas, as the heritability estimates of the EEG/ERP parameters in the older primary areas. The phylogenetically younger brain structures seem to show more interindividual

differences than is apparent for the older ones (Markowitsch, 1988). It is possible to apply genetic multivariate analyses to EEG/ERP parameters, measured over various brain areas. Multivariate analyses can estimate the genetic and environmental contributions to the covariance among brain areas. As we shall see in greater detail later on, not much is known about the differential heritability of the separate areas of the brain.
The previous paragraph about EEG/ERP parameters summarized how part of the variability of the neural indices, especially the EEG power and coherence, is induced by age (Matoušek & Petersén, 1973; Thatcher et al., 1987). During ontogenesis, the observed change in a quantitative character may be due to distinct subsets of genes tuning on and off. The genetic contributions do not need to be stable. During development, there could be a change in the relative magnitude of genetic and environmental variance for a particular characteristic, or another set of genes could be switched on. Developmental changes in heritability do not implicate molecular mechanisms of change. Heritability could increase with growing age if the environmental variances decline during the development. For example, at age 1, 2, and 3 the influence of shared environmental factors on IQ is important, but when children grow up the contribution of these environmental factors decrease and genetic factors increase (Plomin, 1986; Boomsma, 1993). Conversely, heritability could remain the same for a particular trait at two ages, yet completely different sets of genes could be working. Thus, especially in studying sensitive periods of growth, small age-range is required for a meaningful interpretation of the heritability. In this thesis a sample with a small age-range was used.
In this thesis a first impression of the stability of genetic and environmental factors is given in an extensive appendix. The twin correlations for measurements on the two occasions are given plus the within person correlations that give an indication of phenotypic stability.

Outline of the thesis

This thesis deals with genetic and environmental influences on *individual differences* in functioning of the human central nervous system. To index the CNS function, brain activity was measured during rest and during a simple cognitive task. Three neural indices are described in the following chapters, the EEG power, P300 amplitude and latency and EEG coherence. Twohundred twin pairs, all aged 16, were tested twice, with one and half year in between. This thesis mainly concentrates on the genetic analyses of the measures obtained in the 16 year-old twin pairs. In the appendix an overview of the descriptions of measurements of both occasions is given.

To get some insight into the genetic influences on individual differences in the human nervous system, the twin and family studies of normal variation in the human electroencephalography (EEG) and event related potentials (ERPs) are reviewed in the second chapter of this thesis.
Chapter 3 gives the results of the genetic analysis of the EEG power. For 213 twin pairs the heritability of four classical frequency bands of the EEG power, measured on 14 electrode positions, was estimated. Sex differences in genetic architecture will be tested. For the alpha frequency, multivariate analyses will be used to test whether the same genes are expressed in the different brain areas.
In chapter 4, the genetic and environmental influences on the individual differences in the P300 are reported. For the same 213 twin pairs the P300 was obtained in a simple 'oddball paradigm' and its amplitude and latency analyzed with multivariate models.
In chapter 5, within each hemisphere of the brain, the EEG coherence has been estimated for electrode combinations along the anterior-posterior axis. For four frequency bands, the heritability for each combination of electrode pairs has been estimated.
Chapter 6 gives a summary of the thesis. The first part discussed the results in light of the model fitting approach. The second part of the discussion focuses on the descriptions of EEG/ERP parameters in the appendix. The appendix gives an overview of the descriptive statistics of the EEG/ERP parameters obtained on the two measurement occasions.

2

Genetics of the human electroencephalogram (EEG) and event-related potentials (ERPs): a review[1]

C.E.M. van Beijsterveldt & D.I. Boomsma

Abstract

Twin and family studies of normal variation in the human electroencephalogram (EEG) and event related potentials (ERPs) are reviewed. Most of these studies are characterized by small sample sizes. However, by summarizing these studies in one paper, we may be able to gain some insight into the genetic influences on individual differences in central nervous system functioning that may mediate genetically determined differences in behavior. It is clear that most EEG parameters are to a large extent genetically determined. The results for ERPs are based on a much smaller number of studies and suggest medium to large heritability.

Introduction

Individual differences in the functioning of the nervous system may mediate genetically determined differences in behavior. Genetic influences have been documented for a broad range of human behavior (e.g., Eaves et al., 1989; Plomin & Rende, 1991; Bouchard & Propping, 1993) and it is therefore surprising that little is known about genetic influences on individual differences in human nervous system functioning. Central nervous system functioning, and more especially brain activity, can be assessed by neurophysiological techniques. In this review, we summarize our current knowledge about the genetics of the normal human electroencephalogram (EEG) and of event-related brain potentials (ERP).

Both background EEG and task-related ERPs are indicators of brain functioning and organization, and are associated with a wide range of behavioral and cognitive traits, such as information processing (Vogel et al., 1979), cognitive functioning in children and adults (Courchesne, 1978), dyslexia (Duffy & McAnulty, 1990), learning disabilities (John et al., 1980), autism (Courchesne 1987), psychopathology

[1] This chapter is a slighty revised version of a publication in Human Genetics, 1994, 94:319-330.

(Buchsbaum, 1993), and vulnerability for alcoholism (Propping et al., 1981; Polich et al., 1994). EEG and ERP parameters also provide information with respect to aging in healthy subjects (Duffy et al., 1984; Ford & Pfefferbaum, 1985), dementia (Sloan & Fenton, 1993), and Alzheimer's disease (Schreiter-Gasser et al., 1993).

Brain activity is a complex phenotype to study because it is dynamic and changes in response to the environment. Like many behavioral traits, it appears to be influenced by many genes (Vogel, 1970) and by nongenetic factors. Involvement of genetic factors in human behavior can be studied non-invasively with twin, adoption or family studies in which the resemblance for a trait among family members at a given level of genetic relationship is compared. By using correlational or biometrical methods, the observed trait variance may be partioned into a genetic part and an environmental part. These studies are essential as first indicators of possible influences of genes on the functioning of the human nervous system.

The influence of genetic and environmental factors on EEG characteristics has been studied only in intact families. Most of these studies have been carried out in twins. To express the similarity between twins or other family members, product-moment correlations or intraclass correlations, based on an analysis of variance (Haggard, 1958) are often used. The correlation between family members is the ratio of the covariance between them to the total variance of the trait. For identical or monozygotic (MZ) twins, the covariance between them is the sum of the covariance attributable to genetic influences and that attributable to a shared environment. The covariance for dizygotic (DZ) twins differs only in the part that is attributable to genetic influences, because DZ twins share on average only half of their genes. Doubling the difference between MZ and DZ correlations yields an estimate of the broad sense heritability (h^2) (Falconer, 1981), i.e., the proportion of variance attributable to genetic variation. This methodology does not require individuals under study to be twins. As long as the genetic relationships of the subjects are known, it is possible to decompose the covariance between them into genetic and environmental components. Estimates of broad sense heritability based on twin data present an upper bound estimate that includes not only additive genetic variance, but also dominance and epistatic genetic variance. However, if twin experimental designs are extended by including other family members, it becomes possible to obtain separate estimates of additive genetic and dominance variance, and to model effects of assortive mating.

If evidence of familial resemblance and genetic control are suggested for a discrete or quantitative phenotype, the next step is to identify the responsible genetic mechanism (Khoury et al., 1993). The possibility of Mendelian transmission for certain EEG characteristics can be investigated by segregation analysis (Elston & Stewart, 1971; Vogel & Motulsky, 1986). The final evidence for genetic inheritance comes from demonstrating genetic linkage with a known marker (Ott, 1991).

Genetics of EEG

An EEG is a recording, from the scalp, of the electrical activity of the brain over a short period of time. It reflects the present functional state of the brain and its different levels of arousal. An EEG contains a series of wave forms that are classified into various frequencies. In the resting EEG, two dominant frequencies can be observed, viz., alpha (α) and beta (ß). The α-rhythm is the activity in the range from 8 to 13 Hz. Approximately 95% of humans produce a clearly identifiable α-rhythm when awake with the eyes closed. The ß-frequencies are faster (13-10 Hz) and appear in alert subjects. Various methods of quantitative analysis are available to describe these rhythms of the EEG; the α-rhythm is described in terms of its me-an-amplitude, the averaged peak-to-peak amplitude, frequency, number of complete cycles per second, α-index, and an assessment of the percentage of time occupied by α-waves.
An EEG tends to be a stable individual characteristic that varies considerable between subjects. This stability in an individual over time and the marked interindividual variability (Salinsky et al., 1991; Pollock et al., 1991) pose questions regarding the causes of interindividual differences in the EEG.

Genetics of EEG wave forms
After the first description of the EEG by Berger (1929), several studies investigated the possible role of genetics on the EEG. In the earliest twin studies, the resting EEG showed a high degree of similarity in MZ twins (Davis & Davis 1936). Raney (1939) reported high correlations in MZ twins for percentage α-activity (.87), α-amplitude (.76), and α-frequency (.91) for occipital leads. Lennox et al. (1945) compared the resting EEG of MZ twins with that of DZ twins. Almost identical EEGs were seen in MZ twins; they were significantly different from the EEG resemblance in DZ pairs. On the other hand, Gottlober (1938) failed to find an association between EEG patterns of parents and offspring, and assumed that the resemblance in EEG patterns, if any exist, are not marked. Convincing evidence to support genetic influences on the EEG was obtained by Juel-Nielsen and Harvald (1958) who studied eight MZ twins reared apart and who found that various EEG parameters were practically the same in all twins. Later studies used quantitative methods to measure the EEG, because of the lower reliability of visual inspection. The most extensive genetic studies of the human resting EEG were carried out by Vogel (1958, 1962a, 1962b). Vogel (1958) started to investigate 'to what degree the variability of the normal EEG is due to genetic differences'. The resting EEG was measured in a large group of 110 MZ and 98 DZ twins at rest, during hyperventilation, hypoxia, and sleep. On the basis of visual inspection, no consistent differences between MZ twins were seen, unlike the EEGs of DZ twins. This was supported by quantitative measurements; the EEG for MZ twins were alike with respect to α-index, sub α-index, persistence, amplitude, and frequency. Differences between MZ twins did not exceed those encountered in successive EEGs recorded in the same individual and it was concluded that EEG variability is exclusively determined by heredity and that a multifactorial genetic system is most likely for the normal EEG.

At all ages, Vogel (1958) found similar EEG patterns in MZ but not in DZ pairs, suggesting that the speed of brain maturation is genetical determined (Vogel, 1958). Even in old age, EEG parameters seem primarily genetically determined. Heuschert (1963) found that the EEG of 26 MZ pairs (aged 50-79 years) showed no significant differences for amplitude and α-index. The amplitude-differences in MZ pairs did not exceed hemisphere differences recorded in the same person. The only differences were found in active dysrhythmic groups and in subjects with focal abnormalities.
The higher MZ correlations for α-index and mean α-amplitude were confirmed by Young et al. (1972). They also analyzed the EEG in frequency bands by use of bandpass filters that transmitted only a particular range of frequencies. For the α-power (7.5-13.5 Hz), the MZ intraclass correlation was .52, and the DZ correlation was .29; the correlation for unrelated subjects (UR) .02. The only significant differences between MZ (.90) and DZ correlations (0.56) were found for ß-power (13.5-26 Hz). The same pattern of correlations was observed by Hume (1973). For 39 MZ and 43 DZ pairs, the correlations for the α-index were .64 and .32 respectively, and for the ß-frequency .75 and .40, indicating heritabilities for both parameters of around 60%. The higher correlations for ß could have arisen because the EEG was recorded during auditory stimulation and because α-activity was replaced by ß-activity.
Meshkova and Ravich-Shcherbo (1982) also calculated α and ß by means of bandpass filters. For 20 MZ twins, correlations in the range of .58 to .96 were obtained for all α-parameters over all regions of the brain, whereas the correlations in the DZ group (20 pairs) were considerably lower (.11 tot .65). This is the first study to consider different regions of the brain and the results suggest that heredity plays a different role in different brain areas. Genetic influences for occipital and parietal areas were stronger than for frontal, central and temporal regions.
In all these studies, typical resting EEG parameters, such as α-frequency, α-index, and mean α-amplitude show MZ correlations in the range of .4 to .9 and DZ correlations in the range of .3 to .6. The MZ similarity agrees with the similarity seen by visual inspection.
Genetics of EEG powers as defined by spectral analysis techniques.
Standard EEG practice involves recording simultaneously from multiple areas of the scalp, and producing a set of time-series measures of voltage. Spectral analysis converts the EEG from the time domain to a frequency domain. The EEG is decomposed into a set of pure sine waves of different frequencies with estimates of the spectral densities at various frequencies. The result is a power spectrum with the horizontal axis representing the frequencies and the vertical axis representing squared voltages. By using spectral analysis as a quantitative method, the description of the EEG is more accurate. It shows a large intraindividual stability, test-retest reliabilities of .8 were found for absolute and relative power within a 12-16 week interval between assessments for the same person (Salinsky et al., 1991).
Using spectral analysis of the EEG, Dumermuth (1968) found striking similarities in five of six MZ pairs, in comparison with four DZ pairs. Striking similarities for MZ

twins were also seen by Lykken et al. (1974). EEGs were measured in 27 DZ and 39 MZ twin pairs. The intraclass correlations for various frequency bands for MZ twin pairs varied between .76 and .86, leading to heritability estimates of around .80. However, the correlations for the DZ group ranged from -.20 to .15. These correlations are lower than expected on the basis of additive genetic relatedness. However the setting was unusual: EEGs were recorded during hypnosis. The experiment was replicated (Lykken et al., 1982) and the same results were obtained, viz., high correlations for all frequency bands for the MZ group and low correlations for the DZ group. Lykken (1982) explained the low DZ correlation by labeling the α-frequency as an emergenic trait, for which variation is influenced by gene interactions. Stassen et al. (1987) analyzed the data of Propping (1977), collected in a study of EEG and alcohol. A bounded area with a maximum and minimum power as a function of the frequency was analyzed. The average DZ similarity was significantly higher than that of UR persons. The spectral patterns of MZ twins were remarkably similar; an overlap of 84% between the interindividual and within pair distribution was found. This is slightly less than a person resembles himself over time. With the same procedure, Stassen et al. (1988a,b) analyzed EEGs of MZ and DZ twins reared apart (Bouchard et al., 1990). The previous results were confirmed; the similarity of MZ spectral patterns is only slightly less than that of the same subject compared with himself over time, and the average similarity of the DZ pairs differs significantly from the similarity of a group of UR individuals. In a more advanced manner, Whittton et al. (1985) calculated not only power spectra, but also covariances between different frequencies. For these measures, MZ similarity was larger than UR similarity, suggesting a genetic basis. The similarity had a tendency to be larger in the posterior brain areas. Although more sophisticated analyses were used, too few twins were studied to quantify the genetic influence.

EEG parameters during different arousal levels

EEG parameters change markedly during different levels of arousal. A few genetic studies have assessed EEG during sleep and after ethanol ingestion.

During sleep, five stages are distinguished that are characterized by typical EEG patterns. Large individual differences exist for these stages (Merica & Gaillard, 1985). Vogel (1958) studied sleep patterns in twins and found high similarities in MZ twins for all stages. Zung and Wilson (1967) reported concordance of sleeping patterns together with REM (rapid eye movement) pattern in four MZ and dissimilar patterns in two DZ twin pairs. This was confirmed by Linkowski et al. (1989). EEG was recorded during three consecutive nights in 14 MZ and 12 DZ pairs. For stages 2, 4, and delta substantial similarity for MZ twins was found. The stages with the strongest genetic component are those that show the best relative stability from night to night (Merica & Gaillard,1985).

Propping (1977) investigated the genetic influences of alcohol on the central nervous system. In general, alcohol improves the synchronization of the EEG, and the number of α- and theta-waves increases, but the EEG reaction depends on the indivi-

dual resting EEG. Individuals with a continuous regular α-rhythm show little response to alcohol intake. The EEG pattern of MZ twins showed the same reaction to alcohol, whereas the EEG of DZ twins became more dissimilar. This finding and the individual reaction suggest a strong genetic determination of alcohol on the EEG response. Propping et al. (1981) tested whether certain types of EEGs (with poor synchronization, because alcohol improves the synchronization) may reflect a certain predisposition to alcoholism. In women, an EEG pattern that could reflect a disposition to alcoholism was indeed found.

Genetics of rare EEG variants

The mode of inheritance of well-defined EEG variants has been studied in a large number of nuclear families (e.g., Vogel & Götze, 1959; Vogel, 1962a, 1962b, 1966a, 1966b; Dieker, 1967; reviewed in Vogel, 1970). An EEG variant is defined as a stable constant EEG trait that is rare in the population, without implying dysfunction or relationship with a disorder. A number of α- and ß-EEG variants were distinguished. For some EEG variants, especially the low-voltage α and the fast α-EEG variant, the data pointed to an autosomal dominant mode of inheritance (Vogel & Götze 1959; Vogel 1962a, 1966b). Another α-rhythm EEG variant, the monomorphic waves, was extensively studied by Dieker (1967) who found that this variant was also inherited in an autosomal dominant mode. A special rare EEG type with the posterior α-rhythm mixed with slower waves (rhythm of 4-5 Hz) showed complete concordance in two MZ twin pairs, but only four of 40 siblings were seen with the same EEG variant. Kuhlo et al. (1969) mentioned the possibility of exogenous influences for the appearances of this rhythm. Two ß-variants showed a Mendelian pattern of autosomal dominance (Vogel, 1966a, b), but most ß-variants showed a model of multifactorial inheritance (Vogel & Götze, 1962; Vogel, 1966a). Recently, Steinlein et al. (1992) reported the localization of a gene responsible for a low voltage α-EEG variant that is characterized by the almost complete absence of α-waves in occipital leads. The distribution of this EEG variant is bimodal and segregation analyses support an autosomal dominant mode of inheritance (Anokhin et al., 1992; Vogel & Götze, 1959). Evidence for linkage with a marker on the distal part of chromosome 20q was found in a subset of 17 families with the low-voltage EEG variant (Steinlein et al., 1992).

Conclusion

An overview of twin and family studies of EEG parameters is given in Table 2.1. The quantification of the EEG in earlier studies is not completely reliable because it involved visual inspection followed by a subjective estimate of the similarity between the records of twin pairs. Even in modern studies, differences in results depend on subject and EEG factors. Factors that influence EEG measurements include age, level of arousal, pathology, and cognitive state. Dependent EEG factors are electrode position, filtering techniques, degree and type of artifact exclusion, EEG parameter, and EEG epoch length (Oken & Chiappa, 1988). Moreover, the use of various mathematical transforms may affect statistical measures of variability and correlation (Pivik et al., 1993). In spite of these differences, the consensus of studies that focus on the human EEG appears to be large. For α-parameters, enough evidence seems to exist to conclude that genetic factors contribute significantly to variations in α-amplitude and α-index. The high concordance in MZ twins is also seen in MZ twins reared apart (Bouchard et al., 1990), suggesting that common environmental variance is not an important factor. Use of spectral analysis of the EEG has led to high heritabilities being shown for various frequency bands. The lowest correlations in MZ twins are found for theta-frequency and are probably caused by eye movement and other movement artifacts. A normal EEG is assumed to be multifactorial (Vogel, 1970; Lykken, 1982). For some rare EEG variants, a Mendelian pattern of autosomal dominance is seen (Vogel, 1970). The localization of a gene for this EEG variant has recently been determined (Anokhin et al., 1992; Steinlein et al., 1992). Most studies used only a limited number of subjects, and none of the studies quantified the genetic contribution as a function of age and sex. From the work of Vogel (1958) and Heuschert (1963), it appears that the speed of maturation of the brain is genetically determined. Although remarkable developmental changes occur during brain maturation (Vogel, 1958; Courchesne, 1978; Thatcher et al., 1987), no longitudinal genetic study of the EEG has been carried out in genetically informative subjects, so that no information exists on the stability of genetic influences at present.

Table 2.1. Review of twin studies and electroencephalography (EEG). *MZA* Monozygotic twins reared apart, *MZT* monozygotic twins raised together

STUDY	YEAR	SUBJECTS	AGE	EEG PARAMETER	GENETICAL ANALYSIS	RESULTS
Davis & Davis	1936	8 MZ	15-58	α-activity	clinical eye	MZ concordant
Gottlober	1938	15 fam	>14	α-index α-frequency	clinical eye (parent-offspring)	no significant parent-offspring correlations
Raney	1939	17 MZ UR	7-16	α-index	clinical eye spearman rank correlation	α-activity: rMZ=.61 α-frequency: rMZ=.91 α-amplitude: rMZ=.66
Lennox, Gibbs & Gibbs	1945	55 MZ 16 DZ	5-61	frequency and amplitude of EEG waves	clinical eye	MZ concordant, DZ discordant
Juel-Nielsen & Harvald	1958	8 MZA	22-72	α-index, α-frequency α-amplitude	clinical eye	MZ concordant
Vogel	1958	110 MZ 98 DZ	6-30	sub α-index, α-amplitude α-persistence	t-test	MZ concordance > DZ concordance α-persistence
Heuschert	1963	26 MZ	50-79	sub α-index, α-amplitude α-persistence	variance analysis	MZ concordance
Vogel	1966a	30 fam	9-73	EEG-ß variant	segregation-ratio	autosomal dominant
Vogel	1966b	24 fam	9-60	EEG-ß variant	segregation-ratio	autosomal dominant
Dieker	1967	4 MZ 2 DZ 35 fam	12-80	low voltage EEG variant sub α-index, α-amplitude α-persistence.	clinical eye segregation-ratio	MZ concordance > DZ concordance
Kuhlo, Heintel & Vogel	1969	2 MZ 40 probands	12-54	EEG variant 4-5 c/s rhythm	segregation-ratio	EEG variant with genetic basis, possible exogenous causation
Vogel	1970	224 fam	>10	EEG α-variants EEG β-variants	segregation-ratio	certain α- and β-variants: autosomal dominant most normal α- and β-variants: multifactorial
Young, Lader & Fenton	1972	17 MZ 15 DZ	19-40	α-index α-amplitude α-frequency	intraclass correlations	α-index: rMZ=.5, rDZ=.2, rUR=.0 α-amp: rMZ=.5, rDZ=.3, rUR=.1 α-fre: rMZ=.5, rDZ=.3, rUR=.0
Hume	1973	39 MZ 43 DZ		α-frequency α-index	intraclass correlations	α-freq: rMZ=.75, rDZ=.4 α-index: rMZ=.64, rDZ=.33

Lykken, Tellegen & Thorkelson	1974	39 MZ 27 DZ		power spectra (0-19.9 HZ)	intraclass correlations	delta: rMZ=.76, rDZ-.01, theta: rMZ=.86, rDZ=-.03 alpha: rMZ=.82, rDZ=-.20, beta:rMZ=.82, rDZ=.15
Surwillo	1977	7 MZ 14 UR	8.5-11.2	interval histogram	intraclass correlations	median: rMZ=.9, rUR=.15 mode: rMZ=.7, rUR=-.02
Propping	1977	26 MZ 26 DZ	m=23.3 m=23.8	α-frequency α-amplitude ß-frequency	intrapair correlations	α-freq: rMZ=.69, rDZ=.33 α-ampl: rMZ=.63, rDZ=.39 ß-freq: rMZ=.73, rDZ.32
Lykken, Tellegen & Iacono	1982	25 MZ 50 MZ 26 DZ	19-55	power spectra (0-19.9 HZ)	intraclass correlations	α-freq: rMZ=.8, rMZA=.9, rDZ=.4 ß-freq: rMZ=.7, rMZA=.6, rDZ=.5
Meshkova & Ravich Shcherbo (USSR)	1982	20 MZ 20 DZ 20 UR	18-26	power, frequency and amplitude of α & ß	intraclass correlations	For all sites: rMZ between 0.58-0.96 α: rMZ > rDZ, ß: rMZ = rDZ
Whitton, Elgie, Kugel & Moldolsky	1984	6 MZ 6 DZ	4-10	power spectra bispectra	t-test within pair differences	MZ concordance > DZ concordance
Zung & Wilson	1984	4 MZ 2 DZ	8-19	sleep patterns	visual inspection	MZ concordant, DZ discordant
Anokhin	1987	45 fam		power spectra	multivariate genetic analysis	whole brain organization is mainly of genetic nature
Stassen, Bomben & Propping	1987	26 MZ 26 DZ	m=23.3 m=23.8	spectral analysis	theoretical similarity function	MZ concordance > DZ concordance (> UR concordance)
Stassen, Lykken & Bomben	1988	27 MZA 21 DZA	m=40.9 m=42.2	spectral analysis	theoretical similarity function	MZ concordance > DZ concordance > UR concordance
Christian, Li, Norton, Propping & Yu	1988	26 MZ 26 DZ	m=23.3 m=23.8	spectral analysis ß-frequency	intraclass correlations	before alcohol: ß: rMZ=.85, rDZ=.54 after alcohol: ß: rMZ=.91, rDZ=.05
Linkowski, Kerkhofs, Hauspie, Susanne & Mendlewicz	1989	14 MZ 2 DZ	16-35	sleep patterns	genetic variance analysis	genetical influences on stage 2,4 and delta sleep
Bouchard, Lykken, McGue, Segal & Tellegen	1990	35 MZA 42 MZT		α-index α-midfrequency	intraclass correlation	α-index: rMZA=.80, rMZT=.81 α-midfreq: rMZA=.80, rMZT=.82
Anokhin, Steinlein, Fisher, Mao, Vogel, Schalt & Vogel	1992	17 fam		low voltage EEG variant linkage	segregation-ratio localization EEG variant	autosomal dominant
Steinlein, Anokhin, Schalt & Vogel	1992	17 fam		low voltage EEG variant	linkage	localization EEG variant

Genetics of ERP

The (ERP) is the electrical response of the brain to the occurrence of a stimulus and provides an online index of stimulus-locked mental processing. These small changes in electrical activity cannot be distinguished by visual inspection but have to be extracted from the background EEG by averaging. ERPs consist of multiple components that can be described in terms of latency time, polarity, and topography. The various components can be classified into two categories, exogenous and endogenous (Donchin et al., 1978). Exogenous components (N100, P200) are probably controlled by the physical characteristics of the stimulus, are evoked by events extrinsic to the nervous system, and are associated with automatic processing of the stimuli. Endogenous components (N200, P300) are related to the psychological properties of a stimulus and are related to psychological measures and information processes. ERPs are suitable for testing the genetic influence on functional neurophysiological characteristics, rather than on anatomic features. Large individual differences exist for the ERP. In a review by Segalowitz and Barnes (1993), test-retest reliabilities for ERP components were summarized. In general, the reliability correlations varied strongly between the studies, with test-retest correlations ranging from .4 to .9 for latency and amplitude measures of the P300, and from .4 tot .8 for the latency of exogenous components. In their own study, Segalowitz and Barnes (1993) assessed the reliability of auditory ERP, with a time interval of 2 years. The latency and the amplitude of the late component (P300) had a high reliability (r=.7). The reliabilities of the amplitude of exogenous components (N100 and P200) were low; for N100, a test-retest correlation of .09 was found, whereas for P200, it was .23, and for the latency, the correlations were .48 for N100 and .51 for P200. The stability for endogenous components seems higher and so larger heritabilities are expected.

Genetics of exogenous ERP components

Most genetic studies of ERP have examined exogenous components evoked by a series of tones or light flashes. Waveform similarity in twins has been measured by calculating product-moment correlation-coefficients between the ordinates of the ERP waveform. Dustman and Beck (1965) were the first to calculate the similarity of the waveform of the visual ERP in 12 MZ, 11 DZ and 12 UR pairs. For the first 250 ms after the presentation of the stimulus, they found higher average correlations for MZ (.82) than for DZ (.58) and UR pairs (.61). This last correlation is strikingly high and is probably caused by the low number of subjects used. Some of the twins were examined twice and, in some cases, the correlation between twins increased after the retest. Similar results were obtained by Osborn (1970). For visual waveform similarity, MZ correlations averaged .77, DZ correlations .53, and UR correlations .11. Correlations between twins showed a wide range of values. For a number of twins, the correlation with the co-twin was greater than between both sides of their own brain. The study used a few subjects of a large age range. Marked developmental changes in the various ERP components occur until adolescence

(Courchesne, 1978); the variance attributable to age could influence the resemblance between twins. In the only study with a large number of subjects (44 MZ, 46 DZ and 46 UR pairs), Lewis et al., (1972) investigated the response to visual, auditory, and somatosensory stimuli. MZ twins showed a high similarity in wave shape for all modalities compared with DZ and UR pairs. However, the UR correlations were large. A large range of ages was also used in this study. The results were confirmed by Young et al. (1972). Larger similarities in waveshape were observed in MZ twins compared with DZ twins.

In addition to waveform similarity, exogenous components can be quantified by amplitude and latency measures. Rust (1975) analyzed the amplitude and latency components of the ERP with model-fitting techniques. The data of 20 MZ and 20 DZ were tested against the simplest biometrical model specifying additive genetic, and shared and nonshared environmental influences. The results pointed to a genetic model for the amplitude and latency of all components of the auditive ERP; the heritability was between 80% and 88% for the amplitudes of all components. Lower heritabilities were found for latency measures.

The only previous family study of ERPs was performed by Bulayeva et al. (1993). Correlations between family members (parent-offspring and sibling pairs) were used to estimate heritabilities. Parent-offspring and sibling correlations allow possible dominance effects to be tested. However, additive genetic influences contributed to ERP variance. The genetic influences varied from 28% to 88% for the amplitude and latency of various exogenous components.

Buchsbaum (1974) studied the augmenting/reducing response (RAR), which is used as a measure reflecting a central nervous system mechanism that modulates the intensity of the incoming stimuli. Individual differences in RAR are associated with personality characteristics such as sensation seeking (Zuckerman et al., 1974) and affective illness (Buchsbaum et al., 1973). Buchsbaum (1974) measured the ERP in response to varying stimulus intensities in 33 MZ and 34 DZ pairs, and computed amplitude and amplitude-intensity. For MZ, the waveforms were similar, as was the change in amplitude with intensity. For P100-N140 amplitude, MZ correlations were .59 and .57, and DZ correlations were .36 and .10, respectively. For the latency measures of the P100, N140, and P200, the MZ correlations were .47, .50 and .31, whereas the DZ correlations were .03, .56, and .26. The findings indicate low heritability for the latency of N140 and P200. Because of the stability of the RAR and the association of the RAR with affective illness, Gershon and Buchsbaum (1977) used the RAR as a biological marker for affective illness. If a single gene determined both the illness and biological marker, then the ill relatives would share the biological indicator (RAR) but the healthy relatives would not. No differences between healthy and ill relatives were seen for RAR, suggesting that RAR and affective illness are not transmitted by a single genetic factor.

In line with earlier studies of EEG variants, Vogel et al. (1986) investigated visually and auditory evoked potentials in carriers of various EEG variants. It was expected that carriers of hereditary EEG variants would show differences in information

processing and that this would be reflected in different aspect of the ERPs. Subjects with EEG variants indeed showed consistent differences in ERP amplitudes and latencies. According to Vogel et al. (1986), this is the first time that differences in information processing in the central nervous system have been related to a genetically determined EEG trait; this finding opens a way to studying the biological basis of behavior.

Genetics of endogenous ERP components

Endogenous components of the ERP are related to the psychological processing of stimulus information; the P300 has been especially studied extensively as measure of cognitive function (Fabiani et al., 1987; Donchin et al., 1978). The P300 shows a medium to high reliability for both amplitude and latency; test-retest correlations for latency in auditory tasks range from .32 to .81, and for amplitude from .62 to .93 (Segalowitz & Barnes, 1993). Larger heritabilities are expected on the base of higher test-retest correlations. Only four studies have explicitly tested the genetic influences on the P300 amplitude and latency.

Surwillo (1980) recorded the latency of the auditory stimulus in 6 MZ twin and 6 UR pairs. To manipulate the occurrence of endogenous components, twins performed an oddball task in which frequent tones were alternated by infrequent tones that required a response. The latencies of the N200 and P300 showed more similarity in MZ twins than in UR pairs. In contrast, the exogenous components showed little differences in UR pairs and MZ twins. However, the number of subjects was too small to draw a conclusion about the heritability of the ERP. More recently, Polich and Burns (1987) studied the genetic contribution to auditory ERP variation in a comparable experiment. Correlations for N100, P200, N200, and P300 amplitudes and latencies were between .64 and .95 for 10 MZ twins in the infrequent condition. However, no significant correlations were found for the frequent stimuli (except for the N100 latency) that generally involve more trials and that are more reliable. The study used few twins, and no DZ twins to control the environmental influences. Roger and Deary (1991) used the same task, but also measured DZ twins. They found a MZ correlation of .5 and a DZ correlation of .35 for P300 amplitude. The correlations for the latency measures were .63 for MZ and -.21 for DZ pairs. The correlations for the P300 were comparable with the results of Polich and Burns (1-987). O'Connor et al. (1994) used a large number of subjects (59 MZ and 39 DZ twin pairs) to measure the P300 in an oddball paradigm. For the infrequent condition, genetic influences were seen for the amplitude of the P300 in caudal leads; no significant genetic influences were found for the latency of the P300.

Genetics of motor potentials and ERP habituation

Two Russian experiments represent the only studies that have examined the genetics of ERPs related to motor responses (movement-related brain potentials, MRBP) (Malykh & Ravich-Shcherbo, 1986) and habituation (Kotchoubei, 1987). In the first study (Malykh & Ravich-Shcherbo, 1986), 25 MZ and 25 DZ twin pairs performed a

simple reaction task (RT) (movement independent of volition) and a complex RT. Intrapair concordance was assessed for MRBP-amplitude and MRBP-latency. Genetic determination of the MRBP was indicated for the readiness potential: for the central parts of the cortex, MZ correlations were .84 and DZ correlations .61. For the contingent negative variation, the MZ correlations were twice the DZ value. The heritabilities were higher for amplitude than for latency parameters, a result also found in Western studies (e.g., Buchsbaum, 1974; Rust, 1975). Malykh and Ravich-Shcherbo (1986) report a latency heritability-estimate of 20% and a amplitude heritability-estimate of 63%. Heritabilities of amplitude parameters differed between experimental conditions. In general, the influence of the genotype was more typical for the uncertain complex RT than for the simple RT. In contrast to earlier twin studies on waveform similarity, the intrapair resemblance for the ERP waveform was not large. Kotchoubei (1987) measured auditory ERPs in a habituation paradigm. Normally in a habituation task, the amplitude of various ERP components decreases. For different ERP components (N100, P180, N240, P300 and N400), the habituation was calculated as the regression coefficient on the average stimulus. A genetic contribution of genetic factors was seen for the rate of habituation only for louder tones. However, the rate of habituation was estimated from averaged trials, whereas it is more useful to estimate it from single trials (Molenaar & Roelofs, 1987). For the averaged ERP, the heritability was calculated as 19% for N100, 72% for P180, 44% for N240, 36% for P300, and 42% for N400. A common environment seemed to play a role for the N200 and P300.

Conclusion

Most ERP components show genetic influences, but the results are not so robust as for the background EEG. Like the studies of the genetics of EEG parameters, no studies have considered sex or age effects. In some studies, the UR correlations were large, almost the same as the MZ correlations. This could be the result of sampling fluctuations caused by the small numbers of pairs. Alternatively, the high correlations could be induced by the same treatment of the subjects in the experimental procedure. For the exogenous part of the ERP, a significant proportion of genetically induced variability is suggested, as seen by the higher similarity in MZ twins compared with DZ twins and UR subjects (Table 2.2). When looking at waveform similarity,this result is observed repeatedly (Dustman & Beck, 1965; Osborn, 1970; Lewis et al., 1972; Young et al., 1972). MZ correlations between .71 and .88, DZ correlations between .33 and .58, both for auditory and visual waveform ERP, were found. The higher similarity in MZ twins could reflect similar nonspecific anatomical features,

Table 2.2. Review of twin studies and event related potentials (ERPs)

STUDY	YEAR	SUBJECTS	AGE	ERP parameter	PARADIGM	MODALITY	GENETICAL ANALYSIS	RESULTS
Dustman & Beck	1965	12 MZ 11 DZ 12 UR	5-17	waveform similarity	light flashes	visual	product-moment correlation	for C3: rMZ=.8, rDZ=.6, rUR=.6
Osborne	1970	13 MZ 16 DZ 38 UR	11-22	waveform similarity	light flashes	visual	intraclass correlation	rMZ=.8, rDZ=.5, rUR=.1
Lewis, Dustman & Beck	1972	44 MZ 44 DZ 46 UR	4-40	waveform similarity	light flashes clicks electric pulses	visual auditory somatosensory	product-moment correlation	for C4: visual: rMZ=.7, rDZ=.4, rUR=.3 auditory: rMZ=.8, rDZ=.7, rUR=.5 somatosens: rMZ=.5, rDZ=.5, rUR=.4
Young, Lader & Fenton	1972	17 MZ 15 DZ	19-40	waveform similarity	clicks	auditory	product-moment correlation	rMZ=.7, rDZ=.4, rUR=.1
Buchsbaum	1974	33 MZ 34 DZ	18-57	auditory, visual augmenting/reducing response	light flashes & tones at different intensities	auditory visual	intraclass correlation	rMZ = .4 -.6, rDZ =.0 -.4
Rust	1975	20 MZ 20 DZ	17-44	amplitude, latency P2, N2,P3,N3a	tones	auditory	genetic modeling	amplitude heritability from 86 to 89% latency heritability from .35 to 81%
Geshon & Buchsbaum	1977	51 patients 139 relatives		augmenting/reducing response	light flashes at different intensities	visual	intraclass correlation	rSibling-Sibling=.29
Surwillo	1980	6 MZ	9-13	peak-latency for P1,N1,P2,N2,P3	oddball	auditory	mann-whitney U test	for N1,P2: concordance UR≈MZ; for N2,P3: MZ concordance > DZ concord
Malykh & Ravich-Scherbo	1986	25 MZ 25 DZ	18-30	amplitude/latency motor related-brain potential (MRBP)	reaction task		intraclass correlation	amplitude of MRBP components MZ concor. > DZ concord.
Kotcheibei	1987	22 MZ 21 DZ	17-29	Habituation amplitude/latency N1,P2,N2,P3,N4	tones	auditory	genetic modeling	habituation proces: low heritability high heritability (70%) for N1,P2 and N2 ampl. low heritablity for P3
Polich & Burns	1987	10 MZ 20 UR	18-30	amplitude/latency P3 of infrequent tones	oddball	auditory	product-moment correlation P3 lat: rMZ=.89, rUR=.44	P3 amp: rMZ=.64, rUR=-.2 20 UR
Rogers & Deary	1991	10 MZ 10 DZ	18-60	amplitude/latency P3 of infrequent tones	oddball	auditory	intraclass correlation	P3 amp: rMZ=.50 rDZ=.35 P3 lat: rMZ=.63 rDZ=-.21
Bulayeva, Pavlova & Guseynov	1993	family	20-60	amplitude/latency of N60,P1,N70	reversing checkerboard	visual	parent-offspring correlation sibling-sibling correlation	heritabilities various components varied between 28-88%
O'Connor, Morzorati, Christian & Li	in press	59 MZ 39 DZ	22-46	amlitude/latency of P3 of infrequent tones	oddball	auditory	genetic modeling	P3 amp: heritability form 41 to 60% P3 lat: no heritabilities.

N.B. P2 is an abbreviation for P200, N2 for N200, etc.

but Dustman and Beck (1965) found that the correlations were not affected by a larger similarity in head length and width, or by small changes in the placement of electrodes. The results with regard to amplitude and latency measures are more conflicting. In most studies, the correlation for amplitudes is larger than for latencies, although, in the study of Segalowitz and Barnes (1993), the reliability of the latencies was larger than that of the amplitudes. The late (endogenous) components, especially the amplitude of P300, seem to be determined by genetic factors, but heritabilities varied from low to high for latency measures. The different correlations between studies could be attributable to the use of different tasks, stimuli, modalities, scalp location, and different quantitative and statistical methods.

General Discussion

From early on, an interest has been taken in the genetic determination of parameters that serve as indices of brain functioning, such as EEG and ERP. Individual differences in background EEG are almost unanimously conceived of as genetically determined to a large extent. Responses in the EEG, viz., ERP, show a less clear picture. In comparison to background EEG, there are only a few small studies of the genetics of ERPs. Although most studies demonstrate a contribution of genetic factors to the variance in ERP amplitude and latency, there is no agreement to what extent different ERP components are influenced by genetic factors. In general, ERP parameters are assessed with a much lower reliability than EEG variables; this could explain part of the difference in heritability between EEG and ERP parameters. Unless new experimental paradigms are developed that allow the reliable assesment of ERP components, the study of genetically determined individual differences seems of limited value.

Little information on familial resemblances for EEG and ERP parameters in relatives other than twins is available. Although data on twins provide the foundations for building a model for human differences, any model derived from twin studies should ultimately be tested against other kinds of data (Eaves et al., 1989). However, most of the assumptions and biases to which the twin method is exposed (Vogel & Motulsky, 1986) do not seem greatly to effect the conclusion of a substantial heritability for background EEG parameters. For example, the assumption of equal environments for MZ and DZ twins is not of major importance, since there is no evidence for shared environmental factors influencing EEG parameters.

Not much more is known of the genetic architecture of individual differences in background EEG and in ERP than the univariate heritability estimates for parameters such as α-index or P300 amplitude. In this discussion, we want to outline some of the issues that deserve more attention in the quest for genetically mediated differences in central nervous system functioning.

In the earlier EEG studies, quantification of parameters usually was carried out on the basis of visual inspection and manually calculated parameters. Since the arrival of more powerful computers, sophisticated methods such as dipole localization and spatial-temporal modeling (Nunez, 1981; Wong, 1991) are available for analyzing EEG recordings. With these techniques, a refined image of the functioning of the brain can be obtained; this may lead to a better understanding of the biological and genetic basis of behavior and behavioral problems. Some of the more recent EEG studies have employed spectral decomposition of EEG recordings and have analyzed power spectra, but none of the more advanced EEG techniques have been used in genetic studies. For example, there are no studies that have measured genetic influences on EEG coherence and phase, which reflect corticocortical connectivity properties of both short- and long-distance axonal systems (Thatcher et al., 1987).

Most genetic studies of EEG and ERP have employed comparisons of correlations between relatives (twins) as their main method of genetic analysis. Recent developments in quantitative genetic modeling have embraced variances and covariances as the summary statistics of choice. Different genetic models can be tested by the simultaneous estimation of maximum likelihood parameters (Boomsma & Gabrielli, 1985; Neale & Gardon, 1992). This approach provides greater flexibility than the correlation approach in the treatment of some of the processes underlying individual differences such as the genotype x age or genotype x sex interaction. Whereas there are well-documented sex differences in brain functioning (e.g., LeVay, 1993), there are few formal applications of these techniques in EEG or ERP studies.

The multivariate extensions of these methods allow more insights to be gained into genetic processes underlying the associations between different EEG parameters (Martin & Eaves, 1977), individual genetic profiles to be estimated (Boomsma et al., 1991) and interactions to be detect between genetic and environmental influences (Molenaar et al., 1990). We have found one example of a multivariate genetic analysis (Anokhin, 1987) in which the relative and absolute powers of EEG frequency bands in different areas of the brain were analyzed. Analysis of the relationships between frontal, occipital, and temporal EEG derivations showed that these correlations were mainly genetically mediated, strongly suggesting that the organization of the whole-brain EEG is mainly of a genetic nature. For ERP, no studies have been published so far that employ multivariate quantitative genetic techniques to determine, for example, genetic covariances between ERP components assessed for different stimulus modalities.

During neural differentiation and growth, the developing nervous system may be influenced to a varying degree by genetic and environmental factors. Thus, individual differences in phenotype may at one developmental time be primarily influenced by genetic factors and during other periods mainly by environmental factors (Boomsma & Molenaar, 1987). These factors may even be switched 'on' and 'off' during different stages of development, thereby creating distinctive patterns of continuity and change in the phenotype. With respect to the development of EEG and ERP during the life span, it is known that EEG (Matousek & Petersen, 1973) and

ERP parameters (Courchesne, 1978) change and that the rate of development is not a continuous process. There are periods in which important changes in functional organization of the brain are found, especially during early childhood and adolescence (Thatcher, 1992). The extent of genetic control over these developmental changes with age is unknown.

Genetic variation in the normal human EEG is assumed to be polygenic. For some EEG variants such as the low-voltage EEG (found in about 4% of the adult population), a Mendelian pattern of autosomal dominance is seen (Vogel, 1970). The localization of a gene for this EEG variant has recently been reported (Anokhin et al., 1992; Steinlein et al., 1992). Studies in animals suggest that 30% of all genes are expressed specifically in the brain (Sutcliffe & Milner, 1984). Interest in the possibility of studying linkage between a quantitative trait and a genetic marker has been renewed (e.g., Haseman & Elston, 1972; Goldgar, 1990; Schork, 1993). For traits influenced by an unknown number of genetic loci, a high heritability seems to be one of the most important prerequisites for successful linkage with a quantitative trait locus. In this respect, brain functioning as indexed by EEG parameters seems a highly promising phenotype for study.

3

Heritability of Human Brain Functioning as assessed by Electroencephalography[1]

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Abstract

To study the genetic and environmental contributions to individual differences in central nervous system (CNS) functioning, the electroencephalogram (EEG) was measured in 213 twin pairs age16 years. EEG was measured in 91 MZ and 122 DZ twins. To quantify sex differences in the genetic architecture, EEG was measured in female and male same-sex twins and in opposite-sex twins. EEG was recorded on 14 scalp positions during quiet resting with eyes closed. Spectral powers were calculated for four frequency bands: delta, theta, alpha, and beta. Twin correlations pointed towards high genetic influences for all these powers and scalp locations. Model fitting confirmed these findings, the largest part of the variance of the EEG is explained by additive genetic factors. The averaged heritability for the delta, theta, alpha and beta frequencies was 76%, 89%, 89% and 86%, respectively. Multivariate analyses suggested that the same genes for EEG alpha rhythm were expressed in different brain areas in the left and right hemisphere. This study shows that brain functioning, as indexed by rhythmic brain electrical activity, is one of the most heritable characteristics in humans.

Introduction

The study of possible genetic influences on normal and abnormal behavior in humans has received much attention. In the age of molecular biology the chance to unravel the genetic basis of human behavior is enlarged, as, for example, in the localization of the gene for Huntington disease. Human behavior is a complex

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phenotype to study, because behavior is in continuous interaction with the environment. This makes the search for genetic variability in human behavior sometimes difficult. Genetic influences on behavior are most likely to be expressed via the brain. By studying human brain function it may be possible to find genetically determined influences on behavior. Little is known about genetic influences on individual differences in the functioning of the CNS.

To examine the influence of genetic factors on individual differences in CNS functioning, neurophysiological methods such as electroencephalogram (EEG) recordings can be used. The EEG is a registration of the ongoing rhythmical electrical activity of the brain over a short period of time and provides a direct measure of the present functional state of the brain and of its different levels of arousal. EEG is due mostly to the synchronous activity of pyramidal neurons in the cortex (Nunez, 1981). The mechanism of the generation of EEG rhythms is largely unknown. Thalamocortical and corticocortical systems presumably play a role in the generation of, for example, the alpha rhythm (Steriade et al., 1990).

The EEG can be described by various parameters, such as amplitude and rhythm. Often the EEG is analyzed in forms of power (in Hz) per frequency band using Fourier analysis on short time-series. In a normal waking adult human, two rhythms dominate in the resting EEG. A posterior rhythmic activity in the frequency range of 8-13 Hz (alpha), generally with higher voltage over the occipital areas, is observed when subjects close their eyes under the conditions of physical relaxation and relative mental inactivity. A faster rhythm (13-20 Hz), with a lower voltage and an irregular pattern distributed diffusely over the scalp appears in alert subjects.

Although the EEG is a complex trait that varies in many dimensions, such as distribution of frequencies, amplitudes over the different brain areas, and morphology of waveforms, it tends to be a stable individual characteristic. Test-retest correlation coefficients for EEG power were around .8 for both absolute and relative power, with a 12-16-week interval between the measurements (Stassen et al., 1987; Pollock et al., 1991; Salinsky et al., 1991). Even for longer intervals (with an average 10 month interval) the test-retest reliability stays around .7 (Gasser et al., 1985). Among individuals the EEG varies considerably. Simonava and Roth (1967) found alpha amplitudes between 20-60 microvolt in 66% of their subjects; values below 20 microvolt were found in 28% of the sample and values above 60 microvolt in were found in 6% of the sample. The stability in a single individual over time, combined with marked interindividual variability, poses the question of the genetic determination of brain activity.

Several twin and family studies investigated the role of genetic factors in individual differences in EEG parameters. Since the earliest twin studies, it has been clear that the human electroencephalogram (EEG) is mainly determined by genetic factors. Under visual inspection, a high degree of similarity in EEG parameters was found for monozygotic (MZ) twins (Davis & Davis, 1936; Raney, 1939; Lennox et al., 1945).

These observations were confirmed by using more advanced recording methods. For various EEG parameters, high similarities were found for MZ twins, and moderate similarities were found for dizygotic (DZ) twins (for a review see, Van Beijsterveldt & Boomsma, 1994). The normal EEG rhythm appears to be influenced by many genes (Vogel, 1970). Recently, for the low-voltage EEG, a rare variant of a the normal human EEG, localization of a gene has been reported (Anokhin et al., 1992; Steinlein et al., 1992).

Part of the variability in EEG is induced by age. During the maturation of the brain, leading to functional differentiation of various brain areas, the EEG generally decreases in amplitude, and slow activity is substituted by fast activity (Matoušek & Petersén, 1973). Maturation of the brain probably extends into adulthood (Fisher & Rose, 1994). Among individuals, large differences exist in the rate of development. Vogel (1958), who investigated different EEG parameters in a large group of twins age 6 - 80 years, found considerable interindividual differences in EEG maturation, but for MZ twins a complete concordance of EEG was found, which probably indicates that the speed of maturation is genetically determined. It is unclear whether the genetic contribution to EEG parameters is stable over different ages. Most studies consist of small samples of family members and have pooled data from different age groups.

During certain developmental periods the genetic contribution may differ for slow and fast EEG frequencies or for different brain areas. Maturation of the brain is not only a continuous growth process, but discrete growth spurts appear in specific anatomical locations at specific periods (Thatcher, 1992). Advances in the technology underlying the recording and analysis of EEG activity make it possible to study a range of EEG frequencies over different brain areas.

Beside more sophisticated EEG technology, the development of multivariate techniques in genetic model fitting (Martin & Eaves, 1977; Boomsma & Molenaar, 1986) allows more insight to be gained into genetic processes underlying the EEG recorded for different brain areas. It seems that in the prefrontal cortex, corticocortical interconnections are more extensive and appear to be organized in a way fundamental different from those the posterior cortex (Gevins & Ilness, 1991). With multivariate analyses the genetic and environmental bases of covariance between different brain areas may be studied, and questions regarding the involvement of different gene systems may be addressed.

Most twin and family studies that have investigated genetic influences on EEG parameters, have used only a few subjects in a large age range. None of the studies quantified the genetic contribution as a function of sex. Because age and sex are important determinants of EEG parameters, EEG in the present study was measured in a small age range (mean age = 16 years, SD =.55 years) and in female, male same-sex and opposite-sex twin pairs. The EEG was measured at 14 electrode positions during rest in 91 MZ and 122 DZ twins.

We investigated the genetic influences on different rhythms of the EEG in different brain areas and addressed the question of whether

1. heritability is different for the four main rhythmic EEG frequencies i.e. delta, theta, alpha and beta?
2. the same genes contribute to EEG variability in the left and right hemisphere?
3. the heritability is the same in males and females and whether the same genes are expressed in males and females?
4. the heritability of delta, theta, alpha, beta is the same for various brain areas (frontal, central, parietal, occipital, temporal) and whether the same genes are expressed in these areas of the brain?

Methods

Subjects

A group of 213 adolescents twins (mean=16.18 years, SD=.55 years) participated in the study. Addresses of twin pairs were obtained from participants in a large questionnaire study on health-related behaviors (Boomsma et al., 1994). Subjects were asked by letter to participate.

The subjects were divided into five groups, by sex and zygosity: 39 monozygotic males (MZM), 36 dizygotic male males (DZM), 52 monozygotic females (MZF), 38 dizygotic females (DZF) and 48 twins of opposite sex (DOS). For 114 same-sex twins zygosity was determined by blood and DNA typing. For the other same-sex twins zygosity was determined by a questionnaire, completed by the mother of the twins, and consisting of items about physical similarity (similarity of face, eye color, hair color and skin color) and the frequency of confusion of the twins by family and strangers. Seventeen twin pairs completed the questionnaires themselves. Agreement between zygosity based on this questionnaire and zygosity based on blood group polymorphism and DNA fingerprinting was 95%.

Six subjects were discarded from further analyses because of recording artifacts in one or more EEG channels. This left 37 MZM, 35 DZM, 52 MZF, 37 DZF and 46 DOS pairs for analysis.

Procedure

The measurement session lasted three and a half hours and took place in the morning or in the afternoon. Each subjecs visited the laboratory on the same day and were tested during the same segment of the day as was his or her co-twin. The session consisted of four tests: measurement of the EEG/ERP, measurement of nerve conduction velocity (Rijsdijk et al., 1995), reaction time, and intelligence tests. After arrival, a short explanation of the experiment was given for familiarization with the procedure. One twin started with the EEG measurement, and the other one started

with measurement of the other variables. After the EEG and EOG electrodes were put on, the subjects lay down on a bed in an electrically shielded and sound proof cabin. After controlling the EEG and EOG signals, instructions were displayed on a black and white monitor, attached to the ceiling. EEG was recorded during 3 experimental conditions in fixed order: during an auditive habituation task, during a visual oddball task and in a rest condition. In this paper the results of the EEG in the rest condition are presented.
In the rest condition, EEG was recorded during a period of 3 minutes, in which the subject closed the eyes. In this condition the alpha rhythm is clearly visible. If artifacts occurred during the recording, the recording period was lengthened to 4 minutes.

EEG-recording
Tin electrodes mounted in an electrocap were used for measuring EEG activity. Scalp locations were prefrontal (Fp1, Fp2), midfrontal (F3, F4), lateral frontal (F7, F8), central (C3, C4), parietal (P3, P4), occipital (O1, O2) and temporal (T5, T6), according the 10-20 system (Jasper 1958). Linked earlobes were used as references according the method described in Pivik et al. (1993). In brief, two separate preamplifiers with high input impedance for each of the reference electrodes were used and the output was linked electrically. With the ears linked this way, the effects of possible imbalances in electrode impedance are prevented. The electrode impedance for EEG and EOG was less than 5 Kohm. Tin electrodes were placed at the canthus of each eye, for recording horizontal movements. For vertical movement EOG was recorded from intra-orbital and supra-orbital electrodes, in line with the pupil of the left eye. A ground electrode was attached to Fpz. For both EEG and EOG, ECI (electro-gel) EEG paste was used. All EEG signals and EOG signals were displayed and recorded by a 18-channel Nihon Kohden electroencephalograph (type EEG-4414A1K). For EEG and EOG recording time constant was 5 s and a low pass frequency, with a 35-Hz cutoff frequency was used. Subsequently, signals were sent to a 12-bits analog-digital converter and computer-stored for off-line processing. During the EEG recording sampling rate of the AD converter was set to 250 Hz. A set of 100 microvolt sine waves was used for calibration for each of the 16 electrodes prior and after recording.

Data processing
Preprocessing of the EEG consisted of dividing the EEG signal into epochs of 2 s. After automatic removal of epochs with artefacts (e.g., clipping) Fast Fourier Transformation (FFT) was applied to the 2 sec epochs. A minimum of 30 epochs was required for further analyses. Subsequently, eye movements were removed by means of a dynamic regression routine in the frequency domain (Brillinger 1975). The D.C. offset was removed from the data by calculating the mean of the epoch and

subtracting it from each point. Smoothed powers for frequency .5 to 30 Hz, with .5 Hz steps, were calculated by averaging the power values over the valid epochs. The resulting power values were summed together into broad bands: delta (1.5-3.5 Hz), theta (4-7.5 Hz), alpha (8-12.5 Hz), beta (13-25 Hz). Total power was the sum of the absolute powers in these bands. To transform the powers to a Gaussian distribution the EEG power bands (absolute powers) were logtransformed with log10(x) (Pivik et al., 1993). The percentage of variance explained by each band, the relative power, was calculated by dividing the separate bands by the total power.

Statistical Analysis

To test whether there were any mean differences between males and females or between MZ and DZ twins, MANOVA (SPSS) was used. The EEG power bands were used as the dependent variables, with scalp locations (Fp1/Fp2, F3/F4, F7/F8, C3/C4, P3/P4, O1/O2 and T5/T6), hemisphere (left, right), and birthorder (first and second born) as within pair factors and with sex and zygosity as between factors. Sex and zygosity effects were tested in the MZM, DZM, MZF, and DZF, only.

Univariate Genetic Analyses

For each electrode position and for each power (delta, theta, alpha, beta) correlations were computed for MZM, DZM, MZF, DZF and DOS twin pairs. The relative contributions of genetic influences to individual differences in EEG parameters were estimated by the method of genetic model fitting (Eaves et al., 1978; Boomsma & Gabrielli, 1985; Neale & Cardon, 1992).

In genetic model fitting the variation in the observed phenotype is decomposed into genetic and environmental variance. The genetic variance may be due to additive (A) or dominance (D) genetic influences, and the environmental variance may be due to environmental factors shared by twins reared in the same family (C) and to the nonshared environmental factors (E). Their influence on the phenotype is given by parameters a, d, c and e, which are equivalent to the standardized regression coefficients of the phenotype on A, D, C and E, respectively. The amount of variance due to each source is the square of these parameters. To estimate parameters a, d, c and e, for each power and for each electrode position, the data on twin1 and twin2 were summarized into 2x2 variance-covariance matrixes, computed by Prelis (Jöreskog & Sörbom, 1986). Mx (Neale, 1994) was used to fit univariate models separately for each power and each electrode position by the method of maximum likelihood. The overall goodness of fit of a model was assessed by the chi-square (χ^2) goodness-of-fit statistic (Heath et al., 1989; Neale & Cardon, 1992). A large χ^2 indicates a poor fit, whereas a small χ^2 indicates that the data are consistent with the model. The significance of the latent factors D (or C) and A were tested by likelihood ratio tests by comparing the full genetic model to submodels. A significantly worse fit than the full model indicates the significance of the latent factor.

Sex differences in genetic architecture can result from differences in magnitude of the genetic effects and/or environmental experiences. Another possibility is that different genes are expressed in the observed phenotype in males and females. To test the first hypothesis a model that equaled the genetic and environmental estimates for males and females was compared with a model that allowed for different estimates in males versus females. The second hypothesis was tested by estimating the genetic correlation between the DOS twins, instead of fixing it at 0.5.

Bi- and multivariate analysis

To test the hypothesis that the same genes influence the EEG in the left and right hemisphere, the contribution of genetic and environmental factors to the covariances of EEG powers obtained at left and right brain positions was estimated in bivariate analyses. The model is shown in Figure 3.1, with a common genetic (Ac) and a common environmental (Ec) factor and one specific genetic (As) and environmental factor (Es). The two hypotheses to be tested were (1) whether one common genetic factor influences EEG in the left and right hemisphere, or whether an additional, hemisphere-specific factor is needed and (2) that there is no environmental covariance between the two hemispheres. To test the first hypothesis the specific genetic factor was constrained at zero. To test the second hypothesis, the common environmental factor was constrained at zero. These submodels were compared by hierarchic χ^2 tests.

Next, the genetic and environmental contribution to the covariances of the alpha power recorded at prefrontal, midfrontal, lateral frontal, central, temporal, parietal, and occipital areas, separately for the left and right hemispheres, were calculated, to assess to what extent the same genes were expressed in these brain areas. A triangular decomposition, that may be compared with PCA was used (Neale & Cardon, 1992) to obtain estimates of the genetic and environmental correlations between the electrical activity of different brain areas.

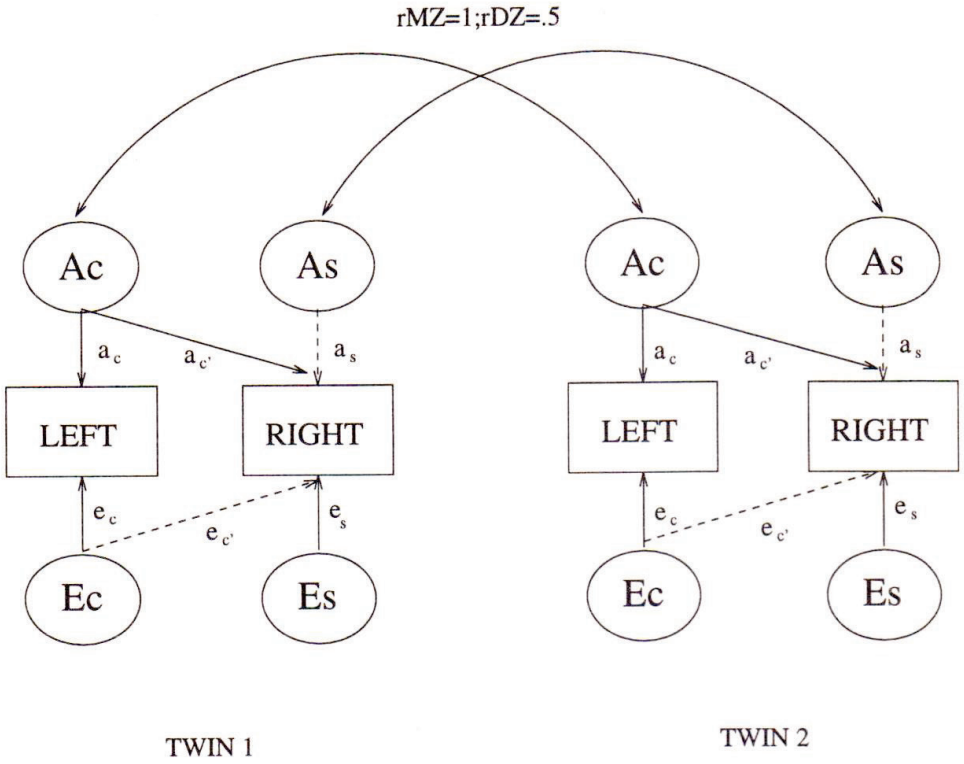

Figure 3.1 Bivariate genetic path model. "Left" and "right" denote the observed EEG power in left and right hemisphere in youngest (twin 1) and oldest (twin 2) twin. "Ac" and "Ec" denote, respectively, the additive genetic and nonshared environmental factors common to the left and right hemispheres. "As" and "Es" are, respectively, specific additive genetic and specific nonshared environment unique for the right hemisphere. The dotted lines represent the paths which were constrained to be zero in the submodels.

Results

Means

In Figure 3.2 an example is shown of a raw EEG signal, for a MZ and a DZ twin pair. It shows both the similarity within a MZ twin pair and the interindividual variation. The power spectrum as a result of the Fast Fourier Transformation of the raw EEG signal of all twins is shown in Figure 3.3. Highest power is found at the posterior brain areas (P3, P4, O1 and O2) with a peak around the 10 Hz frequency, in the anterior regions (Fp1, Fp2, F3 and F4) the power is much lower and peaks at lower frequencies. In Figure 3.4 the absolute and relative powers for each EEG frequency band are given for each scalp location separately. It clearly shows the higher alpha power at posterior positions. At the anterior positions the lower frequencies bands, delta and theta, dominate.

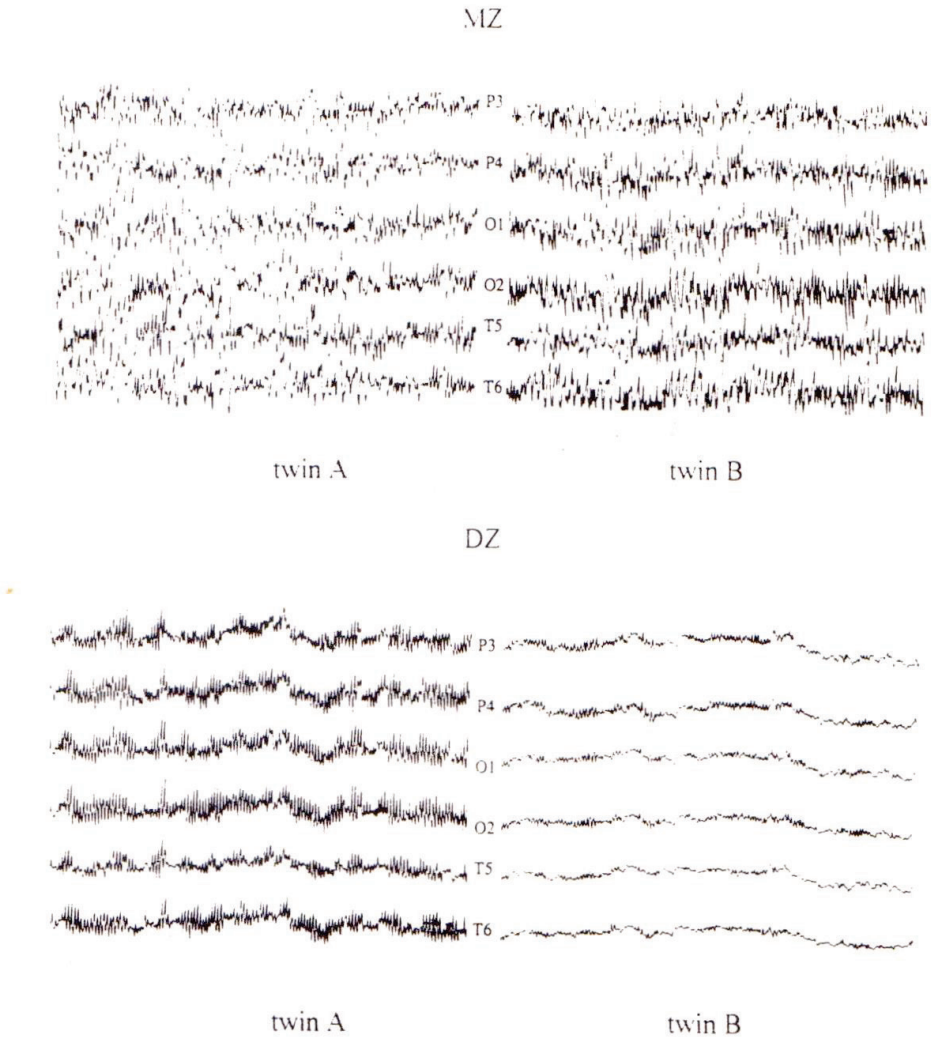

Figure 3.2 Example of a raw EEG signal for the youngest (twin A) and oldest (twin B) of a MZ (*upper panel*) and DZ (*lower panel*) twin pair. The EEG signals were recorded on left and right parietal, left and right occipital and left and right temporal scalp locations.

For the statistical and genetic analysis log-transformed values were used. None of the EEG frequency bands showed a significant difference in power between either the sexes or the zygosities. For all frequency bands the amplitude in the right hemisphere was significantly larger than in the left hemisphere. The amplitude was larger for posterior scalp locations and became smaller in frontal scalp locations (all F ratio's > 100). The smallest amplitudes were found for scalp locations F7 and F8. The larger amplitude in the right hemisphere held for all scalp locations except for the occipital locations, for which the amplitudes were equal (interaction effect of scalp location x hemisphere).

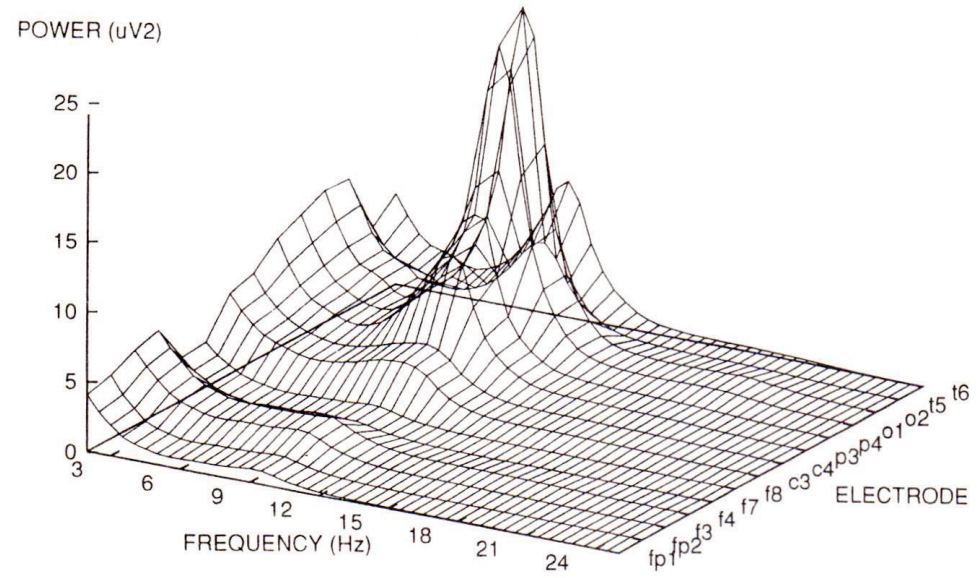

Figure 3.3 Absolute power of EEG spectrum, averaged over all subjects (n=414). The amplitude (in squared microvolt) (Y-axis), the frequencies (X-axis), and the the scalp locations (Z-axis) are given.

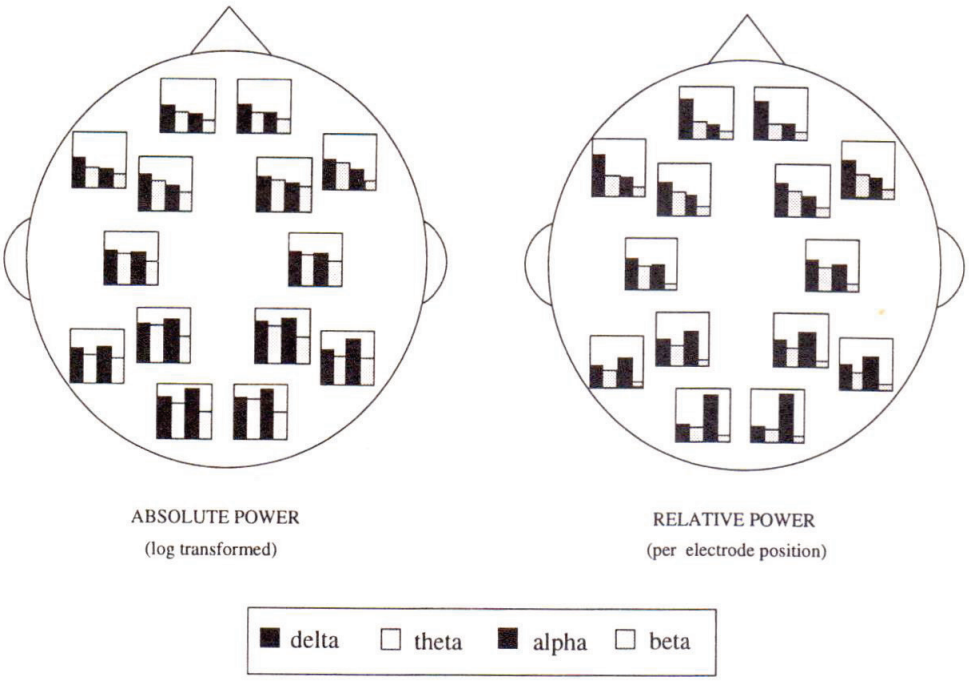

Figure 3.4 Mean values for absolute power (log-transformed) and relative powers for all scalp locations on the left and right hemisphere. The mean values are depicted for all four EEG rhythms (in both ideograms the sequence of the frequencies is delta, theta, alpha, and beta). The scale of the Y-axis for the absolute power range from 0 to 20 μV^2 (log-transformed values * 10) (*left*) and for the relative power range from 0 to .6 (*right*).

Univariate genetic analyses for the different EEG rhythms and brain areas
Appendix A shows the twin correlations for zygosity x sex groups, for all powers. These data indicate that genetic factors play an important role in EEG variability. For all EEG powers and scalp locations, the MZ correlations were large, around .85 and the DZ correlations were approximately half those for MZ. Appendix B presents the chi-square (χ^2) for the best-fitting models. For most EEG rhythms and all brain areas, an AE model is the best fitting model.

Delta. The MZ correlations for the delta power were lower than those for the other EEG powers. Particularly for the frontal scalp locations, the MZF correlations were lower, over all scalp locations, the averaged MZF correlation was lower (.7) than the average MZM correlations (.8). The DZ correlations were approximately half of MZ correlations. For electrode positions F3, F4, C3, P3, O1 and O2 the DZF correlations were almost equal to the MZF correlations, suggesting shared environment influences. However, the DOS correlation did not support such sex differences. If genetic factors contribute to the variance in males but not in females, then the DOS correlations should be zero. In addition, model-fitting results for these data do not suggest significant shared environment influences. Nevertheless, for scalp locations F4, F7, C3, P3 and P4 significant sex differences were found. For the remaining scalp locations, AE models without sex differences were the best fitting models. In Figure 3.5 the proportion of variance explained by additive genetic factors (h^2) is given. The heritabilities averaged over the frontal scalp locations were 70%; they were 80% for the posterior locations. For brain areas with sex differences the females heritabilities were somewhat lower.

Theta. For theta, all MZ correlations were high. Averaged over all scalp locations the MZ correlations were around .9, both for males and females. The averaged DZ correlations were half the averaged MZ correlations. AE models were the best fitting models for most of the scalp locations, except for C4 and P3, for these locations, a model with sex differences was found. However, the heritabilities did not show large differences between males and females. Scalar models were found for scalp locations F4 and C3, meaning that the total amount of variance differed significantly between the sexes; but there were no sex differences in genetic architecture, between males and females.

Alpha. For alpha, both for females and males, the MZ correlations were larger than DZ correlations over all scalp locations. AE models were the best fitting models for all areas of the brain, without sex differences. The heritability, averaged over all scalp locations, was 89%.

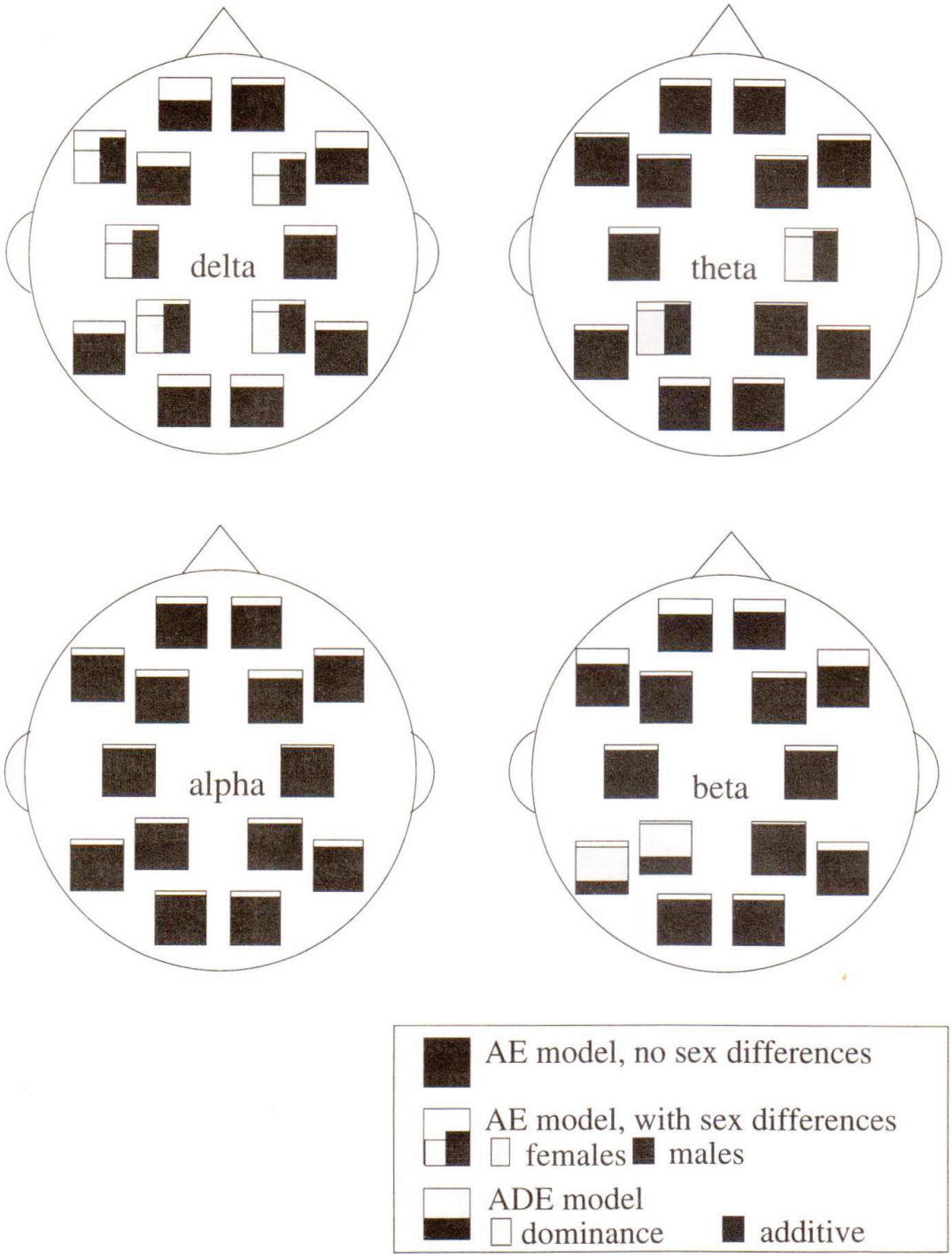

Figure 3.5 Proportion of variance explained by the genetic factors, for all scalp locations and four EEG rhythms (delta, theta, alpha and beta).

Beta. The MZM and MZF correlations for all scalp locations equalled the MZ correlations of alpha and theta. However, the DZF correlations were lower than expected on basis of genetic relatedness, this was emphasized in central and parietal scalp locations. The low female DZ correlation could point to genetic effects due to dominance. With model fitting, genetic dominance was indicated for two scalp locations; for the other scalp locations the mode of the genetic inheritance was additive. With model fitting no sex differences were found. For all scalp locations the variance explained by genetic factors were high.

Bi- and multivariate analysis for the EEG rhythms and brain areas.
In Table 3.1 the results of the bivariate analyses are summarized. Tests for sex differences were only carried out when differences existed in the univariate case. The models shown underlined in Table 3.1 gave the best fit. The covariance between the electrode combinations of the left and right hemisphere seemed primarily influenced by one common genetic factor. Only for the frontal Fp1-Fp2 combination, there was also a specific genetic factor. The covariances were also influenced by a common nonshared environment factor, dropping this factor in the full model led to a large increase in chi-square. However, the covariance between left and right hemisphere was mainly determined by genetic factors, the contribution of genetic factors was much larger (around 90%, for most all brain areas) than the contribution of the nonshared environment factor (see Table 3.1).
Multivariate analyses were performed to characterize the extent to which the same genes contribute to the observed variance of the EEG at different scalp locations. Only alpha powers were analyzed, because alpha was the dominant EEG frequency in the background EEG. The chi-square for the full AE multivariate model for the left hemisphere was: χ^2=654.02 (df=469), and for the right hemisphere: χ^2=581.35 (df=469). In Table 3.2 the genetic correlations and nonshared environmental correlations are presented. The genetic correlation is high between all scalp locations, suggesting that, to a large extent, the same genes underlay the EEG at different scalp locations. For nonshared environmental factors, higher correlations were found between the locations at the frontal part of the brain. The remaining correlations were lower than the genetic correlations.

Table 3.1 χ^2 Values from Bivariate analyses of left and right hemispheres, for each electrode combination and power.

		χ^2 *for electrode combination* of						
models[a]	**df**	**F1-F2**	**F3-F4**	**F7-F8**	**C3-C4**	**P3-P4**	**O1-O2**	**T5-T6**
DELTA								
AE	44	98.37	84.05[b]	79.93[b]	52.97[b]	43.14[b]	55.88	66.06
AE, 1 genetic factor	45	98.37	84.05[b]	79.93[b]	54.05[b]	43.43[b]	56.07	66.32
AE, only specific E	45	386.66	212.78[b]	192.61[b]	261.54[b]	270.12[b]	254.75	103.71
Covariance(left,right)		69	92(male) 74(female)	99(male), 65(female)	94(male), 78(female)	96(male) 81(female)	80	90
THETA								
AE	44	58.29	52.99	64.10	45.94[c]	56.15	45.35	45.76
AE, 1 genetic factor	45	65.39	52.99	64.10	45.94[c]	57.72	49.18	45.76
AE, only specific E	45	319.13	182.53	115.27	213.66[c]	301.09	275.23	68.76
Covariance(left,right)		90	93	94	93	92	90	89
ALPHA								
AE	44	44.95	65.20	45.88	64.33	41.82	44.86	33.43
AE, 1 genetic factor	45	66.44	65.20	45.88	64.34	44.45	45.83	33.99
AE, only specific E	45	529.72	439.72	241.65	152.56	124.04	147.43	36.38
Covariance(left,right)		88	89	91	95	95	93	89
BETA								
AE	44	74.13	80.52	99.04	51.57	66.06	62.82	49.84
AE, 1 genetic factor	45	85.66	80.52	99.10	51.64	68.49	62.86	52.27
AE, only specific E	45	199.46	172.55	157.36	152.86	173.04	175.75	56.22
Covariance(left,right)		81	93	83	94	96	92	98

Note. Best fitting models are underlined.

[a] AE is the most general model, with one additive genetic factor loading on the left and right side, plus a specific factor for the right hemisphere. In the second model (AE, 1 genetic factor), the specific genetic factor for the right hemisphere is dropped. In the last model (AE, only specific E), common environment is dropped, only specific nonshared environment is left. Covariance (left, right) is the proportion of the covariance between left and right hemisphere that is explained by additive genetic factors.

[b] Model has sex differences (df = 38,40,40)

[c] Scalar models (df=43,44,44).

Table 3.2 Genetic (A) and nonshared environmental correlations (B) between EEG alpha power measured at different scalp locations, separately for left and right hemisphere.

A. Genetic correlations

	Right hemisphere						
Left hemisphere	Fp2	F4	F8	C4	P4	O2	T6
Fp1	--	.98	.99	.89	.87	.85	.89
F3	.97	--	.99	.92	.88	.85	.90
F7	.98	.98	--	.91	.88	.87	.91
C3	.88	.92	.90	--	.93	.85	.92
P3	.88	.89	.88	.94	--	.92	.97
O1	.86	.86	.87	.86	.92	--	.93
T5	.91	.91	.91	.92	.96	.94	--

B. Nonshared environmental correlations

	Right hemisphere						
Left hemisphere	Fp2	F4	F8	C4	P4	O2	T6
Fp1	--	.88	.80	.60	.41	.37	.46
F3	.86	--	.83	.74	.42	.33	.41
F7	.86	.86	--	.60	.36	.41	.42
C3	.45	.66	.54	--	.50	.23	.39
P3	.26	.33	.28	.56	--	.52	.67
O1	.39	.38	.44	.29	.64	--	.57
T5	.34	.34	.39	.45	.75	.67	--

Discussion

One of the main results of this study is the remarkable similarity of background EEG in MZ twins, for all EEG frequency bands and all brain areas. The EEGs in DZ twins showed clear familial relatedness. For most power bands and brain areas the MZ correlations were around .9 and the DZ correlations were half the MZ correlations. With model fitting, the genetic contributions were more precisely elaborated and tested. For most EEG powers and brain areas, the results showed mainly additive genetic effects in the 16-year-old males and females. Nevertheless, small differences in heritability existed for different EEG frequencies and brain areas.

In accordance with the typical EEG recording during rest, a large part of the EEG consisted mainly of alpha rhythm with maximum power in the parieto-occipital

regions, delta with highest relative power values at frontal regions and theta with maximum power centrally, with lower power for beta. For the delta, theta, alpha and beta, the variance (averaged over all brain areas) explained by genetic factors was 76%, 89%, 89% and 86%, respectively. Thus, almost no differences in heritabilities for the various EEG rhythms were present. Only for delta somewhat lower heritabilities were suggested.

The high heritabilities and MZ correlations approach the test-retest reliability normally found for EEG powers in adult subjects (Pollock et al., 1991; Salinsky et al., 1991). Thus the similarity of the EEG in a twin pair should equal the EEG similarity within a subject measured on different days. The high contribution of genetic factors to individual differences in the various EEG powers confirms the results of most earlier twin studies. However Lykken et al. (1974) obtained for absolute EEG powers in 37 MZ twin pairs correlations that were comparable to our correlations, but correlations that they measured in 27 DZ twin pairs were around zero, whereas the DZ correlations in our study were around .5. An explanation for the low DZ correlations could be a different arousal state of the subjects, induced by their hypnotic procedure that lykken et al. used during the EEG recording. This could cause the EEG of DZ twins to become more dissimilar while in MZ twins it remains similar. The same phenomenon is seen during alcohol intake: the EEG becomes more similar for MZ twins and more dissimilar for DZ twins (Christian et al., 1988). No other twin studies have reported such low DZ correlations for EEG rhythms; in most of these studies, the correlations were around .5 as in the present study.

For nearly all EEG rhythms and brain areas, the mode of inheritance is additive, except for power in the beta band, for which, at two scalp positions, the models indicated to dominance. However, when using only twins are studied the power to detect dominance is not large.

Different brain areas reflect specific functions. The occipital, posterior areas reflect influences from visual and visuospatial functions and frontal areas reflect the higher cognitive functions. In addition, maturation processes have different onset and speed for different brain areas (Gasser et al., 1988; Thatcher et al., 1992): for example, from the age of 15 until adulthood, brain development involves mainly frontal areas (Thatcher et al., 1987; Hudspeth et al., 1990). Therefore, heritabilities of the EEG power could be different for the various parts of the brain. Most twin and family studies which examined genetic influences on EEG parameters, have not studied more than one brain area. The only twin study that has recorded EEG from more than one brain area, was done by Meshkova et al. (1982). In this study alpha activity was measured in frontal, temporal, central, parietal and occipital areas in 20 MZ and 20 DZ twins. For alpha, higher MZ correlations were found for parietal and occipital areas than for central, temporal and frontal areas. Meshkova et al. (1982) suggested that the genetic influences were larger in phylogenetically older (posterior) regions: "In the more recent organs and functions the variability is higher than in the older

regions, that depend on the effect of genetic factors and have become more refined by selection". However, in their study, only 20 DZ and 20 MZ twins participated. To detect significant differences in heritability among brain areas a larger number of twins is necessary. More recently, a family study (Trubnikov et al., 1993), has estimated heritability for EEG rhythms and their topography in a sample of schizophrenic families (25 proband and 58 first-degree relatives). Additive genetic factors contributed for a large part to the variance in the various EEG rhythms. Averaged over all frequency bands, the genetic influences were smaller for anterior positions, and the highest genetic contributions were found for posterior positions. This agrees quite well with the heritabilities obtained in our study. The heritabilities for the different brain areas were equal for most EEG rhythms, except for delta. For delta rhythm, lower heritability was found for the anterior part of the brain. In this part of the brain eye movements could contribute to the EEG. Eye movement artifacts are always a problem in any attempt to quantify EEG rhythms in the anterior part of the brain. In general, the test-retest reliability is lower for this EEG rhythm (Burgess & Gruzelier 1993).

Since the introduction of quantitative EEG analysis, several developmental studies have looked for possible sex-differences in EEG parameters, especially during puberty. Generally, females show an earlier pubertal growth than do males. However, most EEG studies found no large mean differences between males and females, after age 15. In one of the most extensive developmental EEG studies (Matoušek & Petersén, 1973), relative EEG power was measured in 160 adolescents from 16 to 21 years. The only difference between boys and girls was an increased amount of beta activity in females. Matsuura et al (1985) found in the age range of 14 to 17 years, a higher alpha percentage in males than in females; however, Gasser et al. (1988), who studied children up to 17 years old, reported no sex differences for EEG power. In our group of subjects, no sex differences in mean powers were found either.

For a few electrode positions, sex differences in genetic architecture existed. Particularly for the delta band, for almost half of the electrode positions, significant sex differences were seen. For the other EEG rhythms, no sex differences in genetic architecture existed, except for theta, in which sex differences were found for two scalp locations. The heritabilities differed, only in magnitude, between males and females, with somewhat smaller heritabilities for females. Furthermore, the differences in heritability between males and females were small. These sex differences could have arisen by chance, because many variables have been tested.

The relative contributions of genetic factors did not differ between the left and right part of the brain: for both hemispheres, genetic factors contribute to EEG amplitude to the same extent. In addition, bivariate analyses showed that the same genes are expressed in the left and right hemisphere, with possible exception of prefrontal areas.

The last question addressed is whether the same genes are expressed in the determination of the alpha rhythm in different brain areas. This analysis was restricted to the alpha rhythm because it is the dominant rhythm in resting subjects. The genetic correlations among all scalp locations were very high, indicating that the same genes were expressed in the different brain areas. No other twin studies with multivariate genetic analysis have been carried out, but there is one family study (Anokhin, 1987). In 45 families the alpha and beta rhythm of the EEG was measured in different brain areas. A Principal Components Analysis (PCA) was applied to the frontal, occipital, and temporal EEG electrode positions. Most of the variance was explained by a general EEG factor, with large resemblances between family relatives. This led to the suggestion that the organization of the whole-brain EEG is mainly of a genetic nature. Our results correspond with those of Anokhin (1987). Results from our multivariate analyses suggested that the same genes influence the alpha power in all brain areas.

The nonshared environmental correlations in the anterior part of the brain were also high. This is probably due to variation induced by eye-movement correction, which effect is most prominently seen in the anterior brain areas. Other high correlations were seen among posterior scalp locations. Correlations among other areas were much lower. The nonshared environment variance never explained more than 20% of the total variance. The E may represent stable environment influences, which are not familiar but systematic. Thus, the individual differences in EEG activity measured at rest is mainly determined by the same genetic influences. The absence of differences in genetic influence of the various frequencies and brain areas could point to a strong dependence between the EEG and brain structure. Perhaps the EEG measured at rest is largely a reflection of the neocortical morphology, and individual differences in this morphology may be strongly influenced by genetic factors. Unfortunately, little twin research has been done on neocortical morphology (Steinmetz et al., 1994).

In summary, for 16-year old boys and girls, individual differences in EEG activity measured at rest are mainly determined by additive genetic factors. Very little differentiation in the genetic contribution to the various brain areas and different EEG rhythms was found. For delta power the heritability was somewhat lower, especially in the frontal positions. Except for a few electrode positions of the delta rhythm, no evidence was found for sex differences in genetic architecture.

The high heritability seems comparable with the heritability found in other studies, although it is difficult to compare the results, because nearly all previous studies used a small number of subjects and measured EEG at one brain area only. Also, most other studies have used adult subjects from a wide age range, whereas we have studied adolescents in whom brain maturation is not yet completed. In our laboratory, the same design also has been employed in a study of 200 5-years old twins (Van Baal et al., 1994). In this age group the heritability for theta and alpha

was smaller, though still relatively high (averaged over electrode positions it was 81% and 79%, respectively, for theta and alpha). For these younger twins, the heritability for beta and delta was around 50%, substantially lower than in 16-year old twin pairs.

Finding a trait with a high heritability is one of the conditions for successful linkage between a quantitative trait locus and that trait. The high heritability of the EEG power is a promising starting point for studying the genetic factors that determine CNS function and thereby it may also a promising starting point for complex behaviors.

Appendix 3.A

Table 3.A1 Correlations for each zygosity by sex group (MZM,DZM,MZF,DZF and DOS) for each scalp location (Fp1,Fp2,F3 and so on) and for each power (delta, theta, alpha and beta).

DELTA	*scalp location*													
	Fp1	Fp2	F3	F4	F7	F8	C3	C4	P3	P4	O1	O2	T5	T6
MZM(38)	.66	.76	.82	.86	.80	.70	.88	.86	.90	.93	.78	.73	.76	.87
DZM(36)	.38	.39	.29	.25	.14	.33	.34	.33	.32	.38	.40	.41	.35	.51
MZF(52)	.50	.60	.70	.63	.53	.65	.68	.83	.74	.86	.76	.79	.74	.84
DZF(38)	.25	.28	.64	.43	.26	.19	.59	.48	.52	.54	.62	.63	.43	.57
DOS(45)	.34	.31	.44	.44	.30	.26	.47	.48	.31	.34	.35	.43	.32	.45

THETA	*scalp location*													
	Fp1	Fp2	F3	F4	F7	F8	C3	C4	P3	P4	O1	O2	T5	T6
MZM(38)	.89	.91	.91	.94	.91	.90	.93	.94	.93	.94	.91	.90	.85	.87
DZM(36)	.55	.48	.43	.35	.39	.47	.46	.41	.53	.48	.57	.54	.54	.53
MZF(52)	.88	.88	.89	.89	.88	.87	.86	.88	.87	.91	.86	.89	.88	.89
DZF(38)	.55	.52	.54	.51	.58	.50	.50	.45	.52	.53	.58	.60	.54	.55
DOS(45)	.54	.57	.53	.53	.48	.55	.50	.47	.39	.38	.41	.44	.38	.37

ALPHA	*scalp location*													
	Fp1	Fp2	F3	F4	F7	F8	C3	C4	P3	P4	O1	O2	T5	T6
MZM(38)	.89	.88	.91	.91	.92	.90	.93	.95	.94	.93	.93	.92	.92	.84
DZM(36)	.47	.43	.51	.41	.41	.37	.49	.43	.46	.38	.46	.42	.42	.32
MZF(52)	.87	.87	.87	.88	.88	.88	.90	.92	.90	.93	.90	.88	.86	.90
DZF(38)	.50	.50	.51	.47	.57	.56	.45	.35	.40	.38	.55	.49	.43	.43
DOS(45)	.57	.56	.60	.55	.56	.53	.60	.56	.37	.37	.39	.34	.43	.43

BETA	*scalp location*													
	Fp1	Fp2	F3	F4	F7	F8	C3	C4	P3	P4	O1	O2	T5	T6
MZM(38)	.87	.86	.93	.94	.81	.69	.91	.92	.97	.94	.88	.90	.90	.80
DZM(36)	.31	.34	.43	.38	.48	.37	.42	.37	.33	.34	.42	.39	.36	.43
MZF(52)	.64	.76	.90	.90	.77	.74	.93	.93	.93	.93	.86	.87	.85	.87
DZF(38)	.36	.41	.25	.13	.41	.24	.19	.12	.14	.11	.42	.36	.21	.23
DOS(45)	.36	.24	.36	.32	.25	.35	.41	.52	.33	.44	.40	.43	.26	.38

Appendix 3.B

Table 3.B1 χ^2 Values for all scalp locations and for four EEG rhythms, for an AE model (df=13).

	left hemisphere						
	Fp1	F7	F3	C3	P3	T5	O1
delta	9.36	17.78[a]	22.15	17.18[a]	13.28[a]	26.59	16.82
theta	16.78	10.03	7.15	12.45[b]	7.63[a]	12.67	10.06
alpha	11.12	8.73	16.07	13.88	6.18	5.54	9.29
beta	21.84	11.94	10.03	11.74	15.90[c]	15.36[c]	8.33
	right hemisphere						
	Fp2	F8	F4	C4	P4	T6	O2
delta	10.17	14.10	7.75[a]	16.12	11.20[a]	16.56	15.85
theta	12.61	17.19	13.24[b]	10.14[a]	13.11	10.94	9.58
alpha	11.29	14.37	14.63	16.80	6.58	8.36	8.86
beta	14.93	14.29	11.97	16.41	13.04	7.76	15.82

[a] The AE model with sex differences (df=11) is the best fitting model
[b] The scalar AE model (df=12) is the best fitting model
[c] The ADE model (df=12) is the best fitting model.

4

Individual differences in P300 amplitude: a genetic study in adolescent twins

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Abstract

The amplitude and latency of the P300, a component of the Event Related Brain Potential (ERP) varies greatly across subjects. Quantitative genetics makes it possible to study such individual differences and estimate the relative genetic and environmental contributions to variation in P300 parameters. Decomposition of variability into genetic and environmental contributions can be accomplished by the twin method. In this study the ERP was measured during an oddball paradigm in 213 adolescent twins. Results showed clear familial resemblance in P300 amplitude. However, it remains unclear whether this resemblance is caused by shared environmental or by genetic influences. For targets and nontargets half of the variance in P300 amplitude across eight leads is attributable to familial resemblance. No shared environmental or genetic influences were suggested for P300 latency.

Introduction

This study focuses on the nature of individual differences in amplitude and latency of the P300. The latency and amplitude of P300, a late positive component of the Event Related Brain Potential (ERP), exhibit a wide range of variation among individuals within a task (Polich, 1986; Sklare & Lynn, 1984). The P300 is considered as a cognitive ERP because it is generated when subjects attend and discriminate stimulus events which differ from one another on some dimension and it can be generated even in the absence of a stimulus. The amplitude of the P300 has been hypothesized to reflect the synchronized brain activity during the updating of current memory (Donchin et al., 1986; Donchin & Coles, 1988). Other studies showed the variation in P300 amplitude to be related to the amount of information provided by a given stimulus (Johnson, 1988; Ruchkin et al., 1990). Latency of the P300 has been

associated with the speed of stimulus classification during memory-updating. Because of its reflection of cognitive processes, several studies have used the P300 as physiological trait to index changes in cognition in relation to aging (Ford & Pfefferbaum, 1985; Picton et al., 1984), to index the cognitive development in children (Courchesne, 1983; Wijker et al., 1989) or to develop various diagnostic procedures in neurology and psychiatry (Neshige et al., 1988; Glabus et al., 1994).
Even if task characteristics are held constant or if cognitive task demands (like in an oddball task) are low, one still finds substantial individual variation for the P300 measures. Different results were found for the stability of these individual differences. Test-retest correlations for latency in auditory and visual oddball tasks ranged from .32 to .84 and for amplitude from .67 to .93 (Segalowitz & Barnes, 1993; Fabiani et al., 1987).
With quantitative genetic methodology it is possible to estimate the genetic and environmental contributions to individual differences in P300 parameters (Boomsma & Gabrielli, 1985). Unlike most psychophysiological research, quantitative genetics is not concerned with the variance due to specific experimental manipulations or mean differences between different subject populations, but with the determinants of individual differences in a given phenotype (e.g. P300 amplitude). In the present study the resemblance in P300 components between monozygotic (MZ) and dizygotic twins (DZ) is compared to obtain an estimate of the influence of genetic factors on individual differences in P300. The logic is that MZ twins share 100% of their genes, while DZ twins share on average 50%. Greater resemblance of MZ than DZ twins for the P300 amplitude and latency thus is a first indication for the importance of genetic factors (Plomin et al., 1990). Traditionally, heritability estimates based on twin data have been obtained by doubling the difference between MZ and DZ correlations (Falconer, 1981). More recently quantitative genetics has used model fitting methods (Jinks & Fulker, 1970; Eaves et al., 1978; Boomsma & Molenaar, 1986), which provides a straightforward generalization to multivariate genetic modeling, which allows the covariances between traits to be modeled as a function of genetic and/or environmental correlations between traits.
Information about the genetic or environmental sources of individual differences in P300 parameters is used in studies of alcoholism (Begleiter et al.,1984; Polich et al., 1994) and schizophrenia (Friedman et al., 1986). For these diseases the genetic pattern of inheritance is largely unknown because of their complexity. It has been proposed that the P300 could serve as a psychophysiological marker for identifying individuals who possess biological risk for developing the illness (Friedman, 1988; Iacony, 1985). For example in the case of alcoholism, the smaller P300 amplitude usually found in relatives of alcoholics, is used to guide the search for the underlying molecular genetic factors that contribute to alcoholism. The assumption in these studies is that determination of the P300 is largely genetic. Unfortunately there are only a few studies that explicitly looked at the heritability of the P300. Previous twin

studies found higher MZ correlations (between .71 and .88) than DZ correlations (.33 to .58) for ERP waveform similarity, latency and amplitude (for a review see VanBeijsterveldt & Boomsma, 1994). Four studies explicitly tested genetic influences on the P300 in a traditional oddball paradigm (Surwillo, 1980; Polich & Burns, 1987; Rogers & Deary, 1991; O'Connor et al., 1994), a task in which the subject is to attend to a series of stimuli (nontargets) that alternate with deviate stimuli (targets). Only O'Connor et al. (1994) used a sufficiently large number of subjects to draw firm conclusions about the heritability of the P300. O'Connor et al. (1994) found only a small genetic influence on P300 latency, but a substantial genetic influence on the P300 amplitude in the caudal leads (heritability about 60%).
The present study is a part of a longitudinal project, in which the genetic and environmental influences on brain maturation are estimated in a sample of 213 adolescents twin pairs. The aim of the analyses in this paper is to determine the extent to which environmental and genetic factors influence individual differences in amplitude and latency of the P300, measured on frontal, central, parietal an occipital leads in a simple visual oddball paradigm. Because in our laboratory the same study is also carried out in younger twins (Van Baal et al., submitted) a simple task was used that the younger twins could perform. In addition, P300 in an oddball task is often used in developmental and psychopathology studies and the age effects are well documented.
This study will be the first one to include enough female and male same-sex twin pairs, and opposite-sex twin pairs to systematically test for sex differences in genetic architecture. Multivariate analyses of multilead recordings will further allow us to establish whether the same genetic/environmental sources underlie individual differences in P300 at different scalp locations.

Methods

Subjects
A group of 213 adolescents twins (mean age=16.18 years, SD=.55 years) participated in the study. Addresses of twin pairs were obtained from participants in a large questionnaire study on health-related behavior (Boomsma et al., 1994). Subjects were asked by letter to participate. They received payment for travelling to the laboratory and a present.
The subjects were divided into five groups by sex and zygosity: 39 monozygotic males (mzm), 36 dizygotic males (dzm), 52 monozygotic females (mzf), 38 dizygotic females (dzf), and 48 twins of opposite sex (dos). For 114 same-sex twin pairs zygosity was determined by blood or DNA typing. For the other same-sex twins zygosity was determined by a questionnaire completed by the mother of the twins, consisting of items asking about physical similarity (similarity of face, eye

color, hair color and skin color) and the frequency of confusion of the twins by family and strangers. Seventeen twin pairs completed the questionnaire themselves. Agreement between zygosity based on this questionnaire and zygosity based on blood group polymorphism was 95%.
Results of 9 twin pairs were discarded from further analyses because one of the twin did not count the right number of targets and/or had bad signals.

Procedure and stimuli
The measurement session lasted three and a half hours and took place in the morning or in the afternoon. Subjects visited the laboratory on the same day as their cotwin and were tested in the same segment of the day. The session consisted of four tests: measurement of the EEG/ERP, measurement of nerve conduction velocity (NCV), reaction time tests and an IQ test. After arrival a short explanation of the experiment was given for familiarization with the procedure. One of the twins started with the ERP measurement, the other one with measurement of NCV. After the EEG and EOG electrodes were put on, the subject lay down on a bed in an electrically shielded and sound proof cabin. After controlling the EEG and EOG signals instructions were displayed on a black and white monitor that was attached to the ceiling. EEG was measured during 4 experimental conditions, in fixed order: auditive habituation task, visual oddball task, and background-EEG in rest with eyes open and eyes closed. In the present paper the results for the visual oddball task will be presented.
The task consisted of two types of stimuli, infrequent stimuli (targets, n=25) and frequent stimuli (nontargets, n=100). The stimuli were white line drawings of cats and dogs (Snodgrass & Vanderwart, 1980), which were presented against a black background on a high resolution video monitor. The subjects were instructed to silently count the infrequent stimuli. After the task they were asked how many infrequent stimuli they had counted. The duration of a stimulus was 100 ms and the time between them varied quasi-randomly from 1.5 to 2 sec (mean= 1.75 s). Buildup time was less than 20 ms. During the interstimulus interval (ISI) a central square was shown on the video monitor. To reduce eye movements subjects were instructed to fixate on this central square.

EEG-recording
Tin electrodes mounted in an electrocap were used for measuring EEG activity. Scalp locations were F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, O2, T3, T4, T6, according the 10-20 system (Jasper, 1958). Linked earlobes were used as references according to the method described in Pivik et al. (1993). Briefly, two separate preamplifiers with high input impedance for each of the reference electrodes were used and the output was linked electrically. With the ears linked this way, the effects of possible imbalances in electrode impedance are prevented. The electrode impedance for EEG and EOG was less than 5 Kohm. Tin electrodes were placed at

the canthus of each eye for recording horizontal movements. For vertical movement EOG was recorded from intra-orbital and supra-orbital electrodes, in line with the pupil of the left eye. A ground electrode was attached to FPz. For both EEG and EOG, ECI (electro-gel) EEG paste was used.
All EEG- and EOG-signals were displayed and recorded by a 18-channel Nihon Kohden electroencephalograph (type EEG-4414A1K). For EEG and EOG recordings a time constant of 5 s and a low pass filter, with a 35-Hz cutoff frequency was used. Signals were sent to a 12-bits analog-digital converter and computer-stored for offline processing. During the ERP recording sampling rate of the AD-converter was set to 100 Hz.
Preprocessing of the EEG consisted of automatic removal of single trials with clipping. Single-trial eye movements were removed by means of a dynamic regression routine in the frequency domain (Brillinger, 1975). Subsequently, trials with EEG-artifacts were automatically excluded from further analysis (remaining minimum 20 trials).
For each subject, condition (target and nontarget) and lead the averaged ERPs were computed relative to the mean amplitude of a 100-ms prestimulus baseline period. Before averaging, a correction for latency variability was done with a Woody filter (Woody, 1967). Initially, an averaged waveform was computed and used as a template. The template was moved across each single trial in a stepwise manner (stepwise =10 ms) in the range 200 to 700 ms after the stimulus onset. At each lag the correlation between the signal and template was computed and the timeserie was shift to optimize the cross-correlation of individual ERP with the template. After all trials were shifted, a new average waveform was computed and used as template for a following iteration, until no significant improvement in cross-correlation could be obtained. The final template became the Woody-filtered averaged ERP. Maximum amplitude and latency were automatically scored in a window from 300-600 ms relative to the 100 ms prestimulus level.
In Figure 4.1 the averaged waveforms for targets and nontargets are shown, separately for males and females. Although a P300 is clearly recognizable in the posterior and the central leads only a very small shift was seen in the frontal leads. In fact, in a substantial part of our subjects no recognizable P300 waveforms were found in the frontal leads at all. To maintain adequate power in our genetic modelling it was decided to leave out the F3, Fz, F4, T3, T4 and T6, rather than leaving out these subjects, or entering them with unreliable data.

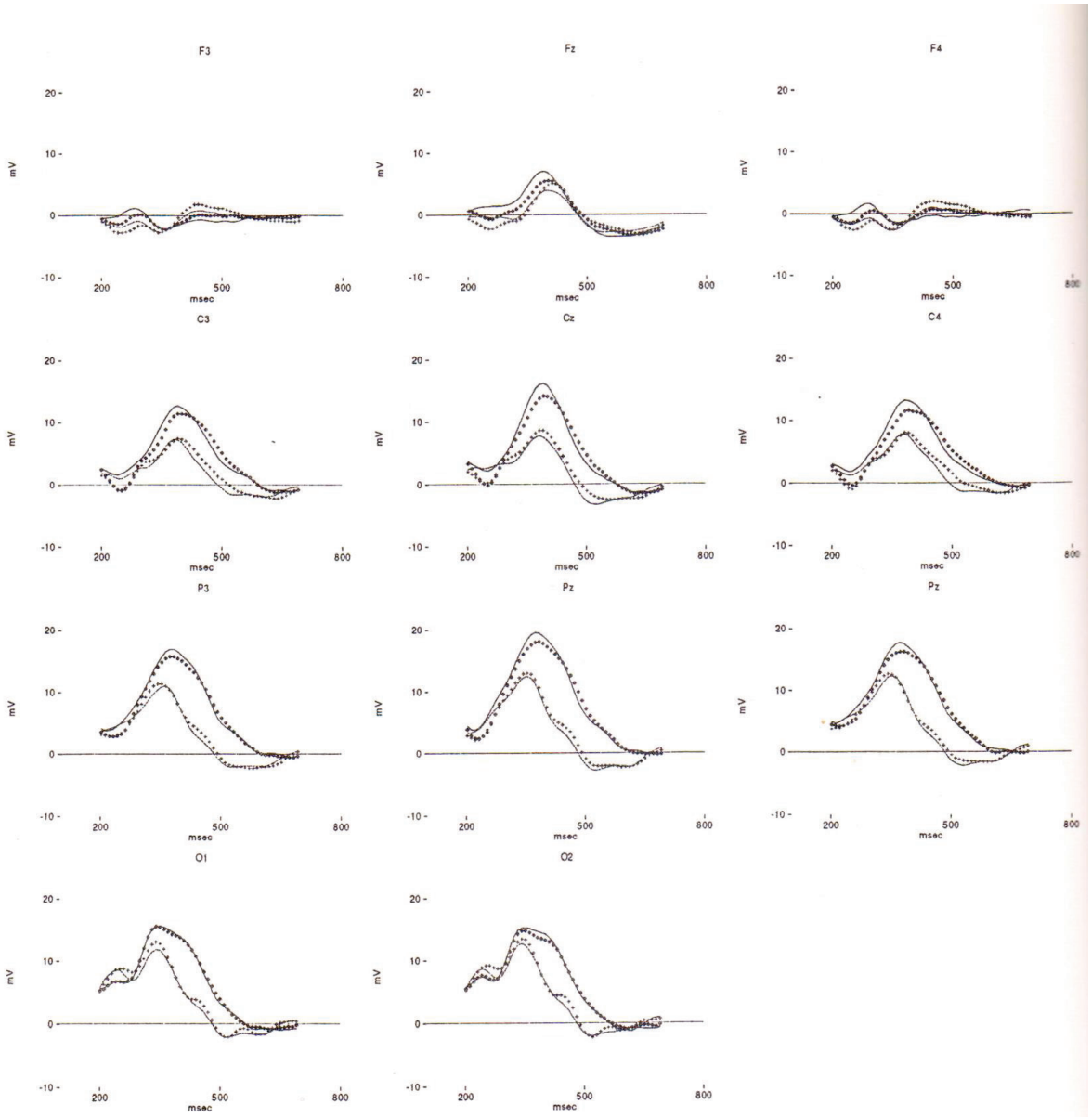

Figure 4.1 Grand averaged ERPs from the oddball task after the signal is filtered with the Woody filter. For each electrode position, the target ERPs of males (■■■line) and females (−line) were given and the nontargets ERPs of males (+++line) and females (---line). The ERP is displayed for the time interval 200-700 after stimulus presentation.

Data Analysis

Manova (SPSS) was used to test for the effect of experimental manipulations on P300 amplitude and latency, and to test whether there were any mean differences between males and females or between MZ and DZ twins. The P300 amplitude and latency were analyzed as dependent variables, with leads, condition (target and nontarget) and birth order (first and second born) as within subject factors and with sex and zygosity as between subject factors. To test the group effects of sex and zygosity, MANOVA was carried out on four groups (MZ and DZ males and MZ and DZ females).

Genetic Analyses

For the genetic analyses the data of the 8 leads, measured in first- and second-born twins were summarized into 16x16 variance-covariance matrices (by PRELIS, Jöreskog & Sörbom, 1986), for each of the 5 zygosity groups (MZM, MZF, DZM, DZF and opposite sex twins (OS)). These matrices were fitted to triangular decomposition genetic models (Neale & Cardon, 1992). The essence of genetic model fitting is the decomposition of the observed variance in the phenotype (here P300) into additive genetic variance (A), due to the additive effects of alleles at multiple loci, shared (common) environmental effects (C), because twins are reared in the same family and nonshared, specific environmental effects (E), which are not shared between siblings.

In terms of structural equations the triangular decomposition of variances and covariances can be represented by a linear model:

$$P_{1i} = a_{11}A_1 + c_{11}C_1 + e_{11}E_1$$
$$P_{2i} = a_{21}A_1 + c_{21}C_1 + e_{21}E_1 + a_{22}A_2 + c_{22}C_2 + e_{22}E_2$$
$$P_{3i} = a_{31}A_1 + c_{31}C_1 + e_{31}E_1 + a_{32}A_2 + c_{32}C_2 + e_{32}E_2 + a_{33}A_3 + c_{33}C_3 + e_{33}E_3$$

and so on. P_{1i} represents the first lead of twin *i (i=1,2)*, P_{2i} denotes the second lead and so on. There are 3 sets of factors; A_1,A_2,A_3 ....A_8, 8 orthogonal additive genetic factors, $C_1,C_2,C_3..C_8$, 8 shared environmental factors and E_1,E_2,E_3 ....E_8, 8 nonshared environmental factors. The first set of factors influence all leads (Pz,O1,O2 and so on), the second set of factors influences all leads except the first lead, the third set of factors influences all leads, except the first two leads, and so on. $a_{11}..$ a_{88} denote factor loadings on the additive genetic factors, $c_{11}..$ c_{88} and $e_{11}..e_{88,}$ are the matrices of factor loadings for shared and nonshared environmental factors, respectively. The factor loadings indicate the degree of relationship between the latent factors and the observed phenotype. In the genetic model, for MZ twins the genetic factors are correlated one, as MZ twins are genetically identical. For DZ twins the additive genetic factors are correlated .5, because DZ twins share on the

average half of their genes. For both MZ and DZ twins the correlations between shared environmental factors are one.
The triangular decomposition of variances and covariances to estimate the genetic, shared, and nonshared environmental covariances, may be compared with PCA. The advantage of the multivariate analyses is that additional information is used that is contained in the covariances between relatives for different variables. This information may be used to estimate to what extent ERP parameters assessed at different locations at the scalp are influenced by the same genes or environmental factors.
Sex differences in genetic architecture may be the result of differences in magnitude of the genetic effects and/or environmental experiences. Another possibility is that different genes are expressed in males and females. To test the first possibility a model which equals the genetic and environmental estimates for males and females was compared with a model which allowed for different estimates in males and females. The second hypothesis is tested by estimating the genetic correlation between males and females in the DOS twin pairs, instead of fixing it .5. Submodels, in which the A or C factors were dropped, were used to test the significance of the genetic and shared environmental factors.
Models were fitted to the twin pair variance-covariance matrices by the method of maximum likelihood (Mx, Neale, 1994). The program provides a chi-square test of the goodness-of-fit for the model (Neale & Cardon, 1992; Neale, Heath, Hewitt, Eaves & Fulker, 1989). The overall χ^2-score tests the agreement between the observed and the predicted variances and covariances in the different zygosity groups. A large χ^2 indicates a poor fit, while a small χ^2 indicates that the data are consistent with the model. To test the submodels hierarchic χ^2-tests were used. A difference χ^2 statistic is computed by subtracting the χ^2 for the full model from that for a reduced model. The degrees of freedom (df) for the test are equal to the difference between df for the full and the reduced model.

Results

Amplitude
MANOVA demonstrated no main effects of zygosity, sex or birth order and no significant interactions between them. There was a significant interaction between sex and condition ($F(1,153)=10.74$, $p<.00$). For females the target P300 amplitude was larger than for males and for males the nontargets had larger amplitudes than for females. A significant main effect for lead was found, $F=(7,147)=137.07$ $p<.00$. Larger amplitudes were found for Pz, Cz, P3 and P4, lower amplitudes for left and right central and occipital leads. Also a main effect for condition was seen $F(1,153)=526.95$, $p<.00$. The P300 amplitude was larger in response to targets than

for nontargets. The difference between targets and nontargets was larger for parietal and central leads and smallest on the occipital leads (interaction lead x condition, $F(7,147)=24.01$, $p<.00$).

Latency
The results showed no significant effects of sex, zygosity, birth order or interactions between them. The only two significant main effects were for condition ($F(1,153)=95.25$, $p<.00$) and leads ($F(7,147)=32.64$, $p<.00$). The latency for targets was larger than for nontargets. Largest latencies were found for the central leads, which became smaller in caudal direction. The differences in latency for targets and nontargets were larger on parietal and occipital leads (lead x condition, $F(7,47)=7.62$, $p<.00$).

Twin Correlations

Amplitude
In the upper part of Table 4.1 twin correlations are presented for the P300 amplitude for targets and nontargets. For males, the MZ correlations were higher than the DZ correlations for most leads, both for targets and nontargets. The higher MZ correlations suggest genetic influences on the P300 amplitude in response to both targets and nontargets. For females, similar evidence of genetic influence was found on the P300 amplitude in parietal and central leads in response to nontargets, as MZ correlations were higher then DZ correlations. In response to the targets, however, the MZ and DZ correlations were the same for all leads or DZ correlations were even higher than MZ correlations, and nontarget occipital leads also showed identical MZ and DZ correlations. This suggests that the target P300 amplitude in females may be influenced by shared environmental influences (Neale & Cardon, 1992). The difference in genetic versus environmental determination of the P300 in males and females would predict correlations in the opposite sex twins that are close to zero. Indeed, low DOS correlations were found throughout, corroborating the sex related differences in P300 amplitude determinants. Pooled correlations, over males and females, are given to make comparisons with other investigations possible. For targets and nontargets at parietal and occipital electrode locations MZ correlations were larger than DZ correlations, suggesting genetic influences.

Latency
In lower part of Table 4.1 the twin correlations of the P300 latency are given. These correlations were lower than the correlations of the P300 amplitude. Moreover, as no meaningful pattern of correlations could be observed, no genetic model fitting was attempted.

Table 4.1 Twin correlations of P300 amplitude and latency for 8 leads (C3, CZ, C4, P3, Pz, P4, O1 and O2), separately for targets and nontargets. In the first row the twin correlations were given for each zygosity group (MZM, DZM, MZF, DZF, OS), in the second row the twin correlations were pooled over males and females.

P300 AMPLITUDE

	Target								Nontarget							
	C3	Cz	C4	P3	Pz	P4	O1	O2	C3	Cz	C4	P3	Pz	P4	O1	O2
MZM(37)	.34	.10	.42	.45	.47	.52	.54	.51	.24	.57	.56	.56	.54	.47	.55	.67
DZM(35)	.33	.32	.16	.03	.10	.21	.21	.26	.35	.17	.45	.19	.30	.32	.15	.28
MZF(48)	.22	.25	.25	.33	.52	.50	.50	.58	.40	.42	.53	.37	.53	.42	.47	.54
DZF(37)	.44	.55	.64	.54	.56	.56	.55	.56	.08	.33	.33	.24	.26	.42	.55	.58
DOS(47)	.11	.15	.11	-.23	.03	-.07	-.08	.04	.31	.15	.32	.08	.17	.11	.20	.09
Twin correlations pooled over males and females:																
MZ (85)	.27	.19	.29	.38	.49	.48	.52	.54	.34	.48	.54	.45	.54	.43	.51	.61
DZ (119)	.27	.33	.31	.12	.24	.23	.21	.27	.26	.22	.36	.16	.22	.24	.29	.29

P300 LATENCY

	Target								Nontarget							
	C3	Cz	C4	P3	Pz	P4	O1	O2	C3	Cz	C4	P3	Pz	P4	O1	O2
MZM(37)	.24	.22	.35	.28	.15	.01	.22	.22	.12	.00	.05	.56	.10	.79	.35	.49
DZM(35)	.22	.37	.19	.05	.46	.19	.09	.18	.20	.24	.16	.03	.25	.07	.09	.16
MZF(48)	.10	.31	.22	.11	.30	.27	.24	.21	-.17	.02	.32	.46	.11	.28	.18	.01
DZF(37)	.53	.49	.22	.33	.47	.46	.26	.01	.04	-.03	-.03	.38	.28	.29	.24	.05
DOS(47)	-.28	.04	.03	.03	-.08	.13	.13	.00	-.21	.05	-.07	-.39	-.27	-.12	.13	.31
Twin correlations pooled over males and females:																
MZ (85)	.17	.28	.29	.20	.21	.14	.23	.22	-.04	-.01	.22	.50	.09	.47.	.27	.23
DZ (119)	.10	.26	.10	.13	.29	.21	.16	.05	-.03	.08	.01	.02	.04	.05	.16	.14

Genetic Modelling

Table 4.2 shows the χ^2 goodness-of-fit statistics for the various models tested. Four models were fitted to test sex differences in the individual variation of the P300

amplitude. The first model had different estimates for males and females and estimated the correlation between genetic factors of males and females in the DOS. A lower correlation than .5 is expected when different sets of genes influence the P300 amplitude in males and females. To test this hypothesis this model is compared with the second model. For the targets and nontargets, the χ^2 did not increase significantly, indicating that the same genes seem to act on the amplitude of the P300 for males and females. In the third model the estimates, a, c and e were constrained to be equal in males and females. When the χ^2 of this model is compared to the χ^2 of the second model, the difference χ^2 exceeded just the critical value. Thus, for targets and nontargets, the best fitting model specified sex differences in parameter estimates.

Table 4.2 Goodness-of-fit tests for different models applied to P300 amplitude for 8 leads (C3, Cz, C4, P3, Pz, P4, O2 and O2). For each model χ^2, probability and differences in χ^2 ($\Delta\chi^2$) are given. a, c, e are the loadings estimated for males, a', c' and e' loadings estimated for females. Rg free means that the correlation between males and females in the DOS group is estimated instead of fixed at 0.5.

		TARGETS		NONTARGETS	
Models	df	χ^2	$\Delta\chi^2$	χ^2	$\Delta\chi^2$
test of sex differences:					
1. males ace, females a'c'e', rg free	456	743.7		725.8	
2. males ace, females a'c'e'	464	744.4	.7	727.9	2.1
3. same a,c,e males and females	572	887.2	142.8*	868.5	140.6*
dropping A or C separately in males or females: (tested against 2, Δdf=36)					
4. males ae, females a'c'e'	500	765.5	21.1	746.4	18.5
5. males ace, females a'e'	500	773.5	29.1	753.4	25.5
6. males ce, females a'c'e'	500	764.2	19.8	747.7	19.8
7. males ace, females c'e'	500	749.9	5.5	740.7	12.8
dropping A or C in both males and females: (tested against 2, Δdf=72)					
8. males ce, females c'e'	536	765.7	21.3	767.7	39.8
9. males ae, females a'e'	536	780.5	36.1	762.8	34.9
dropping A and C: (tested against 9/10, Δdf=72)					
10. males e, females e'	608	909.6	129.1*	926.7	159.1*

critical value of χ^2 with 72 degrees of freedom = 92.80
critical value of χ^2 with 36 degree of freedom = 50.99
critical value of χ^2 with 8 degree of freedom = 15.51
* significant decrease in fit

In the next submodels the significance of the A and C factors was tested. It may be seen, that dropping either A or either C in both males and females, did not lead to a worse fit of the model. However when dropping A and C together, there is a significant deterioration of the fit, for both targets and nontargets. Thus for targets and nontargets there is clearly familial relatedness, but it is not possible to distinguish between A and C factors. Because no distinction could be made between A and C factors, the genetic correlations as a result of an AE model (Table 4.3) and the shared environmental correlations as a result of a CE model (Table 4.4) are presented. The genetic and environmental correlations represent the extent to which the same genes or environmental factors contribute to the observed phenotypic correlation (Neale and Cardon, 1992). Also, the percentage of variance explained by genetic and environmental factors is given. For targets, 25% to 42% of the variance averaged over all leads, is explained by familial relatedness factors, for nontargets 25% to 62% of the variance is explained by familial relatedness. For both sexes and both kind of stimuli, the amount of variance explained by genetic factors is usually larger then the amount of variance explained by environmental factors. Still, in both males and females, a substantial portion of the variance in target and nontarget P300 amplitude had to be attributed to nonshared environmental influences.

For targets there is one homogeneously block of high correlations (around .9, see Table 4.3), especially for central and parietal leads. A second block with higher correlations is formed by the occipital leads. In contrast with the structure of genetic correlations, the nonshared environmental correlations were lower and without clear pattern. Almost an equal structure of correlations was seen for the nontargets, 2 blocks of highly homogeneous correlations, one for central and parietal leads, and one for the occipital leads. The structure of genetic correlations did not show large differences between females and males. The nonshared environmental correlations were larger for females. Almost no differences in heritability were seen, except for central leads, for which males had larger heritabilities.

For the shared environmental factors the same structure was found as for the structure of the genetic factors (Table 4.4). There is a pattern of high correlations among central and parietal leads, and a second block of higher correlations for the occipital leads. The correlation structure of nonshared environmental factors is without a clear pattern and showed lower correlations among leads.

Tabel 4.3 Genetic correlations (below diagonal) and nonshared environmental correlations (above diagonal) for males and females, as a result of an AE model. In the upper part correlations for targets are given, in the lower part correlations for nontargets. Below each matrix of correlations the variation explained by genetic factors is given (h^2).

TARGETS

	MALES								FEMALES							
	environmental correlation								environmental correlation							
	C3	Cz	C4	P3	Pz	P4	O1	O2		C3	Cz	C4	P3	Pz	P4	O1	O2
genetic correlation									genetic correlation								
C3	-	.69	.61	.59	.49	.50	.23	.31	C3	-	.76	.72	.77	.75	.66	.63	.53
Cz	.98	-	.73	.53	.61	.56	.27	.37	Cz	.99	-	.75	.68	.75	.62	.51	.43
C4	.92	.96	-	.48	.46	.51	.24	.31	C4	.97	.99	-	.61	.66	.72	.50	.48
P3	.89	.88	.93	-	.86	.77	.67	.55	P3	.89	.90	.91	-	.85	.77	.78	.68
Pz	.86	.92	.97	.90	-	.85	.65	.60	Pz	.88	.91	.91	.99	-	.83	.70	.67
P4	.70	.74	.88	.91	.91	-	.69	.61	P4	.86	.87	.87	.98	.96	-	.70	.75
O1	.68	.67	.70	.78	.73	.74	-	.70	O1	.53	.53	.52	.80	.79	.84	-	.81
O2	.60	.59	.65	.79	.72	.80	.96	-	O2	.61	.61	.60	.80	.79	.86	.93	-
h^2	53	29	58	39	45	47	57	55	h^2	27	34	34	39	54	50	49	56

NONTARGETS

	MALES								FEMALES							
	environmental correlation								environmental correlation							
	C3	Cz	C4	P3	Pz	P4	O1	O2		C3	Cz	C4	P3	Pz	P4	O1	O2
genetic correlation									genetic correlation								
C3	-	.53	.45	.59	.46	.42	.29	.44	C3	-	.70	.68	.62	.60	.41	.45	.30
Cz	.85	-	.55	.35	.29	.28	.15	.41	Cz	.99	-	.66	.44	.55	.37	.41	.30
C4	.97	.83	-	.36	.42	.38	.20	.28	C4	.97	.99	-	.42	.48	.49	.43	.36
P3	.80	.89	.85	-	.76	.69	.39	.42	P3	.87	.88	.89	-	.76	.59	.64	.44
Pz	.78	.93	.82	.94	-	.82	.34	.42	Pz	.86	.87	.86	.96	-	.73	.53	.42
P4	.64	.79	.76	.93	.91	-	.39	.48	P4	.84	.85	.84	.97	.96	-	.56	.57
O1	.49	.57	.57	.86	.73	.79	-	.65	O1	.28	.30	.33	.66	.61	.72	-	.81
O2	.45	.51	.60	.83	.75	.88	.93	-	O2	.42	.42	.41	.71	.68	.81	.94	-
h^2	49	59	71	62	59	61	62	72	h^2	41	43	61	47	59	58	49	59

Table 4.4 Shared environmental correlations (below diagonal) and nonshared environmental correlations (above diagonal) for males and females, as a result of a CE model. In the upper part correlations for targets are given, in the lower part correlations for nontargets. Below each matrix of correlations the variation explained by shared environmental experiences is given (c^2).

TARGETS MALES

	nonshared environmental correlation							
	C3	Cz	C4	P3	Pz	P4	O1	O2
shared environmental correlation								
C3	-	.73	.75	.69	.61	.60	.44	.48
Cz	.99	-	.78	.60	.67	.61	.39	.45
C4	.85	.85	-	.66	.65	.65	.50	.52
P3	.82	.82	.72	-	.88	.83	.73	.65
Pz	.87	.89	.93	.81	-	.89	.72	.69
P4	.56	.61	.82	.80	.82	-	.74	.69
O1	.48	.49	.44	.66	.54	.62	-	.81
O2	.37	.38	.37	.65	.52	.72	.91	-
c^2	30	17	25	18	21	23	35	35

FEMALES

	nonshared environmental correlation							
	C3	Cz	C4	P3	Pz	P4	O1	O2
shared environmental correlation								
C3	-	.76	.71	.78	.78	.66	.63	.54
Cz	.99	-	.75	.69	.74	.61	.48	.43
C4	.98	.98	-	.63	.66	.71	.52	.49
P3	.87	.91	.88	-	.86	.79	.78	.70
Pz	.88	.93	.88	.98	-	.84	.69	.68
P4	.85	.90	.85	.98	.96	-	.72	.77
O1	.48	.57	.47	.79	.80	.81	-	.82
O2	.56	.62	.56	.79	.78	.84	.93	-
c^2	26	33	38	34	48	46	46	52

NONTARGETS MALES

	environmental correlation							
	C3	Cz	C4	P3	Pz	P4	O1	O2
shared environmental correlation								
C3	-	.64	.62	.67	.57	.52	.36	.46
Cz	.81	-	.68	.53	.49	.43	.26	.40
C4	.92	.76	-	.59	.62	.54	.33	.40
P3	.77	.95	.82	-	.84	.80	.61	.64
Pz	.73	.95	.72	.94	-	.87	.52	.58
P4	.57	.81	.73	.89	.87	-	.58	.67
O1	.50	.64	.60	.82	.68	.72	-	.80
O2	.39	.55	.62	.77	.69	.84	.87	-
c^2	33	34	45	31	37	37	33	42

FEMALES

	environmental correlation							
	C3	Cz	C4	P3	Pz	P4	O1	O2
shared environmental correlation								
C3	-	.77	.77	.69	.69	.54	.45	.35
Cz	.99	-	.76	.56	.66	.51	.41	.35
C4	.96	.98	-	.56	.64	.61	.41	.40
P3	.82	.83	.85	-	.82	.67	.62	.48
Pz	.81	.81	.80	.93	-	.80	.53	.47
P4	.80	.80	.79	.98	.95	-	.57	.61
O1	.23	.25	.30	.72	.62	.74	-	.82
O2	.38	.38	.36	.75	.69	.81	.94	-
c^2	22	24	41	32	42	47	45	53

Targets and nontargets in one analysis

On the basis of these results, we investigated whether the same set of genes influences the target and nontarget P300 amplitude. The triangular decomposition was extended to both targets and nontargets. The analysis was done separately for males and females. The result of the goodness-of-fit test showed for females a CE model as the best model and for males an AE model. However, dropping either the A

or the C matrix in both sexes did not lead to a significant decrease in fit. For males the first genetic factor influenced both targets and nontargets, but loadings were systematically higher for targets. In addition, a second genetic factor had higher loadings for the nontargets.
In females factor loadings on C showed the same pattern as the factor loadings on G in males, the first factor had higher loadings on the targets than on nontargets. The factor structure of the nonshared environment showed a unique pattern of loadings for targets and nontargets, a first factor had higher loadings on targets than on nontargets and a second factor showed higher loadings on nontargets.

Discussion

The aim of this study was to estimate the genetic and environmental contributions to individual differences in P300 parameters. Because P300 greatly varies with age (Courchesne, 1983; Wijker et al., 1989) and different genetic sources may be active with different ages (Molenaar et al., 1991) the age span of the subjects was held very small on purpose (mean age was 16.18 years with a SD of .55 years). To systematically investigate sex differences in genetic architecture, the twin sample included an equal proportion males and females.
The grand means for P300 amplitudes and latencies were quite comparable to those generally observed in the classical oddball task (Donchin & Coles, 1988). The P300 amplitude is larger for target than for nontarget stimuli and larger amplitudes were found over central-parietal leads. This confirms the results obtained in a typical P300 design, in which the amplitude of the P300 depends on the probability or occurrence of the stimulus and the task relevance of that stimulus (Donchin & Coles, 1988).
We found evidence for a familial resemblance of the individual variation of P300 amplitude for nontargets and targets in both sexes. However it is difficult to determine whether these familial resemblances are caused by genetic or shared environmental factors. Because it was not possible to choose between an AE and an CE model we have presented the multivariate results both for an AE and a CE model. In the case of an AE model, the variance explained by genetic factors is, averaged over leads, 42% for targets and 62% for nontargets. Differences between males and females were small. In the case of a CE model, the amount of variance explained by familial factors is smaller. For both targets and nontargets, the amount of variance explained by shared environmental factors is 25% for males and 40% for females. The MZ and DZ correlations found for the target P300 suggest genetic influence for males and the influence of shared environmental factors for females. For nontargets, both for females and males the MZ correlation is twice the DZ correlation, suggesting genetic influence. However with formal testing, for both targets and nontargets, neither the genetic nor the shared environmental factor was significant.

There is clear familial relatedness, because dropping both genetic and environmental factors leads to a significant worsening of the model.
This is the first twin study of ERP in which possible sex differences in genetic architecture were explicitly taken into account. This may be the reason that our results, no distinct genetic or shared environmental contributions to the individual differences in P300 amplitude, do not agree with earlier studies. Furthermore, the amount of variance explained by genetic/environmental factors, averaged over all leads, is in the range from 25 to 42% for targets. This is lower than the amount of variance explained by heredity reported in earlier studies including the study of O'Connor et al. (1994). The last study found in an auditory oddball task a heritability for targets in the caudal leads of 60%. O'Connor et al. (1994) also found evidence that besides additive genetic effects, genetic dominance plays a role. Dominance is due to interaction of alleles at a locus. With the twin method the presence of genetic dominance is detected if the MZ correlation is substantially larger than the DZ correlation (at least larger than twice the DZ correlation). In the O'Connor et al. study the DZ correlations were very low. By pooling our MZ and DZ correlations over males and females, the results can be compared with those of O'Connor et al. We found no indication for the presence of genetic dominance, the MZ correlations were about twice the DZ correlations. Differences between the O'Connor et al. study and our study could be due by the use of the auditory modality. Johnson (1989) suggested different generators of the P300 activity for different modalities and possibly different genes are responsible for these generators. Another explanation could be the different age of the subjects compared to our subjects. Genetic differences are not constant throughout life. Many examples of genes being switched on and off at different ages exist in the literature with simultaneous shifts in heritability (Molenaar etal., 1991). In our group of subjects, the brain maturation is still incomplete and it is possible that different genes are expressed in this age group.
The differences in brain maturation could also be a reason why there is a male-female difference in the genetic architecture of the P300 amplitude. Segalowitz and Barnes (1993), who used subjects with the same age as our sample, found for 15 years old females larger P300 amplitudes of the targets than for males, while at 17 years the opposite was seen i.e. a larger amplitude for males than for females. These effects could be due to differences in processing strategies in males and females at different ages (Friedman et al., 1985), for instance because of sex differences in hemispheric specialization for visuo-spatio tasks (McGlone, 1980) or other neuroanatomic structural differences (Lacoste-Utamsing & Holloway, 1982). However, the rate of maturation may not be the same for males and females. Differences in maturational phase in the males could account for a difference in the genetic architecture of males and females.
Supposing that shared environmental factors really influence the P300 amplitude, how could one specify these shared environmental influences? What could both MZ

and DZ twins have in common that can account for their likeness in P300 amplitude? Half of the twin pairs were tested in the morning whereas the other half were tested in the afternoon. Within each twin pair no more than an hour elapsed between the EEG measurements. Synchronization of time of last meal, therefore, may be a first possible explanation of a shared environmental effect, because fasting state influences P300 (Geisler & Polich, 1992). Since P300 amplitude has been suggested to be sensitive to state anxiety effects created by an experimental setting (Grillon & Ameli, 1994), a tentative explanation would point to twin resemblance in arousal induced by the experimental setup and the visit to the lab perhaps as a function of joint twin preparation for this event. Obviously, these explanations never leave the realm of speculation. Our provisional maturational hypothesis should be tested in a longitudinal setup, e.g. by retesting these subjects after two years. Exactly such a longitudinal follow-up is currently underway.

The multivariate genetic analyses approach used in this study yields an insight into the sources of covariation between amplitudes at different scalp locations. Covariation can arise if the same genes or the same shared environmental experiences influence the P300 amplitude at different cortical regions. For both targets and nontargets, the structure of genetic and shared environmental correlations showed that there is one set of factors that influences all electrode positions. In addition a likely second factor influences the occipital leads. So, both for targets and nontargets, the P300 amplitude measured at different cortical regions is determined by the same set of genetic/environmental factors.

The question arises whether the same structure of genetic/environmental factors influences targets and nontargets. Therefore we did an overall analysis in which target and nontarget P300 amplitudes were analyzed simultaneously. The first genetic factor is still the most important factor, but there is a second genetic factor that also has high loadings. Targets load higher on the first genetic factor and nontargets on the second genetic factor. This implies an interesting interaction between psychological test condition and genetic influences: the genetic influences that are expressed depend on information processing demands.

Recently an association of the TaqI A D2 dopamine receptor allele with phenotypic expression of P300 latency was reported by Noble et al. (1994). Ten-to-14 year old boys with the A1 allele showed longer P300 latencies. Three previous studies have reported high heritability for P300 latency (Surwillo, 1980; Polich & Burns, 1987; Rogers & Deary, 1991). However, these studies used very few subjects (<20), so the results could depend on chance. In our study no effects of either genetic or common environmental factors were suggested for P300 latency. Our data agree with those of O'Connor et al. (1994) who also found no genetic effects on P300 latencies. Sample sizes in O'Connors study (N=98 twin pairs) and in our own study (N=213 twin pairs) were large in comparison to the previous studies (N<20), so we favor the idea that genetic influences on P300 latency are small. Clearly, some caution is in order with

our conclusion. Peak-picking of the P300 wave is not always straightforward, particularly in subjects who have a diffuse late positive wave. Also, the number of averaged trials ("only" 25 targets) may have been too low to optimize the signal-to-noise ratio. Since all error variance will enter the nonshared environment term, both shared environmental and genetic effects will be reduced. However, we took various measures to maximize the signal to noise ratio: we deliberately left out the frontal and temporal leads because the P300 was less clear here (notable frontal) and we reduced latency jitter by applying a Woody filter for each individual for each separate lead, before latency detection. In spite of these measures, no genetic effects on latency were found.

A large part of the individual differences in both target and nontargets P300 amplitude was due to nonshared environmental sources. These nonshared environment represent environmental factors, not shared by the twins. This suggests that as much as half of the variance in the P300 amplitude may be due to variables that are not manipulated like variance in the arousal state during the specific experimental session, variance in task motivation and attention, or error variance. The test-retest reliability for amplitude over various time periods is .62 to .81, which corresponds with a reliable variance of 38-64% (Fabiani, Gratton, Karis & Donchin, 1987; Segalowitz & Barnes, 1993). This suggests that the nonshared environmental source is mainly due to measurement error of the P300 amplitude.

The heritability of the P300 amplitude is lower than found for EEG background (Van Beijsterveldt & Boomsma, 1994). Background EEG is almost unanimously conceived as genetically determined. We have found a familial resemblance in the individual differences in P300 amplitude, but we could not distinguish between shared environmental and genetic factors. This has important consequences for the interpretation of studies associating P300 amplitude with various traits. P300 has been proposed as genetic marker for alcoholism but our results showed that caution is needed in interpretation of the P300 as a genetic trait.

5

Genetic and environmental influences on EEG coherence

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Abstract
EEG coherence measures the covariation between two electrode locations as a function of the frequency and is used to study the electrophysiological coupling between cortical regions. The aim of this study was to determine the heritability of EEG coherence. Using genetically related subjects it is possible to partition the variability of EEG coherence among individuals into a genetic and an environmental part. EEG coherence was measured in a group of 213 twin pairs. By including male and female twin pairs in the sample, sex differences in genetic architecture were systematically examined. The EEG was obtained during quiet supine resting. EEG coherence was estimated for nine electrode combinations along the anterior-posterior axis within a hemisphere for four frequency bands (delta, theta, alpha and beta). Averaged over all electrode-combinations about 60% of the variance was explained by genetic factors for theta, alpha and beta. For delta, the heritability was somewhat lower. No systematic sex differences in genetic architecture were found. All environmental influences were nonshared, i.e. unique factors including measurement error. Environmental factors shared by twin siblings did not influence variation in EEG coherence.

Introduction

The aim of this study is to investigate the contributions of genetic and environmental factors to individual differences in the connections between human brain areas.
The human brain has a modular organization consisting of brain areas which differ markedly in their morphology and in their function. The brain areas do not work isolated but are linked, coordinated and integrated by complex neural circuits. In humans, the number of cortico-cortical connections is very large and their development continues at least until the age of 20. The general program of corticocortical pathways seems to be under genetic control, but, the final number of synapses is far too large to be controlled by a specific genetic program (Changeux & Danchin, 1976). For example, the morphology of the corpus callosum in monozygotic (MZ) twins is more similar than in unrelated subjects (Oppenheimer,

1989; Steinmetz et al., 1993), pointing to genetic influences. However, the corpus callosum in MZ twin pairs is not completely identical, suggesting a possible influence of environmental experiences on CNS properties. It seems likely that only the general outlines of neural connectivity are genetically programmed (Huttenlocher, 1994) while the fine-tuning of pattern of neural connections is determined through the interactions with its environment (Wiesel, 1994). Growth of the central nervous system (CNS) is an epigenetic process: the CNS develops in interaction with the environment resulting in modification of both the CNS and the environment (Benno, 1990; Molenaar et al., 1993). It may be expected that in addition to genetic factors, effects of specific experiences will account for individual differences in connectivity of the brain.

One noninvasive technique for studying functional connections between brain regions is the electroencephalgrahic (EEG) coherence. The coherence of two EEG signals recorded from two spatially separated brain areas estimates the in-phase components of waveforms generated by the action of neurons underlying the cortical regions. Thatcher (1987) has speculated that the coherence between two scalp regions reflects the degree to which there are axonal connections among these brain regions. The strength and number of these axonal connections are reflected by coherence values. High coherence, which indicates that two cortical areas show synchronized wave patterns in the EEG, is considered as an index of "connectivity" between areas, because neural networks show synchronized waves if they are connected. Although volume conduction may lead to "false" increase in coherence, phase relations or the fall in coherence as function of distance may be used to obtain "true" coherence (Thatcher, 1994).

Maturation of the brain is not completely finished before the first twenty years of life (Fisher & Rose, 1994). Research indicates that even in the period of adolescence and young adulthood there are still processes like elimination of excess synapses (Goldman-Rakic, 1987) and an increase in the degree of myelination in the prefrontal cortex (Benes, 1989). Evidence for development of the frontal lobe in adolescence and young adulthood, has also been found using EEG measures. In re-analyzing the large data set of Matoušek and Petersén (1973), Hudspeth and Pribram (1992) found that from the age of 15 the development of the frontal lobes becomes especially prominent. Late maturation of the frontal lobe is also suggested by the results obtained by Buchsbaum et al. (1992). In a cross-sectional study with subjects aged 16 to 22 years, it was shown that delta activity of absolute power decreased throughout this age range, especially in left frontal and temporal regions. Coherence also changes with increasing age. In a large cross-sectional study of Thatcher et al. (1987, 1994) coherence was used to study the cerebral development of normal children in the range from a few months to early adulthood. The outcome of this study showed large changes in the coherence during development. From age 15 to adulthood, frontal lobe connections were primarily involved.

Between subjects there are large individual differences in coherences. With quantitative genetics it is possible to study the contribution of genetic and environmental factors into the individual differences in coherences. Heritability can be calculated from data measured in genetically related subjects such as twins. In a twin design monozygotic twins, who are 100% genetic related, are compared to dizygotic (DZ) twins, who share on average 50% of their genetic material. If coherence is influenced by genetic factors, MZ twins should resemble each other to a greater extent than DZ twins.
In the present study a twin design was used to investigate the genetic influences on individual differences in coherence. The study was conducted in a large sample of 213 twin pairs. The age range of the subject was small (mean age = 16 year, sd=.55). For genetic studies a small age range is an advantage because heritability may differ across ages. The twin sample included male and female same-sex twin pairs and opposite-sex twin pairs. This offers the opportunity to analyze sex differences in genetic architecture. Different heritabilities for males and females could be expected, since several studies have found sex differences in the structure of the human brain (Gur et al., 1995; Steinmetz et al., 1995) and sex differences in the functional brain organization (Kimura, 1987). EEG was measured on 14 scalp locations, if coherence is calculated for all scalp combinations, this would lead to an enormous number of dependent variables. Since our interest was mainly in frontal connections we have selected the electrode combinations along the anterior-posterior axis.

Methods

Subjects

A group of 213 adolescents twins (M=16.18. years, SD=.55 years) participated in the study. Addresses of twin pairs were obtained from participants in a large questionnaire study on health-related behaviors (Boomsma et al., 1994). Subjects were asked by letter to participate.
The subjects were divided into five groups by sex and zygosity: 39 monozygotic male pairs (MZM), 36 dizygotic male pairs (DZM), 52 monozygotic female pairs (MZF), 38 dizygotic female pair (DZF) and 48 twins of opposite sex (DOS) twin pairs. For 114 same-sex twin pairs zygosity was determined by blood and DNA typing. For the other same-sex twins zygosity was determined by a questionnaire filled in by the mother, consisting of items about physical similarity (similarity of face, eye color, hair color and skin color) and the frequency of confusion of the twins by family and strangers. Seventeen twin pairs completed the questionnaires themselves. Agreement between zygosity based on this questionnaire and zygosity based on blood group polymorphism and DNA fingerprinting was 95%.
Six subjects were discarded from further analyses because of recording artifacts in one of more EEG channels. This left 37 MZM, 35 DZM, 52 MZF, 37 DZF and 46 DOS twin pairs for analysis.

Procedure

The measurement session lasted three and a half hours and took place in the morning or in the afternoon. Subjects visited the laboratory on the same day as their cotwin and were tested in the same segment of the day. The session consisted of four tests: measurement of the EEG/ERP, measurement of nerve conduction velocity (Rijsdijk et al., 1995), reaction time and intelligence tests. After arrival, a short explanation of the experiment was given, for familiarization with the procedure. One twin started with the EEG measurement, and the other one with the measurement of the other variables. After the EEG and EOG electrodes were put on, the subjects lay down on a bed in an electrically shielded and sound proof cabin. Instructions were displayed on a black and white monitor, attached to the ceiling. EEG was recorded during 3 experimental conditions, in fixed order: during an auditive habituation task, during a visual oddball task and in a 3-minute rest condition. If artifacts occurred during the recording, the recording period was lengthened until 3 minutes of artifact free EEG was obtained. In the present paper the results of EEG coherence in the supine rest condition with eyes closed are presented.

EEG-recording

Tin electrodes mounted in an electrocap were used for measuring EEG activity. Scalp locations were prefrontal (Fp1, Fp2), midfrontal (F3, F4), lateral frontal (F7, F8), central (C3, C4), parietal (P3, P4), occipital (O1, O2) and temporal (T5, T6), according the 10-20 system (Jasper 1958). Linked earlobes were used as references according the method described in Pivik et al. (1993). Briefly, we used two separate preamplifiers with high input impedance for each of the reference electrodes and linked the output electrically. With the ears linked this way, the effects of possible imbalances in electrode impedance are prevented. The electrode impedance for EEG and EOG was less then 5 Kohm. Tin electrodes were placed at the canthus of each eye for recording horizontal movements. For vertical movement EOG was recorded from intra-orbital and supra-orbital electrodes, in line with the pupil of the left eye. A ground electrode was attached to Fpz. For both EEG and EOG, ECI (electro-gel) EEG paste was used.

All EEG- and EOG-signals were displayed and recorded by a 18-channel Nihon Kohden electroencephalograph (type EEG-4414A1K). For EEG and EOG recording time constant was 5 s and a low pass frequency, with a 35-Hz cutoff frequency was used. Signals were sent to a 12-bits analog-digital converter and computer-stored for offline processing. The sampling rate of the AD-converter was 250 Hz. A set of 100 microvolt sine waves was used for calibration prior and after recording.

Data Processing

Preprocessing of the EEG consisted of dividing the EEG signal into epochs of 2 sec. After automatic removal of epochs with clipping, Fast Fourier Transformation (FFT) was applied to the remaining 2 sec epochs. A minimum of 30 epochs was required for further analyses. Eye movements were removed by means of a dynamic regression routine in the frequency domain (Brillinger, 1975). The D.C. offset was removed from the data by calculating the mean of the epoch and subtracting it from each point. Smoothed power spectra and cross spectra for frequency range from .5 to 30 Hz, with .5 Hz steps, were calculated by averaging the power and cross spectra over the valid epochs. The coherence was calculated for the following electrode combinations: Fp1-F3, Fp1-C3, Fp1-P3, Fp1-O1, F3-O1, C3-O1, F3-C3, C3-P3, P3-01 and the same combinations for the right hemisphere: Fp2-F4, Fp2-C4, Fp2-P4, Fp2-O2, F4-O2, C4-O2, F4-C4, C4-P4, P4-02. Coherence was computed as:

$$Coh(f)^2 = 2 \frac{Gxy(f)}{Gxx(f)Gyy(f)}$$

where Gxy is the cross spectrum of two EEG locations and Gxx(f) and Gyy(f) are the respective autopower spectra of these two EEG locations. The resulting coherence values were averaged over broad bands: delta (1.5-3.5 Hz), theta (4-7.5 Hz), alpha (8-12.5 Hz) and beta (13-25 Hz). All values were log-transformed with $^{10}\log(x/1-x)$ to transform the coherence into a more Gaussian distribution.

Statistical Analysis

Before the statistical analyses the data were examined for extreme values of the coherence (procedure EXAMINE, SPSS). If there were extremes scores, subjects were discarded from further analysis. For the delta band 8 twins were discarded, for theta 3 twin pairs, and for beta 12 twin pairs were discarded, respectively. MANOVA (SPSS) was used to test whether there were any differences between males and females or between MZ and DZ twins. Per frequency band, the coherence of all electrode combinations was used as the dependent variable, with electrode combinations (Fp1-O1, Fp1-P3, Fp1-C3, F3-O1, C3-O1, Fp1-F3, F3-C3, C3-P3, and P3-O1), hemisphere (left, right) and birthorder (first, second born) as within pairs factors and with sex and zygosity as between factors. To test for sex and zygosity effects the MANOVA was carried out without the DOS group.

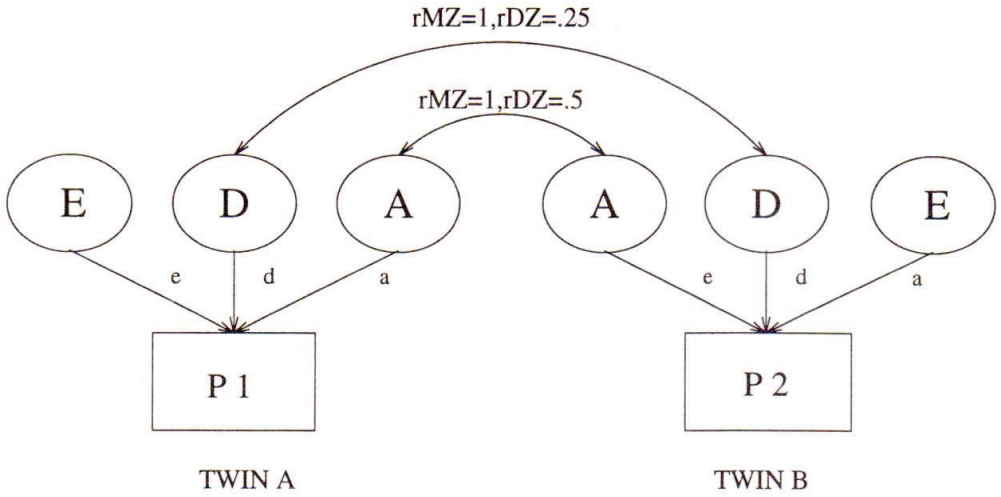


Figure 5.1 Univariate genetic model. a,e and d are the loadings of observed phenotype in twin 1 and twin 2 (P1 and P2) on the latent factors A (additive genetic), D (genetic dominance) and E (nonshared environment) and indicate the degree of relationship between the latent factors and the observed phenotypes.

Genetic Analyses

The correlations for MZM, DZM, MZF, DZF and DOS were computed for the coherence of each electrode combination and in each frequency band. The relative contributions of genetic influences to individual differences in EEG parameters were estimated by the method of genetic model fitting (Neale & Cardon, 1992; Eaves et al., 1978; Boomsma & Gabrielli, 1985). In genetic model fitting the total variation in the observed phenotype (P) is decomposed into genetic and environmental variance. The genetic variance may be due to additive (A) or dominance (D) factors; the environmental variance to environmental factors shared by twins reared in the same family (C) and nonshared environmental factors (E). The path diagram of a twin model is depicted in Figure 5.1. The genetic factors are correlated one in MZ twins, as they are genetically identical. For DZ twins, the additive genetic factors are correlated .5, because DZ twins share on the average half of their genes. The genetic effects due to dominance correlate .25 in DZ twins. Environmental influences shared by twins reared in the same family may also contribute to the variation in a trait. In the model the genetic dominance is then replaced by the shared environment (C) factor. D and C cannot both be estimated with twin data only. The correlation for the shared environmental factor in both MZ and DZ twins is one. The parameters *a*, *d (or c)* and *e* are loadings of the observed phenotype on the latent factors A, D (or C) and E and indicate the degree of relationship between the latent factors and the observed

phenotype. The proportion of the variation accounted for heritability or environment influences is calculated by squaring the parameters *a, d (or c*) and *e*, and dividing them by the total variance ($a^2 + d^2 + e^2$).

To estimate the parameters *a*, *d* (*or c)* and *e* for the coherence of each electrode combination, the data of twin1 and twin2 were summarized into 2x2 variance-covariance matrixes, computed by Prelis (Jöreskog & Sörbom, 1986). Mx (Neale, 1994) was used to test the fit of the univariate twin model for the coherence of each electrode combination by the method of maximum likelihood. Mx yields a chi-square (χ^2) goodness-of-fit statistic which assesses the overall goodness-of-fit of the model (Heath et al., 1989; Neale & Cardon, 1992). The overall χ^2 indicates the agreement between the observed and the predicted variances and covariances in the 5 sex by zygosity groups. A large χ^2 indicates a poor fit, while a small χ^2 indicates that the data are consistent with the model. Submodels were compared to the full models to test the significance of the latent factors D (or C) and A using hierarchical χ^2 tests. The chi-square statistic is computed by subtracting the χ^2 for the full model from that for a reduced model. The degrees of freedom (df) for this test are equal to the difference between the df for the full and the reduced model.

Sex differences in genetic architecture can be the result of differences in magnitude of the genetic effects and/or environmental experiences or in total variance. Another possibility is that different genes are expressed in males and females. To test the possibility of a different magnitude a model which constrains the genetic and environmental estimates to be the same for males and females was compared with a model which allowed for different estimates in males and females. In a scalar model the heritabilities are constrained to be equal across sexes, but in which total variance may differ. In the scalar model, the variance components for males are constrained to be equal to a scalar multiple of the female variance components. The third hypothesis was tested by estimating the genetic correlation between the DOS twins, instead of fixing it at .5. An estimate of this correlation that is significantly lower than .5 indicates that genetic influences on EEG coherence that are expressed in males, are imperfectly correlated with genetic influences that are expressed in females.

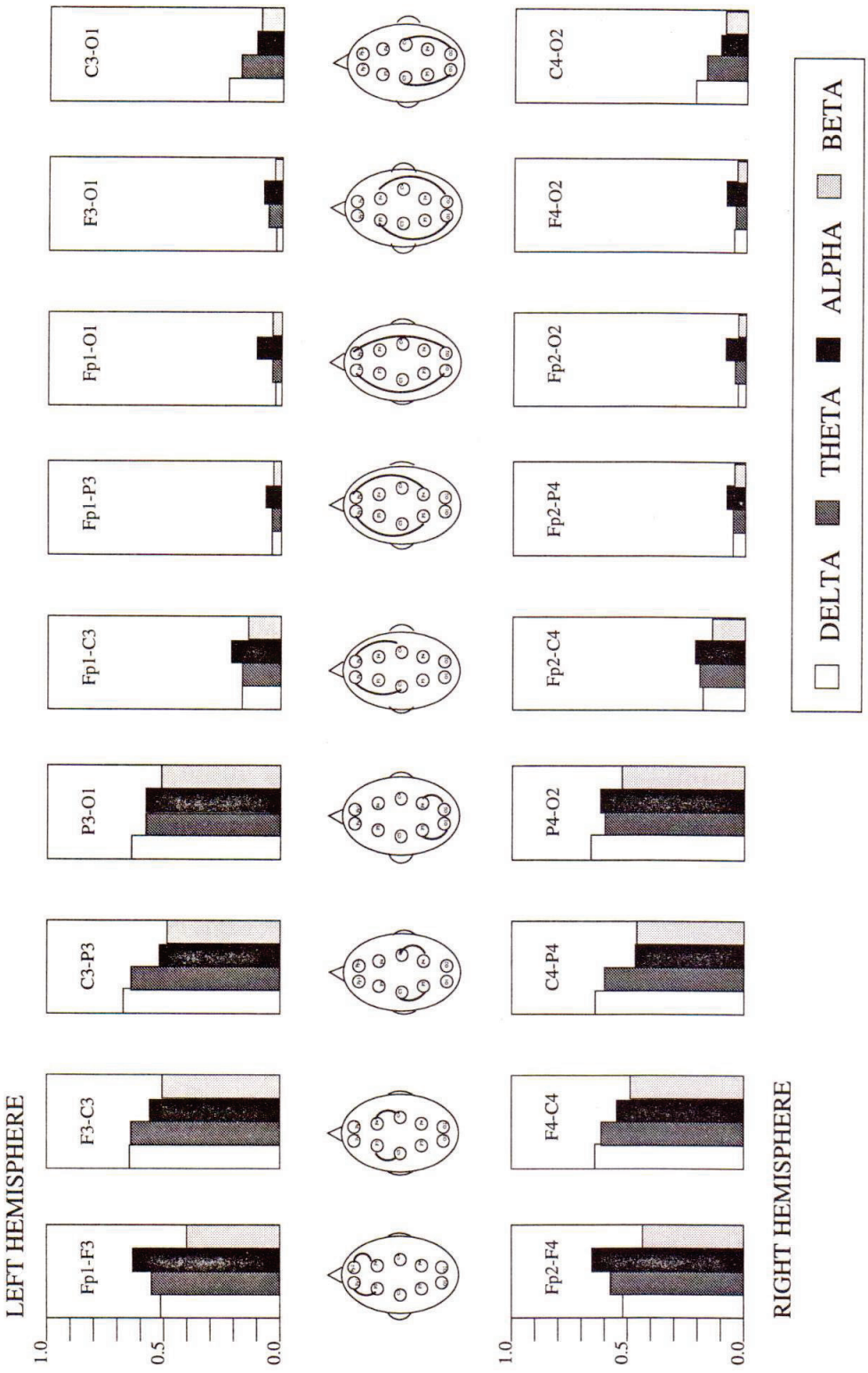


Figure 5.2 Mean values of the untransformed coherence for all electrode-combinations for 4 frequency bands (delta, theta, alpha, and beta). The scaling is from 0 to 1.

Results

Mean Data

Figure 5.2 presents the coherence for the electrode combinations for each frequency band in the left and right hemisphere across all subjects. The mean coherence of all frequency bands decreased as the interelectrode distance increased. Higher coherences were found for the shorter distances. On first sight the coherences in the left and right hemisphere showed no mean differences. Manova showed no significant main effect of hemisphere in any of the frequency bands. A significant sex effect was found for all bands (alpha, $F(1/157)=6.91$, $p<.009$; delta, $F(1/151)=5.65$, $p<0.019$; theta, $F(1/155)=19.57$, $p<.000$; beta, $F(1/149)=13.97$, $p<.000$). For most electrode combinations in all frequency bands the coherence in females was larger than the coherence in males. There were no significant main effects of birth order and zygosity and no significant interactions of zygosity by sex, except a small sex by zygosity interaction for delta ($F(1/151)=4.17$, $p<.043$).

Genetic Analyses

The MZ and DZ in female and male twin pairs correlations are given in Table 5.1. Generally, for all electrode combinations in all frequency bands, the correlations for MZ twins were higher than the DZ correlations. The higher MZ correlations point to the influence of genetic factors. The DOS correlations were the same as the same-sex DZ correlations, suggesting no sex differences in the genetic architecture. Table 5.2 presents the chi-squares for the best-fitting models for each electrode combination of the left and right hemisphere. The chi-square indicates the goodness-of-fit, the smaller the χ^2 the better the agreement of the observed data with the model. For most electrode combinations the fit of the model was good (χ^2 of 6.26, gives a probability of .85) to reasonable (χ^2 of 15, gives a probability of .30). The heritabilities are displayed in Table 5.3. The details of each frequency band are discussed below.

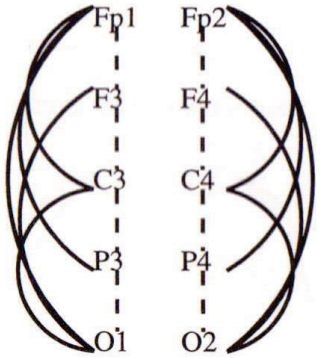
Table 5.1 MZ and DZ twin correlations for electrode combinations for the left and right hemisphere. Above each column the number of twins is given.

	left/right	left/right	left/right	left/right	left/right
DELTA	mzm (35)	dzm (34)	mzf (50)	dzf (36)	dos (44)
longer distances					
Fp-O	.21/.30	.39/.31	.29/.31	.29/.19	.10/-.01
Fp-P	.39/.53	.05/.17	.31/.39	.20/.09	.08/.35
F-O	.60/.51	.14/.28	.34/.36	.46/.36	.12/.05
Fp-C	.70/.51	.14/.22	.50/.49	.22/.13	.13/.21
C-O	.67/.58	.10/.05	.43/.47	.34/.41	.37/.36
shorter distances:					
Fp-F	.51/.50	.32/.29	.56/.55	.28/.39	.15/.53
F-C	.70/.60	.31/.17	.36/.57	.04/.30	.32/.32
C-P	.72/.60	.14/.10	.39/.51	.02/.25	.27/.12
P-O	.63/.18	-.01/.10	.45/.46	.36/.25	.41/.26
THETA	mzm (37)	dzm (35)	mzf (51)	dzf (36)	dos (45)
longer distances					
Fp-O	.79/.74	.26/.02	.62/.64	.34/.28	.24/.24
Fp-P	.36/.38	.53/.31	.55/.54	.27/-.04	.23/.28
F-O	.58/.62	-.04/.02	.59/.54	.26/.-.07	.10/.18
Fp-C	.59/.64	.58/.35	.76/.78	.23/.16	.40/.48
C-O	.73/.75	.20/.11	.58/.64	.38/.39	.37/.49
shorter distances:					
Fp-F	.66/.62	.58/.47	.76/.74	.41/.44	.41/.48
F-C	.60/.68	.49/.24	.56/.56	.01/.20	.11/.39
C-P	.76/.71	.35/.33	.55/.62	.19/.22	.27/.20
P-O	.61/.58	.20/.28	.50/.51	.28/.48	.26/.36
ALPHA	mzm (37)	dzm (35)	mzf (52)	dzf (52)	dos (46)
longer distances:					
Fp-O	.76/.89	.25/.25	.73/.72	.33/.29	.24/.34
Fp-P	.80/.81	.12/.15	.64/.60	.47/.38	.08/.02
F-O	.70/.86	.19/.19	.71/.73	.35/.41	.25/.32
Fp-C	.71/.68	.23/.12	.69/.82	.32/.37	.45/.53
C-O	.59/.59	.03/.10	.54/.63	.07/.05	.00/.15
shorter distances:					
Fp-F	.71/.71	.26/.19	.80/.88	.30/.47	.43/.44
F-C	.83/.69	.43/.11	.64/.68	.20/.24	.40/.39
C-P	.61/.65	.29/.32	.58/.57	.36/.21	.31/.07
P-O	.67/.73	.41/.21	.52/.48	.21/.23	.01/.20
BETA	mzm (34)	dzm (33)	mzf (50)	dzf (36)	dos (42)
longer distances					
Fp-O	.49/.61	.30/.27	.66/.69	.53/.34	.28/.36
Fp-P	.72/.72	.35/-.04	.54/.51	.44/.48	.23/.14
F-O	.51/.53	.11/.12	.59/.44	.09/.04	.17/.06
Fp-C	.70/.69	.46/.06	.68/.67	.50/.61	.21/.20
C-O	.57/.61	.29/.35	.64/.59	.55/.37	.22/.39
shorter distances:					
Fp-F	.51/.75	.26/-.13	.59/.65	.43/.31	.11/.05
F-C	.60/.60	.28/.09	.64/.58	.38/.40	.38/.25
C-P	.65/.64	.17/.38	.68/.65	.58/.30	.21/.26
P-O	.52/.57	.25/.43	.55/.51	.14/.29	.17/.31

Table 5.2 Chi-squares of the AE model, the best fitting model (df=13) for all electrode combinations and four frequency bands. ** refer to a scalar AE model (df=12), and *** refer to an ADE model (df=12).

CHI-SQUARES AE MODEL

	DELTA	THETA	ALPHA	BETA
LONG				
Fp1-O1	19.31	9.33	8.33	12.69
Fp1-P3	15.77	11.75	15.65	8.39
F3-O1	14.85	15.78	7.72	16.83
Fp1-C3	11.80	15.45	9.68	15.25
C3-O1	16.00	24.59	23.96	7.28
SHORT				
Fp1-F3	7.61	9.97	13.99	34.32
F3-C3	16.00	11.79	16.33	13.90
C3-P3	27.15	13.18	19.09	14.37
P3-O1	13.39	12.91	20.15	11.14



ELECTRODE COMBINATIONS

long distances

short distances

	DELTA	THETA	ALPHA	BETA	
LONG					
	19.85	14.22	11.65	6.12	Fp2-02
	20.80	10.38	17.78	17.89	Fp2-P4
	16.68	16.41	18.47	27.63	F4-O2
	23.36	8.51	17.80	21.64	Fp2-C4
	14.56	18.81	18.56	10.36	C4-O2
SHORT					
	18.22	14.41	23.28	25.48***	Fp2-F4
	9.61	8.82	11.26	18.47	F4-C4
	27.25	13.94	15.90**	14.28	C4-P4
	15.29	14.61	24.94	5.20	P4-O2

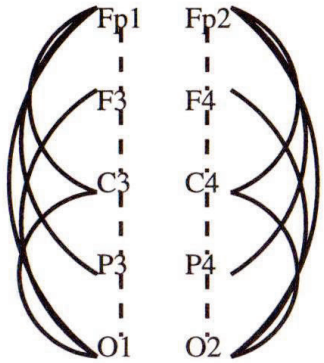
** AE scalar model

*** ADE model

Table 5.3 Heritabilities for all electrode combinations and four frequency bands.

HERITABILITIES

	DELTA	THETA	ALPHA	BETA
LONG				
Fp1-O1	28	69	71	65
Fp1-P3	30	48	67	62
F3-O1	44	52	68	50
Fp1-C3	52	70	67	70
C3-O1	55	60	47	60
SHORT				
Fp1-F3	52	73	77	58
F3-C4	46	54	68	62
C3-P3	49	60	55	65
P3-O1	52	51	54	53



ELECTRODE COMBINATIONS

——— long distances

– – – short distances

	DELTA	THETA	ALPHA	BETA	
LONG					
	28	68	77	68	Fp2-O2
	41	43	65	56	Fp2-P4
	43	48	74	40	F4-O2
	41	73	73	66	Fp2-C4
	56	68	56	62	C4-O2
SHORT					
	54	69	81	67	Fp2-F4
	54	59	64	58	F4-C4
	53	62	56	62	C4-P4
	36	52	54	52	P4-O2

Delta. For all electrode combinations an AE model gave the best fit to the observed data, suggesting that genetic influences play a role in the individual differences in coherence. No sex differences in genetic architecture were found. The amount of variance explained by genetic factors is shown in Table 5.3. For the coherences over the short distances the heritability, averaged over all electrode combinations in the left and right hemisphere, was 50%. For combinations over longer distances in left and right hemisphere, 40% of the variance in individual differences in delta coherence was explained by genetic factors.

Theta. The MZ correlations for EEG coherence in theta frequency band were about twice the DZ correlations and both the MZ and DZ correlations were higher than the correlations found for the delta band. With model fitting no sex differences in heritability were found. For all electrode combinations the best fitting models were AE models. The fit of these models was passably good. The percentage of variance explained by genetic factors, averaged over all electrode combinations, was around 60% for both hemispheres. No differences in heritability existed for coherences calculated over shorter and longer distances.

Alpha. The MZ and DZ correlations for EEG coherence could be compared to those of the theta band; the MZ correlation was twice the DZ correlation. AE models without sex differences were the best fitting models. For the C4-P4 an AE scalar model was found, indicating that there was a significant difference in variance for males and females. Averaged over all electrode combinations the contribution of the genetic factors to the variance was around 65% for the left and right hemisphere. For longer and shorter distances the differences in heritability were not large, the lowest heritabilities were found for C-O, C-P and P-O connections.

Beta. The MZ correlations for the EEG coherence in the beta band were almost the same as the MZ correlations for alpha and theta. AE models were again the best fitting models. Additive genetic factors explained more than the half of the variance. Averaged over all electrode combinations, 60% of the variance is explained by genetic factors. No differences in heritability existed for coherences calculated over shorter and longer distances. For the combination Fp2-F4 dominance was found. No sex differences were found.

Discussion

To our knowledge, this is the first large study that investigated the contribution of genetic and environmental influences to individual differences in coherence. Sex differences in genetic architecture were systematically examined by including males

and female twin pairs in the analysis. The main finding of this study is that for all frequency bands at least 50% of the variance of the individual differences in coherence is explained by genetic factors. The largest amount of variance explained by genetic factors was found for the coherences in the higher frequency bands. The heritability, averaged over all electrode combinations was .60, .65 and .60 in the theta, alpha and beta frequency band respectively. The heritabilities were somewhat lower for the delta frequency band. The heritabilities of the coherence calculated over short and long distances did not differ, and the heritabilities for left and right hemisphere also seemed equal. Coherence yields a distinct aspect of brain activity, it is suggested as a measure of the degree to which there are axonal connections among brain areas. This would mean that in 16 years-old subjects at least 50% of the variability in the connections among brain areas can be explained by genetic factors. The observed heritabilities for coherence are somewhat lower than the heritabilities for EEG power spectra obtained in the same group of twins. For all electrode positions and frequency bands, the heritability of EEG power spectra, measured during rest, was around .85 (Van Beijsterveldt et al., 1996). The lower heritability of the coherence, as compared to power, is most likely a result of the lower reliability of coherence. The upper bound of the estimated heritability is limited by the reliability of a trait, because heritability is calculated as the variance accounted for genetic factors divided by the total variance of the trait. A high measurement error would lower the heritability. A few earlier studies have measured the reliability of the coherence (Gasser et al., 1987; Dunkin et al., 1994; Harmony et al., 1993). The results were obtained in very different samples of subjects, with different ages and population group (children, clinical group) and the time between the measurements varies. With a time-interval of one year, Gasser et al. (1987) found in a young group of subjects test-retest correlations of .40, in an older group (mean age 72 years) the test-retest correlation was around .60. Thus it seems that the test-retest correlations of the EEG coherence are lower than the test-retest correlations normally obtained for EEG power (Gasser et al., 1987; Pollock et al., 1991; Salinsky et al., 1991). If coherence is indeed less reliable than the EEG power, the estimate of heritability of the coherence will tend be lower, given that the heritability is dependent on the total variance.

Although we do not have yet data to measure test-retest correlations our sample, we can infer reliability from the MZ correlations. The MZ correlation can be regarded as an indication of the lower bound of the test-retest reliability, since the MZ correlation can not exceed the correlation of the same subject measured on two occasions. This would mean that the reliability of the coherence should be at least is .7 in the alpha frequency band and be somewhat lower in the other frequency bands. A larger measurement error for coherence than for EEG power could be due to more statistical variability or to larger sensitivity for coherence to the state of the subject. Although, all subjects were measured under the same conditions and did receive the

same instructions, the impact of the experimental procedure may differ among subjects. The lower heritabilities found in the delta frequency band are probably caused by eye movements, increasing the measurement error. The eye-movement artifacts are especially a problem for the lower bands, because most eye-movement artifacts are below 6 Hz (Gasser et al., 1995). Lower heritabilities were also obtained for the delta EEG power spectra. A study of Ibatoullina et al. (1994) is the only work, known to us, investigating genetic and environmental influences on coherences. They calculated heritabilities for interhemispheric coherences from 20 MZ and 17 DZ twin pairs, aged 5 and 6 years old. For most combinations of electrode pairs the contribution of genetic influences to the coherence was low. In our laboratory a twin study is conducted with an age comparable to the twins of Ibatoullina et al. (Van Baal et al., 1994). For 200 twin pairs the coherence of the theta frequency, the dominant frequency band in younger children, was analyzed along the anterior-posterior axis. The first results pointed to genetic influences for the various intrahemispheric connections. The heritabilities were somewhat lower than in our 16-year old twin pairs, but significantly higher than observed in study of Itatoullina (1995). Therefore, the low genetic contribution to the individual differences in intrahemispheric connectivity in the study of Itatoullina is probably due to the lower reliability of the estimated coherence. The coherence was calculated over five 5-sec epochs, and the accuracies of coherence estimates depend on the number used in the average (Nunez, 1995). Coherence, estimated with a larger number of epochs, has a higher reliability.

Thus, for most frequency bands, averaged over all combinations of electrode pairs a large part of the variance is explained by genetic factors. The remainder of the variance is explained by nonshared environmental influences. Various studies (Benno, 1990; Wiesel, 1994) have reported the interaction of genetic and the environmental experiences during the development of the brain. In the introduction we have suggested that in addition to genetic factors, effects of specific experiences can account for individual differences in EEG coherence. However, the large influence of genetic factors to individual differences of the coherence precludes supposedly the contribution of epigenetic processes to coherence. Coherence is probably a relatively rough measure of neural connectivity. It may be that epigenetic processes became only of importance on a more detailed level. A large part of the nonshared environmental factor probably exists of measurement error and thus the estimate of the nonshared environmental may be inflated. In the univariate model it is not possible to make a distinction between stable environmental influences and measurement error. Using information over the reliability of the coherence of the same sample may resolve this issue.

Sex-differences

The finding of sex differences for mean coherences agrees with previous findings (Flor-Henry et al., 1987; Marosi et al., 1993). These studies used different ages, different methods of EEG recording and processing, and different combinations of electrode pairs, so the direction of the differences in coherences between females and males is not completely consistent. Flor-Henry et al. (1987) measured the coherence during rest and task conditions, in all conditions there was a significant difference between males and females; females showed higher intra- and interhemispheric coherences. In a sample of subjects of younger age (ranging in age from 7.6 to 13.3 years), females had higher right intrahemispheric coherences values than males in all frequency bands (Marosi et al., 1993). Differences for interhemispheric coherences were slight, with higher interhemispheric coherences for girls in all frequency bands, except for alpha, for this band the interhemispheric coherence in boys was higher. In our study, a significantly main effect of sex was found for all frequency bands. Comparison of coherence mean values of males and females, revealed for almost all combinations of electrode pairs higher coherences in females. These sex differences could be a result of suggested sex differences in structural brain organization. For example, sex differences have been suggested in the size and shape of the human corpus callosum (Steinmetz et al., 1995), the amount of gray matter (Gur et al., 1982). A larger ratio of white to gray matter would yield a pattern of higher connectivity among brain areas.

Elaborate models were fitted that tested specified sex differences in the genetic architecture of coherence. In spite of the phenotypic differences, no evidence was found for sex differences in genetic influences. Heritabilities were equal in male and female and the same genetic influences are expressed in males and females.

Left/right hemisphere differences in mean coherence

Larger coherences in the right hemisphere than in the left hemisphere have been found in various studies (Thatcher et al., 1986; Tucker et al., 1986). Tucker et al. (1986) calculated multiple coherences (representing the variance in one channel shared with all other channels together), measured during rest, for 14 right-handed males, and they found larger coherences in the right hemisphere. In a large group of children, Thatcher et al. (1986) found also higher coherences in right hemisphere locations compared to the left hemisphere locations. It is suggested that coherence should be larger in the right hemisphere because the proportion white matter to the gray matter is larger in the left hemisphere (Gur, 1980), which could be indicative of a larger "interconnectivity" among regions in the right hemisphere. In contrast with these studies, we did not find a significant main effect of hemisphere for any of the frequency bands. Possibly due to the fact that our study included both left- and right-handed subjects in the sample.

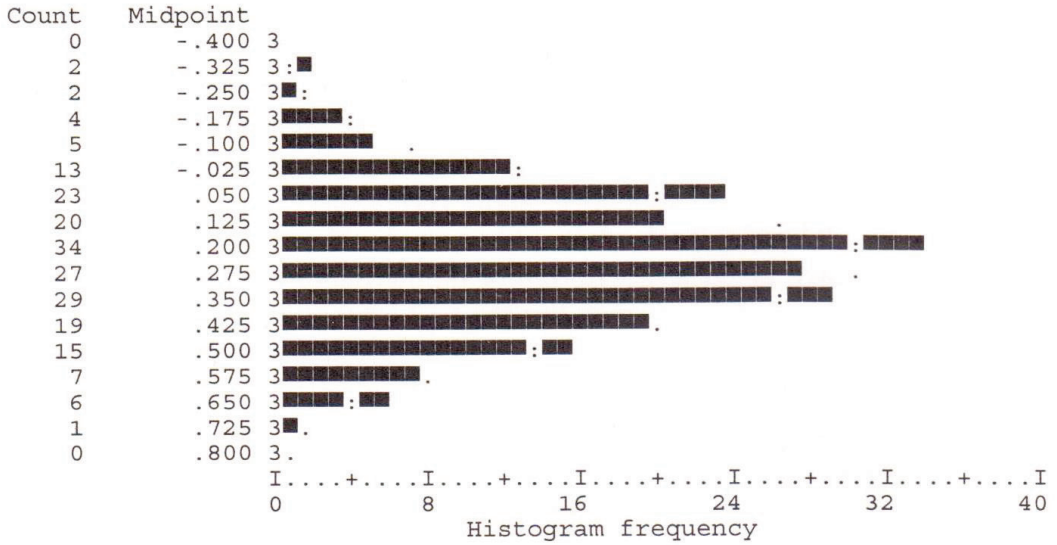
Variability

In general, the mean value of the EEG coherence, as depicted in Figure 5.2, showed moderate values, especially the values for the longer distances were low. Thus, the shared variance is small between areas over longer distances. The low average value of the coherence may raise the question if it is worthwhile to use such low coherences in the genetical analysis. To answer this question, a histogram of the estimated coherence over a short and long distance is depicted in Figure 5.3. It may be that for coherence at a longer and a shorter distance the variance is equally spread and is large enough to indicate interindividual differences in coherences for both short and long distances. This variability suggests that for some subjects the connections between areas over a longer distance are well established and not for other subjects.

Conclusion

In this paper we have given a description of the heritability of coherence for 4 frequency bands, obtained during rest. It is the first large study that dealt with the genetic contribution of individual differences in brain coherence. For all electrode combinations in the four frequency bands, a substantial part of the variance of the individual differences of coherence is explained by genetic factors. Sex differences in genetic architecture were systematically investigated. However, no differences between males and females in the heritabilities were obtained. The heritability of the coherence estimates is lower than of the EEG power spectra obtained in the same group of twins. Most likely the larger measurement error of the coherence inflates the nonshared environmental factor and thus lowers the heritability.

A. Histogram of the combination of electrode-pair Fp1-F3, alpha frequency



B. Histogram of the combination of electrode-pair Fp1-P3, alpha frequency

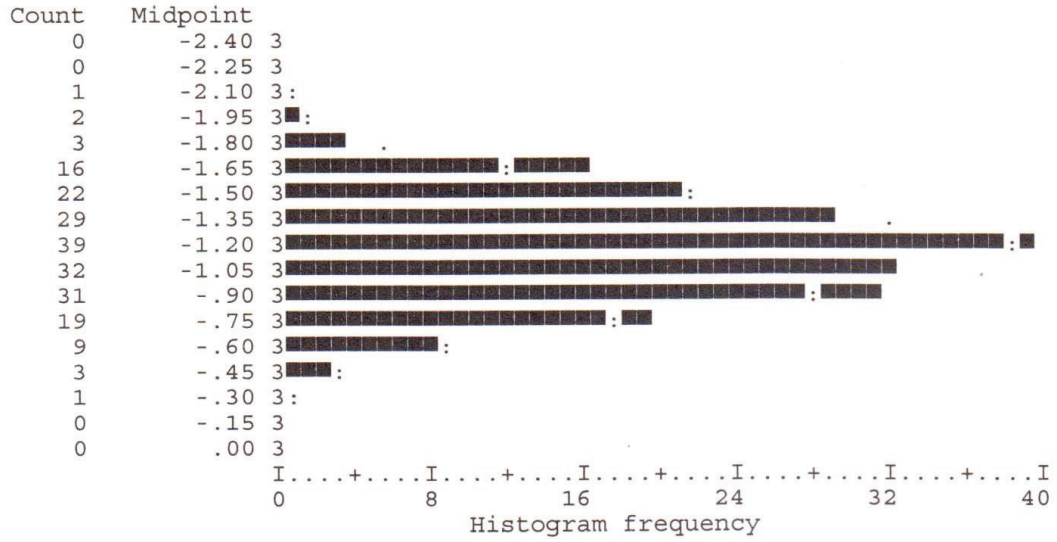


Figure 5.3 Two examples of variability in the EEG coherence. Figure A is an example of EEG coherence of an electrode-pair over a short distance and figure B an example of EEG coherence of an electrode-pair over a long distance. Since the EEG coherence is log-transformed, values can be negative.

6

Summary and conclusions

The present study investigated the genetic and environmental contributions to individual differences in three indices of the central nervous system (CNS); EEG power, P300 amplitude and EEG coherence. EEG power and coherence were obtained during quiet resting, and P300 amplitude was measured during a simple oddball task. In the experiment 213 twin pairs (aged 16 years) participated twice, with one and half year in between. The thesis dealt with the genetic analyses of the data obtained on the first occasion, and the descriptive statistics of both measurements.

Behavior genetics is interested in the problem whether and to what degree individual differences of human behavior are influenced by genetic factors. For most behaviors genetic influences are substantial. They contribute to cognitive abilities, most personality traits, but also to psychopathological behaviors like schizophrenia, alcoholism and psychoses (Plomin et al., 1990). Because behavior is in continuous interaction with the environment, the mechanism of genetic involvement in human behavior is a complex issue to study. Genetic influences on behavior are most likely to be expressed via the brain. Therefore, by studying human brain functioning it may be possible to find an explanation for the genetically determinated influences on behavior. For behavioral traits such as cognition, several studies indicate that slight genetic effects early in the development are magnified as development proceeds, creating increased genetic variance while genetic covariance remains high. It may be that genetic differences in neuroanatomy or neurophysiology early in life could cascade into increasingly larger behavioral differences among children as life goes on (Plomin, 1986, p. 328). Until now, there is not much information about the heritability of neurophysiological indices.

Chapter 2 presented a review of the twin and family studies of normal variation in the human EEG and ERPs. The discussion of chapter 2 listed several issues that deserved more attention in the quest for the genetically mediated differences in the CNS functioning. An issue that deserved attention is, that most of genetic studies of EEG/ERP have employed comparisons of correlations between relatives as their main method of genetic analysis. Almost no twin study of EEG/ERPs parameters applied the more powerful method of genetic model fitting, although this approach

provides many advantages (Eaves et al., 1978). Model fitting methods yield formal tests of the significance of genetic factors, tests of significance of sex differences in genetic architecture, and a relatively straightforward extension to multivariate analysis.
The present study has taken these issues into account. Most important, a large number, 213, twin pairs participated in the study. Furthermore by including female and male MZ and DZ twin pairs and DZ opposite-sex twin pairs, it was possible to test for sex differences in genetic architecture. Brain activity was measured on 14 brain locations and multivariate analyses have been applied to the EEG alpha band and P300 amplitude, allowing more insight into the underlying genetic factors of the covariances among brain areas.
In the next paragraph the results of the genetic analyses of EEG power, P300 and coherence of the first measurement are discussed with respect to the following issues: heritabilities in the different brain areas, multivariate genetic analysis, and sex differences. In the next paragraph methodological issues are considered. In third paragraph the stability of phenotypic values of the EEG/ERP parameters and the genetic stability are discussed.

Heritability estimates of measurement on time 1

The neural indices obtained in the 16-year old subjects showed a high heritability. A large part of individual differences in brain activity could be explained by genetic factors. The averaged heritability of the EEG power is above 80%, of the EEG coherence around the 60%. The brain response to a stimulus, obtained during the oddball task showed, however, a less clear result. Though clear familial resemblance for the P300 amplitude was found, no distinction could be made between the resemblance attributable to genetical or to shared environmental factors. For the P300 latency no heritable influences were found.
The environmental influences on the individual differences of the EEG power and EEG coherence consisted of influences nonshared within twin pairs. The mode of the inheritance of EEG power and coherence was additive. For some brain areas of the beta frequency the heritability consisted of additive genetic factors and genetic dominance.

Heritabilities of neural indices measured in different brain areas
EEG power varies as function of state of the subject and of the area of the brain over which the signals are measured. Figure 3.3 in chapter 3 presented the distribution of the EEG signals over the different brain areas, obtained during rest. It clearly shows the different distribution of frequencies and the larger amplitudes of the alpha frequency at the posterior positions and almost no EEG power for the

beta frequency band. The various brain areas seem to differ in anatomy and function. Also the function of the hemispheres seems to differ (Gur & Gur, 1987). If there are structural/functional differences among brain areas, different heritabilities could be expected. However, for EEG power the heritability is large in all brain areas and for all frequencies. The lowest heritabilities were found in the frontal areas of the lower frequency bands. It may be that eye-movements interfere with the frontal EEG activity and reduce the reliability and as a consequence lower the heritability estimates.
Little differentiation of the heritability was also found for the P300 amplitude and EEG coherence. For the P300 the genetic analysis was employed only to the central, parietal and occipital electrode positions. The results did not show large differences among these brain areas. EEG coherence was estimated for electrode-combinations along the anterior-posterior axis within a hemisphere for four frequency bands. Again, little differentiation of the heritabilities was found for various combinations of electrode pairs in the four frequency bands.
Thus, in spite of the anatomical and functional differences of brain areas, no differences in heritability in these brain areas were found for the three EEG/ERP parameters. Although it has been suggested that the variability in brain morphology is larger (and heritability lower) in the younger, frontal brain regions (Meshkova & Ravich-Shcherbo, 1982; Markowitsh, 1988), this is not reflected in the genetics of EEG/ERP measures.

Multivariate genetic analyses
Multivariate genetic analysis provides information on the causes of covariance among various brain regions, i.e. whether the covariance between two or more measures arises because they are influenced by the same genes or by the same shared environmental factors. Multivariate analyses were applied to EEG power and P300 amplitude.
The phenotypic correlations of the EEG power between the left and right hemisphere and among the various brain areas were very high. Therefore, it was investigated in chapter 3, whether this covariation is due to the same underlying genetic factors. From the results it appears that, for all frequency bands, the covariances between the left and right hemisphere seemed primarily determined by the same genetic factors. Within each hemisphere, the covariance among the various brain areas for the alpha frequency seems primarily determined by the same genetic factors. A high phenotypic correlation among brain areas within a hemisphere is also seen for the other frequency bands, most probably due to the same genetic influences. Since neurophysiological mechanisms of alpha rhythm generation are complex and involve different brain structures with a complex interaction between them (Steriade et al., 1990), the mechanisms of genotypic

influence on brain electric activity may be rather complex and may involve intermediate levels, such as, a morphological and a biochemical level.
For the amplitude of the P300 the multivariate analyses were used to test whether the same genes/shared environmental factors were expressed over the different brain areas. The genetic analysis was carried out for the frequently occurring stimuli, the nontargets, and the infrequently occurring stimuli, the targets. The results showed that individual differences in the P300 amplitude of both targets and nontargets were influenced by the same genetic/shared environmental influences. In addition, a likely second factor influenced the P300 amplitude in the occipital positions. If this second genetic factor for the targets is significant, then it could be used as a possible indicator of more than one neural generator of the P300. The multivariate genetic analysis was extended to include both kinds of stimuli in the analysis, to investigate whether the same structure of genetic/shared environmental factors influences the targets and nontargets. The results showed one factor underlying both targets and nontargets, but also a second factor with a higher loading for nontargets. This implies an interesting interaction between a psychological test condition and familial resemblances: the familial resemblances depended on information processing demands.

Sex differences
In the human brain structural and functional sex differences are suggested (Gur et al., 1995; Kimura, 1987). For example, using in vivo magnetic resonance morphology Steinmetz et al. (1995) found sex differences in size and morphology of the corpus callosum. Sex differences in hemisphere specialization of function have also been found (McGlone, 1980; Gur et al., 1982). In spite of these differences, brain activity obtained with EEG/ERP measures showed no consistent results regarding sex differences in means. In the study reported in this thesis, no sex differences in mean EEG powers were found. For the P300 a significant interaction between sex and condition was found: females had slightly larger amplitudes for the infrequent target stimuli than males. Males had slightly larger amplitudes for the nontarget P300. The EEG coherence showed significant differences between males and females. The sex differences were significant for all four frequency bands. For most combinations of electrode pairs the coherence was larger for females than for males.
This is the first study that explicitly tested sex differences in the genetic architecture of individual differences. Models were used to test for sex differences in the magnitude of genetic influences and to test whether the same genes were expressed in males and females. For EEG power and EEG coherence, the analysis of individual differences in brain activity did not show sex differences in genetic architecture. Except, in some brain areas the heritability of EEG power was lower in females than in males. The differences in heritabilities, however, were very

small. No indication was found that different genes were expressed in males and females. For the EEG coherence no sex differences in genetic architecture were found.
The relative contribution of the genetic and/or environmental factors to the P300 amplitude differed in males and females. Although the nearby zero correlations of the opposite twin pairs suggested a different source for the familial resemblance in males and females, model fitting did not find any evidence for this hypothesis. An interpretation of these sex differences in terms of genetic and/or environmental factors is not possible. Although clear familial resemblance for the P300 amplitude was found, was it not possible to determine whether these familial resemblances are due to genetic or due to shared environmental factors. The problem of resolving whether the familial resemblance for the P300 amplitude is genetic or not, probably lies in statistical power, this topic is discussed in the next paragraph.

Methodological issues

Statistical power of the twin study
The statistical power of a twin study depends on a number of factors, these include the number of twin pairs and the size of effect of the heritability or shared environmental factors in the population being studied (Neale and Cardon, 1992). Genetic analysis of the P300 amplitude showed clear familial resemblance, nonetheless with the current data set it was not possible to distinguish whether this resemblance was attributable to genetic or shared environmental factors. Probably no optimum statistical power was achieved to detect the presumably smaller genetic and/or shared environmental effects. In Table 6.1 the number of subjects is depicted that is required to reject the false model with a statistical power of 80%. The heritabilities of 80%, 60%, and 40% are values based on the heritabilities obtained for EEG power, P300 amplitude, EEG coherence, respectively. A CE model (=model with as latent factors shared and nonshared environmental factors) without sex differences was fitted to data that were simulated with an actual AE model (model with additive genetic factors and nonshared environmental factors).

Table 6.1 Number of subjects required to reject, at the .05 level and 80% power, a CE model when the true model is AE and the ratio MZ to DZ pairs is 1:1. h^2 refers to true heritability

$h^2 = 80\%$	52
$h^2 = 60\%$	180
$h^2 = 40\%$	597

With 52 twin pairs a statistical power of 80% is obtained to detect a trait which is largely determined by (h^2=.80) genetic influences. To detect a smaller heritability of about 40%, a larger set of twin pairs is required. To make a distinction between genetic and shared environmental factors for the P300 amplitude a larger sample thus will be needed. Alternatively statistical power can be increased by considering measurement error in the phenotype. For 60% and 80% heritability the sample size used in this study was clearly sufficient, however to detect a 40% heritability it was too small.

Implications of reliability for the heritability

Split-half correlations are informative for the heritability. The reliability of a trait sets an upper limit to its heritability (Falconer, 1981). Heritability is calculated as the variance accounted for genetic factors divided by the total variance (Va/(Va+Vc+Ve)). Because the Ve part includes both the nonshared environment and the measurement error, a high measurement error could give a biased picture of the heritability. In the review of the twin and family studies about the EEG and ERP it was already noticed that the reliability of the ERP is lower than that of the background EEG.

In this thesis the heritability of the EEG power, P300 amplitude and EEG coherence was estimated with traditional genetic models. In the traditional method the nonshared environmental factor includes the measurement error. Inclusion of reliability data would allow for explicit representation of assumptions about measurement error. For the EEG power the proportion of total variance accounted by measurement error is very small, so no large effect of separately estimating the measurement error is expected on the heritability. However, as the split-half correlations indicate, the effect of measurement error on the P300 amplitude is larger. If the heritability would be estimated from the proportion of reliable variance, the heritability would be enlarged by only analyzing the reliable part of the variance in the genetic model. Likely, the nonshared environmental part of the EEG coherence is also inflated by the measurement error. The split-half correlations of the combinations of electrode pairs over longer distances of the delta and theta frequency bands were lower than of the alpha and beta band. For these bands the heritability, corrected for measurement error, is probably higher than it was estimated in chapter 5.

Stability

Stability of phenotypes values

For EEG power, high test-retest correlations for all electrode positions of the four frequency bands were found, especially for alpha frequency. For each electrode position of the alpha frequency the test-retest correlation was above .8. Lower test-retest correlations wer found for the frontal electrode positions of the delta frequency. Possible contamination of eye-movements, which are in the same range of the delta frequency, could account for these low test-retest correlations. However, the period between the two measurements concurs with a period of maturation in the frontal lobes (Thatcher et al., 1987; Hudspeth & Pribram, 1992; Buchsbaum et al., 1992). Different rates of development changes could account for these lower test-retest correlations (additional variability).
In contrast with the EEG power, the test-retest correlations obtained for the P300 amplitude are lower (see appendix). For target P300 the test-retest correlation was, averaged over all leads, .6. For the nontarget amplitude similar correlations were found. These correlations agree with those obtained by Segalowitz and Barnes (1993). In the same age group (15 years) and with a comparable time-interval (2 years) they found for the target P300 amplitude a correlation of .62. Polich (1986) and Fabiani et al. (1987), however, reported higher test-retest correlations. The stability is smaller than obtained for the EEG power, which is probably due to the lower reliability, as the split-half correlations were also lower than for the EEG power.
Concerning the magnitude of the test-retest correlations, EEG coherence occupy a midposition between EEG power and P300 amplitude. As far as we know, only three earlier studies mentioned the test-retest correlations. However, the test-retest correlations were calculated in very different subject samples (children, patients and normal adults) with different methods to estimate the EEG coherence. The values for the test-retest correlations fluctuate from .4 to .8. (Gasser et al., 1987; Dunkin et al., 1994; Harmony et al., 1993). In the present study the test-retest correlations vary per frequency band and electrode combination. For alpha reasonable correlations have been found, varying between .7 and .8. Stability was low for the combinations of electrode pairs over longer distances of the delta frequency, the split-half correlations were also low for these combinations of electrode pairs. Again, the interval between the two sessions was 1.5 years and the possibility exists that true changes are reflected in the size of the test-retest correlations. Preliminary, it can be concluded that the EEG parameters, obtained during quiet rest, are very stable characteristics, and that P300 amplitude is less stable, which most likely is due to its lower reliability.

Stability of genetic effects
Heritability is not a fixed parameter, but may change during life. That is, the relative contribution of genetic factors could increase as people grow older (as seems the case for IQ) or decrease (as seems the case for blood pressure). A change

in heritability need not mean a change of the molecular mechanism. For example, the heritability could increase even if the same genes were involved because the environmental influences decrease or because the effects of genetic factors are amplified. Conversely, the heritability can remain similar but different genes can affect the phenotype. A longitudinal design has the potential to study if the same genes contribute to the observed trait on different time-points. In this thesis the discussion on changes in heritability is limited to a comparison the twin correlations at both occasions and thus only gives a first impression of the stability of the size of the genetic influences. As we have already mentioned in the introduction looking only at twin correlations has limitations. Therefore it is only meant as first indication of the stability in heritability of the neural indices used in this study. In the appendix the twin correlations for the neural indices are given for the measurement at time 1 and time 2.
On first sight the twin correlations of the three neural indices used in the current study showed no large changes between the measurement for the 16-year-old and 17.5-year-old subjects. For P300, the male and female MZ correlations remain predominantly similar for the target and nontarget P300 amplitude. Only the female MZ correlations for the targets increase slightly. For EEG power, the only differences that are suggested are for delta and theta frequency bands and mainly in the prefrontal and lateral frontal electrode positions. The male MZ correlations decreased, suggesting lower influence of genetic factors on these electrode positions. The twin correlations of the other frequency band remained the same. Twin correlations for the EEG coherence in the alpha and beta frequency band did not differ between the two measurements. Differences occurred in the lower frequency bands, delta and theta. The MZ and DZ correlations became smaller at the second measurement, suggesting a lower genetic influence, especially those estimated from the prefrontal positions. Changes of the twin correlations may reflect real changes in heritability. However, in the lower frequency bands the reliability of these electrode-combinations was also low. This is a difficult problem, because in the age between 16 and 18, developmental changes are primarily expected in the frontal part of the brain, while in these brain areas it is more difficult to obtain reliable EEG parameters. On basis of these data it could be concluded that the heritability for the EEG/ERP parameters remains rather stable. If there are any changes in the heritability, these are rather small.

Final remarks

This thesis has focused on the genetic analysis of EEG/ERP parameters obtained in sixteen year-old twins. The results indicated that the individual differences in EEG parameters are mainly influenced by genetic factors. Especially the EEG power is a

highly genetic characteristic. With a heritability of over 80%, EEG power is one of the most heritable human traits. Of course, this does not tell us what the genes are that underlay brain function. To identify these genes linkage studies have to be carried out, that use both the recent developments in molecular genetics and DNA technology as well as the recent advantages in statistical methodology for genetic linkage between DNA markers and complex traits. In general, large numbers of sibling pairs (DZ twins) are needed to detect linkage between a quantitative trait locus (QTL) and a DNA marker, especially if the heritability of the trait is small. For EEG power the total heritability is large, and this is a favorable condition to start looking for linkage (Risch & Zhang, 1995). Our strategy to increase power to detect linkage is to analyze multivariate phenotypes or estimated individual genotypic values (Boomsma, 1996). This study has employed multivariate measures and together with the high heritabilities of these measures therefore offers promising possibilities to start looking for genes that influence brain activity.

This is the first longitudinal study of the genetics of neural indices of brain functioning, but the data of the second measurement are still to be analyzed. Therefore, some questions remain unanswered at his moment about the genetic influence on the development of the brain. However, the data are available to apply model fitting methods to test stability of the genetic and environmental factors. Also, it will be possible to investigate the genetic and environmental influences on the growth process of the brain themselves.

7

References

Anokhin, A. (1987). On the genetic nature of individual peculiarities of the whole-brain EEG organization. *The psychological Journal, 8,* 146-153.

Anokhin, A., Steinlein, O., Fisher, C., Mao, Y., Schalt, E. & Vogel, F. (1992). A genetic study of the human low-voltage electroencephalogram. *Human Genetics, 90,* 99-112.

Begeleiter, H., Porjesz, B., Bihari, B. & Kissin, B. (1984). Event-related brain potentials in boys at risk for alcoholism. *Science, 225,* 1493-1496.

Benes, M. (1989). Myelination of cortical-hippocampal relays during late adolescence. *Schizophrenia Bulletin, 15,* 585-593.

Benninger, C., Matthis, P. & Scheffner, D. (1984). EEG development of healthy boys and girls. Results of a longitudinal study. *Electroencephalography and Clinical Neurophysiology*, 57, 1-12.

Benno, R. (1990). Development of the nervous system: Genetics, epigenetics, and phylogenetics. In: M. Hahn, J. Hewitt, N. Henderson & R. Benno (Eds.). *Development behavior genetics. Neural, biometrical and evolutionary approaches* (pp. 113-143). New York: Oxford University Press.

Berger, H. (1929). Über das Electroencephalogramm des Menschen. *International Archives of Psychiatry, 87*, 527-570.

Boomsma, D. (1993). Current status and future prospects in twin studies of the development of cognitive abilities: Infancy to old age. In T. Bouchard Jr. & P. Propping (Eds.). *Twins as a tool of behavioral genetics* (pp.67-82). Chichester: John Wiley & Sons Ltd.

Boomsma, D. (1996). Using multivariate genetic modeling to detect pleiotropic quantitative trait loci. *Behavior Genetics, 26,* 1996, in press.

Boomsma, D. & Gabrielli Jr., W. (1985). Behavioral Genetic approaches to psychophysiological data. *Psychophysiology, 22,* 249-260.

Boomsma, D., Koopmans, J., VanDoornen, L. & Orlebeke, C. (1994). Genetic and social influences on starting to smoke: A study of dutch twins and their parents. *Addiction, 89,* 219-226.

Boomsma, D. & Molenaar, P. (1986). Using LISREL to analyze genetic and environmental covariance structure. *Behavior Genetics, 16,* 237-250.

Boomsma, D., Molenaar P. & Dolan C. (1991). Estimation of individual genetic and environmental profiles in longitudinal designs. *Behavior Genetics, 21,* 243-255.

Bouchard, T., Lykken D., McGue M., Segal N. & Tellegen A. (1990). Sources of human psychological differences: The minnesota study of twins reared apart. *Science, 250,* 223-228.

Bouchard, T. & Propping, P. (1993). *Twins as a tool of behavioral genetics*. Chichester: John Wiley and Sons.

Brillinger, D. (1975). *Time series. Data analysis and theory*. London: Holt, Rinehart and Winston Inc.

Buchsbaum, M. (1974). Average evoked response and stimulus intensity in identical and fraternal twins. *Physiological Psychology, 2,* 365-370.

Buchsbaum, M. (1993). Critical review of psychopathology in twins: Structural and functional imaging of the brain. In: T. Bouchard & P. Propping (Eds.). *Twins as a tool of behavioral genetics* (pp. 257-271). Chishester: John Wiley and Sons.

Buchsbaum, M., Landau, S., Murphy, D. & Goodwin, F. (1973). Average evoked response in bipolar and unipolar affective disorders: Relationship to sex, age of onset, and monoamine oxidase. *Biological Psychiatry, 7,* 199-212.

Buchsbaum, M., Mansour, G., Teng, D., Zia, A., Siegel, J., Benjamin, & Rice, D. (1992). Adolescent developmental change in topography of EEG amplitude. *Schizophrenia Research, 7,* 101-107.

Bulayeva, K., Pavlova, T. & Guseynov, G. (1993). Visual evoked potentials: Phenotypic and genotypic variability. *Behavior Genetics, 23,* 443-447.

Burgess, A. & Gruzelier, J. (1993). Individual reliability of amplitude distribution in topographical mapping of EEG. *Electroencephalography and Clinical Neurophysiology, 86,* 219-223.

Changeux, J. & Danchin, A. (1976). Selective stabilisation of developing synapses as a mechanism for the specification of neuronal networks. *Nature, 264,* 705-712.

Christian, J., Li, T., Norton, J., Propping, P. & Yu, P. (1988). Alcohol effects on the percentage of beta waves in the electroencephalograms of twins. *Genetic Epidemology, 5,* 217-224.

Claridge, G. & Mangan, G. (1983). Genetics of Human Nervous System Functioning. In: J. Fuller & E. Simmel (Eds.). *Behavior Genetics* (pp. 33-87). Hillsdale, New Yersey: Lawrence erlbaum associates Inc.

Courchesne, E. (1978). Neurophysiological correlates of cognitive development: Changes in long latency event related potentials from childhood to adulthood. *Electroencephalography and Clinical Neurophysiology, 45,* 468-482.

Courchesne, E. (1983). Cognitive components of the event-related brain potential: Changes associated with development. In: A. Gaillard & W. Ritter (Eds.). *Tutorials in ERP research: Endogenous Components* (pp. 329-344). Amsterdam: North-Holland Pusblishing Company.

Courchesne, E. (1987). A neurophysiological view of autism. In: E. Schopler & G. Mesibow (Eds.). *Neurobiological issues in autism* (pp. 285-324). New York, London: Plenum Press.

Davis, H. & Davis, P. (1936). Action potentials of the brain. *Archives of Neurology, 36,* 1214-1224. Dieker, H. (1967). Untersuchungen zur genetik besonders regelmassiger hoher Alpha-Wellen im EEG des Menschen. *Humangenetik, 4,* 189-216.

Donchin, E. & Coles, M. (1988). Is the P300 component a manifestation of context updating? *Behavioral and Brain Sciences, 11,* 357-427.

Donchin, E., Karis, D., Bashore, T., Coles, M. & Gratton, G. (1986). Cognitive psychophysiology and human information processing. In M. Coles, E. Donchin & W. Porges (Eds.). *Psychophysiology, systems, processes, and applications* (pp. 244-267). Amsterdam, Oxford: Elsevier.

Donchin, E., Ritter, W. & McCallum, W. (1978). Cognitivie psychophysiology: The endogenous components of the ERP. In: E. Callaway , P. Teuting & S. Koslow (Eds.). *Event-related brain potentials in man* (pp. 349-411). New York: Academic Press.

Duffy, F., Albert, M., McAnulty, G. & Garvey, J. (1984). Age-related differences in brain electrical activity of healthy subjects. *Annals of Neurology, 16,* 430-438.

Duffy, F. & McAnulty, G. (1990). Neurophysiological heterogeneity and the definition of dyslexia: Preliminary evidence for plasticity. *Neurophysiologica, 28,* 555-571.

Dumermuth, G. (1968). Variance spectra of electroencephalograms in twins. In: P. Kellaway & I. Petersen. *Clinical electroencephalography of children* (pp. 119-154). New York: Grune and Stratton.

Dunkin, J., Leuchter, A., Newton, T. & Cook, A. (1994). Reduced EEG coherence in Dementia: State or trait marker? *Biological Psychiatry, 35,* 870-879.

Dustman, R. & Beck, E. (1965). The visually evoked potential in twins. *Electroencephalography and Clinical Neurophysiology, 19,* 570-575.

Eaves, L. Eysenck, H. & Martin, N. (1989). *Genes, culture and personality: An emperical approach.* London: Academic Press.

Eaves, L., Last, K., Young, P. & Martin, N. (1978). Modelfitting approaches to the analysis of human behavior. *Heredity, 41,* 249-320.

Elston, R. & Stewart, C. (1971). A general model for the genetic analysis of pedigrees. *Human Heredity, 21,* 523-542.

Fabiani, M., Gratton, G., Karis, D. & Donchin, E. (1987). Definition, identification, and reliability of measurement of the P300 components of the event related brain potentials. In: D. Ackles, J. Jennings & M. Coles. (Eds.). *Advances in Psychophysiology, 2,* (pp.1-78.). Greenwich: JAI Press.

Falconer, D. (1981). *Introduction to quantitative genetics.* New York: Longman Scientific & Technical.

Fisher, R. (1918). The correlation between relatives on the supposition of Mendelian inheritance. *Transactions of the Royal Society of Edinbutgh, 52*, 399-433.

Fisher, K. & Rose, P. (1994). Dynamic development of coordination of components in brain and behavior: A framework for theory and research. In G. Dawson & K. Fischer. (Eds.). *Human behavior and the developing brain* (pp. 3-66). New York, London: The Guilford Press.

Flor-Henry, P. & Koles, Z. (1982). EEG characteristics of normal subjects: A comparison of men and women of dextrals and sinistrals. *Research Communications in Psychiological Psychiatric Behavior, 7*, 21-38.

Flor-Henry, P., Koles, Z. & Reddon, J. (1987). Age and sex related configurations in normal subjects. In A. Glass (Ed.). *Individual differences in Hemisphere Specialization (pp 121-148)*. New York: Plenum Press.

Ford, J. & Pfefferbaum, A. (1985). Age-related changes in ERPs. In P. Ackles, J. Jennings & M. Coles (Eds.). *Advances in Psychophysiology* (pp. 301-339). New York: JAI Press.

Friedman, D. (1988). Event-related potentials in populations at genetic risk: A methodological review. In J. Rohrbaugh, R. Parasuraman & R. Johnson Jr. (Eds.). *Event-related Brain Potentials. Basic issues and applications* (pp. 310-332). New York, Oxford: Oxford University Press.

Friedman, D., Boltri, J., Vaughan, H. & Erlenmeyer-Kimling, L. (1985). Effects of age and sex on the endogenous brain potential components during two continuous performance tasks. *Psychophysiology, 4,* 440-453.

Friedman, D., Cornblatt, B., Vaughan, H. & Erlenmeyer-Kimling, L. (1986). Event-related potentials in children at risk for schizophrenia during two continuous performance tests. *Psychiatric Research, 18,* 161-177.

Gasser, T., Jennen-Steinmetz, C. & Verleger, R. (1987). EEG coherence at rest and during a visual task in two groups of children. *Electroencephalography and Clinical Neurophysiology, 67,* 151-158.

Gasser, T., Sroka, L. & Möcks, J. (1985). The transfer of EOG activity into the EEG for eyes open and eyes closed . *Electroencephalography and Clinical Neurophysiology, 61,* 181-193.

Gasser, T., Verleger, R., Bächer, P. & Sroka, L. (1988). Development of the EEG of school-age children and adolescents. I. Analysis of band power. *Electroencephalography and Clinical Neurophysiology, 69,* 91-99.

Gasser, T., Jennen-Steinmetz, C., Sroka, L., Verleger, R. & Möcks, J. (1988). Development of the EEG of school-age children and adolescents. I. Topography. *Electroencephalography and Clinical Neurophysiology, 69,* 100-109.

Geisler, M. & Polich, J. (1992). P300, food consumption, and memory performance. *Psychophysiology, 29,* 76-85.

Gershon, E. & Buchsbaum, M. (1977). A genetic study of average evoked response

augmentation/reduction in affective disorders In: C. Shagss, S. Gershon & A. Friedhoff (Eds.). *Psychopathology and brain dysfunction* (pp. 279-290). New York: Raven Press.

Gevins, A. & Illes, J. (1991). Neurocognitive networks of the human brain. In R. Zappulla, A. LeFever, J. Jaeger & R. Bilder (Eds.). *Windows on the brain* (pp. 22-56). New York: The New York Academy of Sciences, vol. 260.

Glabus, M., Blackwood, D., Ebmeier, K., Souza, V., Walker, M., Sharp, C., Dunan, J. & Muir, W. (1994). Methodological considerations in measurement of the P300 component of the auditory oddball ERP in schizophrenia. *Electroencephalography and Clinical Neurophysiology, 90,* 123-134.

Goldman-Rakic, P. (1987). Development of cortical circuitry and cognitive function.

Child Development, 58, 601-622.

Gottlober, A. (1938). The inheritance of brain potential pattern. *Journal of Experimental Psychology, 22,* 193-200.

Grillon, C. & Ameli, R. (1994). P300 assessment of anxiety effects on processing novel stimuli. *International Journal of Psychophysiology, 17,* 205-217.

Gur, R.,C. & Gur, R.,E. (1987). Hemispheric specialization and regional cerebral blood flow. In A. Glass (Ed.). *Individual differences in hemispheric specialization* (pp. 93-102). New York: Plenum Press.

Gur, R.,C., Gur, R.,E., Obrist, W., Hungerbuhler J., Skolnick, B. & Reivich, M. (1982). Sex and handedness differences in the cerebral blood flow during rest and cognitive activity. *Science, 217,* 659-660.

Gur, R.,C., Mozley, L., Mozley, P., Resnick, S., Karp, J., Alavi, A., Arnold, S. & Gur, R.,E. (1995). Sex differences in Regional cerebral glucose metabolism during a resting state. *Science, 267*, 528-531.

Gur, R., C., Packer, I., Hungerbuhler, J., Reivich, M., Obrist, W., Amarnek, W. & Sackeim, H. (1980). Differences in the distribution of gray and white matter in human cerebral hemisphere. *Science, 207,* 1226-1228.

Haggard, E. (1958). *Intraclass correlation and the analysis of variance.* New York, Oxford: Dryden Press.

Harmony, T., Fernandez, T., Rodriguez, M., Reyes, A., Marosi, E. & Bernal, J. (1993). Test-retest reliability of EEG spectral parameters during cognitive tasks: II coherence. *International Journal of Neursosciene, 68*, 263 -271.

Heath, A., Neale, M., Hewitt, J., Eaves L. & Fulker D. (1989). Testing structural equation models for twin data using LISREL. *Behavior Genetics, 19,* 9-29.

Heuschert, D. (1963). EEG-untersuchungen an eineiigen Zwillungen in hoheren Lebensalter. *Zeitschrift für Menschlichen Vereb- und Konstitutionslehre, 37,* 128-172.

Hoffman, R., Buchsbaum, M., Escobar, M., Makuch, R., Nuechterlein, K. & Guich, S. (1991). EEG coherence of prefrontalareas in normal and schizophrenic males during perceptual activation. *Journal of Neuropsychiatry, 3*, 169-175.

Hudspeth, W. & Pribram, K. (1990). Stages of brain and cognitive maturation. *Journal of Educational Psychology, 82,* 881-88.

Hudspeth, W. & Pribram, K. (1992). Psychophysiological indices of cerebral maturation. *International Journal of Psychophysiology, 12,* 19-29.

Hume, W. (1983). Physiological measures in twins. In G. Claridge, S. Canter & W. Hume (Eds.). *Personality differences and biological variations: A study of twins* (pp. 87-114). Oxford, New York: Pergamon.

Huttenlocher, P. (1994). Synaptogenesis in human cerebral cortex. In G. Dawson & K. Fische. (Eds.). *Human behavior and the developing brain* (pp. 137-152). New York, London: The Guilford Press.

Iacono, W. (1985). Psychophysiologic markers of psychopathology: A review. *Canadian Psychology, 26,* 96-112.

Ibatoullina, A., Vardaris, R. & Thompson, L. (1994). Genetic and environmental influences on the coherence of background and orienting response EEG in children. *Intelligence, 19,* 65-78.

Jasper, H. (1958). Report of the committee on methods of clinical examination in electroencephalography. *Electroencephalography and Clinical Neurophysiology, 10,* 370-375.

Jinks, J. & Fulker, D. (1970). Comparison of the biometrical genetical, MAVA and classical approaches to the analysis of human behavior. *Psychological Bulletin, 73,* 311-349.

John, E., Ahn, H., Prichep, L., Trepetin, M. & Kaye, H. (1980). Developmental equations for the electroencephalogram. *Science, 210,* 1255-1258.

Johnson, R. (1988). The amplitude of the P300 component of the event-related potential: Review and synthesis. In P. Ackles, J. Jennings & M. Coles (Eds.). *Advances in Psychophysiology* (pp. 69-137). New York: JAI Press.

Johnson, R. (1989). Developmental evidence for modality-dependent P300 generators: a normative study. *Psychophysiology, 26*, 651-667.

Jöreskog, K. & Sörbom, D. (1986). *PRELIS. A preprocessor for LISREL.* Chicago: National Educational Resources.

Juel-Nielsen, N. & Harvald, B. (1958). The electroencephalogram in uniovular twins brought up apart. *Acta Genetica, 8,* 57-64.

Katada, A., Ozaki, H., Suzuki, H. & Suhara, K. (1981). Developmental characteristics of normal and mentally retarted children's EEGs. *Electroencephalography and Clinical Neurophysiology,* 52, 192-201.

Khoury, M., Beaty, T. & Cohen, B. (1993). *Fundamentals of genetic epidemiology.* New York, Oxford: Oxford University Press.

Kimura, D. (1987). Are men's and women's brains really different? *Canadian Psychology, 28,* 133-147.

Kotchoubei, B. (1987). Human orienting reaction: The role of genetic and environmental factors in the variability of evoked potentials and autonomic components. *Arch Ner Sup (Praha), 29,* 103-207.

Kuhlo, W., Heintel, H. & Vogel, F. (1969). The 4-5 c/sec. rhythm. *Electroencephalography and Clinical Neurophysiology, 26,* 613-618.

Lacoste-Utamsing, C. & Holloway, R. (1982). Sexual dimorphism in the human corpus callosum. *Science, 216,* 1431-1432.

Lennox, W., Gibbs, E. & Gibbs, F. (1945). The brainwave pattern, an hereditary trait. Evidence from 'normal' pairs of twins. *Journal of Heredity, 36,* 233-243.

LeVay, S. (1993). *The Sexual brain.* Cambridge: The MIT Press.

Lewis, E., Dustman, R. & Beck, E. (1972). Evoked repsonse similarity in monozygotic, dizygotic and unrelated individuals: A comparative study. *Electroencephalography and Clinical Neuro-physiology, 32,* 309-316.

Linkowski, P., Kerkhofs, M., Hauspie, R., Susanne, C. & Mendlewicz, J. (1989). EEG sleep patterns in man: A twin study. *Electroencephalography and Clinical Neurophysiology, 73,* 279-284.

Lykken, D. (1982). Research with twins: The concept of emergenesis. *Psychophysiology, 4,* 361-373.

Lykken, D., Tellegen, A. & Iacono, W. (1982). EEG spectra in twins: Evidence for a neglected mechanism of genetic determination. *Physiological Psychology, 10,* 60-65.

Lykken, D., Tellegen, A. & Thorkelson, K. (1974). Genetic determination of EEG frequency spectra. *Biological Psychology, 1,* 245-259.

Malykh, S. & Ravich-Shcherbo, I. (1986). Geneotypical dependence of movement related brain potentials. In V. Gallai (Ed.). *Maturation of the CNS and evoked potentials* (pp. 247-252). Amsterdam: Elsevier.

Markowitsch, H. (1988). Individual differences in memory performance and the brain. In H. Markowitsch (Ed.). *Information processing by the brain views and hypotheses from a physiological-Cognitive perspective* (pp 125-148). Toronto: Hans Huber Pusblisher

Marosi, E., Harmony, T., Becker, J., Bernal, J., Reyes, A., Rodriguez, M. & Fernandez, T. (1993). Sex differences in EEG coherence in normal children. *International Journal of Neuroscience, 72,* 115-121.

Martin, N. & Eaves, J. (1977). The genetical analysis of covariance structure. *Heredity, 38,* 79-95.

Matoušek, M. & Petersén, I. (1973). Frequency analysis of the EEG in normal children and adolescents. In P. Kellaway & I. Petersén (Eds.). *Automation of Clinical Electroencephalography* (pp. 75-102). New York: Raven.

Matsuura, M., Yamamoto, K., Fukuzawa, H., Okubo, Y., Uesugi, H., Moriiwa, M., Kojima, T. & Shimazono. (1985). Age development and sex differences of various EEG elements in healthy children and adults -quantification by a computerized wave form recognition method. *Electroencephalography and Clinical Neurophysiology, 60,* 393-406.

Matthis, P., Scheffner, D., Benninger, C., Lipinski, C. & Stolzis, L. (1980). Changes in the background activity of the electroencephalogram according to age. *Electroencephalography and Clinical Neurophysiology,* 49, 626-635

McGlone, J. (1980). Sex differences in human brain asymmetry: A critical survey. *The Behavioral and Brain Sciences, 92,* 215-263.

Meshkova, T. & Ravich-Shcherbo. (1982). Influence of the genotype on the determination of individual features of the human EEG at rest. In H. Schmidt & G. Tembrock (Eds.). *Evolution and determination of animal and human behavior* (pp. 92-107). Berlin: VEB Deutscher Verlag der Wissenschaft.

Molenaar, P., Boomsma, D. & Dolan, C. (1991). Genetic and environmental factors in a developmental perspective. In D. Magnusson & L. Bergman (Eds.). *Problems and methods in longitudinal research. Stability and change* (pp. 250-273). Cambridge: University Press.

Molenaar, P., Boomsma, D. & Dolan, C. (1993). A third source of developmental differences. *Behavior Genetics, 23,* 519-524.

Molenaar, P., Boomsma, D., Neeleman, D. & Dolan, C. (1990). Using factor scores to detect GxE origin of 'pure' genetic or environmental factors obtained in genetic covariance structure analysis. *Genetic Epidemiology, 7,* 93-100.

Molenaar, P. & Roelofs, J. (1987). The analysis of multiple habituation profiles of single trial evoked potentials. *Biological Psychology, 24,* 1-21.

Neale, M. C. (1994). *Mx: Statistical Modeling*. Box 710 MCV Richmond, VA 23298: Department of Psychiatry. 2nd edition.

Neale, M. & Cardon, L. (1992). *Methodology for genetic studies of twins and families*. NATO ASI series: Behavioral and social sciences. Dordrecht: Kluwer Academic Publishers.

Neale, M., Heath, A., Hewitt, K., Eaves, L. & Fulker, D. (1989). Fitting genetic models with LISREL: Hypothesis testing. *Behavior Genetics, 19,* 37-69.

Neshige, R, Barret, G. & Shibaski, H. (1991). Auditory long latency event-related potentials in Alzheimer's disease and multi-infarct dementia. *Journal Neurological Neurosurgery Psychiatry, 51,* 1120-1125.

Niedermeyer, E. (1993). The normal EEG of the waking Adult. In E. Niedermeyer & F. Lopes da Silva (Eds.). *Electroencephalography, basic principles, clinical applications and related fields* (3rd) (pp. 97-118). Baltimore: Williams and Wilkins.

Noble, E., Berman, S., Ozkaragoz, T. & Ritchie, T. (1994). Prolonged P300 latency in children with the D_2 Dopamine receptor A1 Allele. *American Journal of Human Genetics, 54,* 658-668.

Nunez, P. (1981). *Electric fields of the brain. The neurophysics of EEG*. New York, Oxford: Oxford University Press.

Nunez, P. (1995). *Neocortical dynamics and human EEG rhythms*. New York: Oxford University Press.

O'Connor, S., Morzorati, S., Christian. J. & Li, T. (1994). Heritable features of the auditory oddball event-related potential: Peaks, latencies, morphology and topography. *Electroencephalography and Clinical Neurophysiology, 92,* 115-125.

Oken, B. & Chiappa, K. (1988.) Short-term variability in EEG frequency analysis. *Electroencephalography and Clinical Neurophysiology, 69,* 191-198.

Oppenheim, J., Skerry, J., Tramo, M. & Gazzaniga, M. (1989). Magnetic resonance imaging morphology of the corpus callosum in monozygotic twins. *Annals of Neurology, 26,* 100-104.

Osborn, R. (1970). Heritabiltiy estimates for the visual evoked response. *Life Science, 9,* 481-490.

Picton, T., Stuss, D., Champagne, S. & Nelson, R. (1984). The effects of age on human event related potentials. *Psychophysiology, 21,* 312-325.

Pivik, R., Broughton, R., Coppola, R., Davidson, Fox, N. & Nuwer, M. (1993). Guidelines for the recording and quantitative analysis of electroencephalographic activity in research contexts. *Psychophysiology, 30,* 547-558.

Plomin, R. (1986). D*evelopment, Genetics, and psychology*. New Jersey: Lawrence Erlbaum Associates.

Plomin, R., DeFries, J. & McClearn, G. (1990). *Behavioral genetics: A primer*. San Francisco: Freeman.

Plomin, R. & Rende, R. (1991). Human behavioral genetics. *Annual Review of Psychology*, 42

Polich, J. (1986). Normal variation of P300 from auditory stimuli. *Electroencephalography and Clinical Neurophysiology, 65,* 236-240.

Polich, J. & Burns, T. (1987). P300 from identical twins. *Neuropsychologica, 25,* 299-304.

Polich, J., Pollock, V. & Bloom, F. (1994). Meta-analysis of P300 amplitude from males at risk for alcoholism. *Psychological Bulletin, 115,* 55-73.

Pollock, V., Schneider, L. & Lyness, S. (1991). Reliability of topographic quantitative EEG amplitude in healthy late middle aged and elderly subjects. *Electroencephalography and Clinical Neurophysiology, 79,* 20-26.

Propping, P. (1977). Genetic control of ethanol action on the central nervous system: An EEG study in twins. *Human Genetics, 35,* 309-344.

Propping, P., Kruger, J. & Mark, N. (1981). Genetic disposition to alcoholism: An EEG study in alcoholics and their relatives. *Human Genetics, 59,* 51-59.

Raney, E. (1939). Brain potentials and lateral dominance in identical twins. *Journal of Experimental Psychology, 24,* 21-39.

Rappelsberger, P. & Petsche, H. (1988). Probability Mapping: Power and coherence analyses of cognitive processes. *Brain Topography, 1,* 46-54.

Reynolds, C. & Hewitt, J. (1995). Issues in the Behavior Genetic Investigation of Gender Differences. In J. Turner, L. Cardon & J. Hewitt (Eds.). *Behavior Genetic Approaches in Behavioral Medicine (pp. 189-200).* New York: Plenum Press

Risch, N. & Zhang, H. (1995). Extreme discordant sib pairs for mapping quantitative trait loci in humans. *Science, 268*, 1584-1589.

Rijsdijk, F., Boomsma, D. & Vernon, P. (1995). Genetic analysis of peripheral nerve conduction velocity in twins. *Behavior Genetics, 25,* 341-348.

Rogers, T. & Deary, I. (1991). The P300 component in the auditory event-related potential in monozygotic and dizygotic twins. *Acta Psychiatric Scandinavica, 83,* 412-416.

Ruchkin, D., Johnson, R., Canoune, H. Ritter, W. & Hammer, M. (1990). Multiple sources of P3b associated with different types of information. *Psychophysiology, 27,* 157-176.

Rust, J. (1975). Genetic effects in the cortical auditory evoked potentials:
A twin study. *Electroencephalography and Clinical Neurophysiology, 39,* 321-327.

Salinsky, M., Oken, B. & Morehead, L. (1991). Test-retest reliability in EEG frequency analysis.
Electroencephalography and Clinical Neurophysiology, 79, 383-392.

Schmid, R., Tirsch., Rappelsberger, P., Weinmann, H.-M., Pöppl, S. (1992). Comparative coherence studies in healthy volunteers and Down's syndrome patients from childhood to adult age. *Electroencephalography and Clinical Neurophysiology*, *83*, 112-123

Schreiter-Gasser, U., Gasser, T. & Ziegler, P. (1993). Quantitative EEG analysis in early onset Alzheimer's disease: A controlled study. *Electroencephalography and Clinical Neurophysiology, 86,* 15-22.

Segalowitz, S. & Barnes, K. (1993). The reliability of ERP components in the auditory oddball paradigm. *Psychophysiology, 30,* 451-459.

Simonava, O. & Roth, B. (1967). EEG studies of healthy population-normal rhythms of resting recording. *Acta Universitatis Carolinae Medica (Praha), 13,* 543-551.

Sklare, D. & Lynn, G. (1984). Latency of the P3 event-related potential: Normative aspects and within-subject variability. *Electroencephalography and Clinical Neurophysiology, 59,* 420-424.

Sloan, E. & Fenton, G. (1993). EEG power spectra and cognitive change in geriatric psychiatry: A longitudinal study. *Electroencephalgraphy and Clinical Neurophysiology, 86,* 361-367.

Snodgrass, J. & Vanderwart, M. (1980). A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity. *Journal of Experimental Psychology: Human learning and memory, 2,* 174-215.

Stassen, H., Bomben, G. & Propping, P. (1987). Genetic aspects of the EEG: An investigation into the within-pairs similarity of MZ and DZ twins with a new method of analysis. *Electroencephalography and Clinical Neurophysiology, 66,* 489-501.

Stassen, H., Lykken, D. & Bomben, G. (1988a). The within-pair EEG similarity of twins reared apart. *Eur Arch Neurolog Sci, 237,* 244-252.

Stassen, H., Lykken, D., Propping, P. & Bomben, G. (1988b). Genetic determination of the human EEG. Survey of recent results on twins reared together and apart. *Human Genetics, 80,* 165-176.

Steinlein, O., Anokhin, A., Yping, M., Schalt, E. & Vogel, F. (1992). Localization of a gene for the human low-voltage EEG on 20q and genetic heterogenity. *Genomics, 12,* 69-73.

Steinmetz, H., Herzog, A., Huang, Y. & Hacklander, T. (1994). Discordant brain surface anatomy in monozygotic twins. *New England Journal of Medicine, 331,* 952-953.

Steinmetz, H., Staiger, J., Schlaug, G., Huang, Y., & Jäncke, L. (1995). Corpus callosum and brain volume in women and men. *NeuroReport, 6,* 1002-1004.

Steriade, M., Gloor, P., Llinás, R., Lopes da Silva, F. & Mesulam, M. (1990). Basic mechanisms of cerebral rhythmic activities. *Electroencephalography and Clinical Neurophysiology, 76,* 481-508.

Surwillo, W (1977). Interval histograms of period of the electroencephalography and the reaction time in twins. *Behavior Genetics, 7,* 161-170.

Surwillo, W. (1980). Cortical evoked potentials in monozygotic twins and unrelated subjects: Comparisons of exogenous and endogenous components. *Behavior Genetics, 10,* 201-209.

Thatcher, R. (1992). Cyclic cortical reorganization during early childhood. *Brain and Cognition, 20,* 24-50.

Thatcher, R. (1994). Cyclic cortical reorganization. Origins of human cognitive development. In G. Dawson & K. Fischer (Eds.). *Human behavior and the developing brain* (pp. 232-266). New York, London: The Guilford Press.

Thatcher, R., Krause, P., & Hrybyk, M. (1986). Cortico-cortical associations and EEG coherence: A two-compartmental model. *Electroencephalography and Clinical Neurophysiology, 64,* 123-143.

Thatcher, R., Walker, R. & Guidice, S. (1987). Human cerebral hemispheres develop at different rates and ages. *Science, 236,* 1110-1113.

Trubnikov, V., Uvarova, L., Alfimova, M., Orlova, V. & Ozerova, N. (1993). Neurophysiological and psychological predictors of genetic risk for schizophrenia. *Behavior Genetics, 23,* 455-460.

Tucker, D. & Roth, D. (1986). Functional connections among cortical regions: Topography of EEG coherence. *Electroencephalography and Clinical Neurophysiology, 63,* 242-250.

Van Baal, G., Van Beijsterveldt, C., de Geus, E. & Boomsma, D. (1995). Genetic influences on coherence in brain activity in 5-year-old children. *Behavior Genetics, 25,* 291.

Van Baal, C., De Geus, E. & Boomsma, D. (submitted). Longitudinal study of genetic influences on ERP-P3 in early life.

Van Beijsterveldt, C. & Boomsma, D. (1994). Genetics of the human electroencephalogram (EEG) and event-related brain potentials (ERPs): A review. *Human genetics, 94,* 319-330.

Van Beijsterveldt, C., Molenaar, P., Geus, E. & Boomsma, D. (1996). Heritability of human brain functioning as assessed by electroencephalography. *American Journal of Human genetics*, in press

Vogel, F. (1958). *Über die erblichkeit des normalen elektroenzephalogramms. Vergleichende untersuchungen an ein- und zweieiigen zwillingen.* Stuttgart: Georg thieme verlag.

Vogel, F. (1962a). Ergänzende Untersuchungen zur Genetik des menschlichen Niederspannungs-EEG. *Deutsche Zeitschrift für Nervenheilkunde, 184,* 105-111.

Vogel, F. (1962b). Untersuchungen zur Genetik der ß-Wellen im EEG des menschen. *Deutsche Zeitschrift für Nervenheilkunde, 184,* 137-173.

Vogel, F. (1966a). Zur genetischen grundlage fronto-präzentraler ß-wellen-gruppen im EEG des Menschen. *Humangenetik, 2,* 227-237.

Vogel, F. (1966b). Zur Genetischen Grundlage occipitaler langsamer ß-Wellen im EEG des Menschen. *Humangenetik, 2,* 238-245.

Vogel, F. (1970). The genetic basis of the normal human electroencephalogram (EEG). *Humangenetik, 10,* 91-114.

Vogel, F. & Götze, W. (1959). Familienuntersuchungen zur Genetik des normalen Electroencephalogramms. *Deutsche Zeitschrift für Nervenheilkunde, 178,* 668-700.

Vogel, F., Krüger, J., Höpp, H., Schalt, E. & Schnobel, R. (1986). Visually and auditory evoked potentials in carriers of four heredity EEG variants. *Human Neurobiology, 5,* 49-58.

Vogel, F. & Motulsky, A. (1986). *Human genetics: Problems and approaches.* Berlin, Heidelberg, New York: Springer.

Vogel, F., Schalt, E., Krüger, J., Propping, P. & Lehnert, K. (1979). The electroencephalogram (EEG) as a research tool in human behavior genetics: Psychological examinations in healthy males with various inherited EEG variants. I. Rationale of the study; materials; methods. Heritability of test parameters. *Human Genetics, 47,* 1-15.

Whitton, J., Elgie, S., Kugel, H. & Moldofsky, H. (1985). Genetic dependence of the electroencephalogram bispectrum. *Electroencephalography and Clinical Neurophysiology, 60,* 293-298.

Wiesel, T. (1994). Genetics and behavior. *Science, 264,* 1648.

Wijker, W., Molenaar, P. & Van der Molen, M. (1989). Age-changes in scalp-distribution of cognitive event-related potentials elicited in an oddball task. *Journal of psychophysiology, 3,* 179-189.

Witelson, S. & Kigar, D. (1992). Sylvian Fissura morphology and asymmetry in men and women: Bilateral differences in relation to handedness in men. *Journal of Comparative Neurology, 323,* 326-340.

Wong, P. (1991). *Introduction to brain topography.* New York, London: Plenum Press.

Woody, C. (1967). Characterization of an adaptive filter for the analysis of variable latency neuroelectric signals. *Medical and Biological Engineering, 5,* 539-553.

Young, J., Lader, M. & Fenton, G. (1972). A twin study of the genetic influences on the electroencephalography. *Journal of Medical Genetics, 9,* 365-370.

Zuckerman, M., Murtangh, T. & Siegel, J. (1974). Sensation seeking and cortical augmenting-reducing. *Psychophysiology, 11,* 35-542.

Zung, W. & Wilson, W. (1967). Sleep and dream patterns in twins: Markov analysis of a genetic trait. *Recent Advances in Biological Psychiatry, 9,* 119-130.

8

Appendix A

Descriptive statistics of EEG power, P300 amplitude, and EEG coherence.
In this appendix an overview of decriptive statistics of the EEG\ERP parameters, EEG power, P300 amplitude, and EEG coherence is given. The data are based on two recordings in the same group of twins. At the first measurement the average age of the subjects was 16 years old and at the second measurement 17.6 years. The mean values and their standard deviations of the neural indices in the two measurements are presented. In addition, the test-retest and split-half correlations are presented. Furtermore, the twin correlations gathered at time 1 and time 2 are described to get a first impression of the stability of the genetic and environmental influences. Details regarding the methode are described in earlier chapters of this thesis.

Subjects:
The brain activity variables is measured in the same twins twice, with one and half year between. The first time 213 twins were measured (mean age = 16.05 years, SD = .55 years), the second time 196 twins (mean age = 17.56 years, SD = .54 years).
The first time the total group of twins consisted of the following zygosity by sex twin pairs: 39 MZM, 36 DZM, 52 MZF, 38 DZF and 48 DOS. Seventeen twin pairs did not particiapte the second time. The following twin pairs were left: 38 MZM, 31 DZM, 47 MZF, 36 DZF and 44 DOS. For the three EEG/ERP parmaters the number of subjects is different, depending on the artefacts during the recording and outlier detection of the statistical analysis.

Procudure:
Procedure of the measurement at time 1 and time 2 were the same.
P300 was obtained during a simple visual oddball task.
EEG power and EEG coherence were obtained during quiet rest, with eyes closed.

Descriptive statistics:
Mean and standard deviation of both measurements.
Test-retest correlation.
Split-half correlation of EEG/ERP parameters of measurement 2.
Twin correlations (MZM, DZM, MZF, DZF, DOS) of both measurements.

Tables of appendix: Page

Table 8.1 *Measurement 1 and 2*: Estimated means and standard deviations of the P300 amplitude for targets and nontargets on electrode positions: C3, Cz, C4, P3, Pz, P4, O1 and O2.
(Measurement 1: number of males = 191 and number of females = 217; Measurement 2 number of males =174 and number of females= 217).

Measurement 1								
	C3	Cz	C4	P3	Pz	P4	O1	O2
Targets								
males	13.76	17.16	14.36	16.69	19.17	17.07	16.22	15.79
	4.43	5.54	4.46	4.96	5.54	4.95	6.13	5.80
females	14.16	18.18	14.43	17.57	20.12	17.93	16.44	15.96
	4.45	5.49	4.89	4.99	5.64	5.23	5.43	5.21
Nontargets								
males	10.03	12.40	10.67	12.84	14.62	13.27	12.99	13.62
	3.36	4.10	3.58	3.80	4.66	4.39	4.64	4.76
females	9.22	11.30	9.68	11.94	13.69	12.44	12.19	12.77
	3.56	4.71	3.42	3.61	4.20	4.01	4.54	4.66

Measurement 2								
	C3	Cz	C4	P3	Pz	P4	O1	O2
Targets								
males	13.56	16.89	13.56	15.76	18.06	15.75	15.05	14.72
	4.17	4.97	3.96	4.35	4.86	4.34	4.87	4.61
females	14.78	18.59	14.96	17.66	19.97	17.83	16.41	16.20
	4.36	5.30	4.17	5.05	5.30	4.81	4.80	4.40
Nontargets								
males	9.26	11.11	9.40	11.37	12.83	11.42	11.86	12.00
	2.66	3.41	2.64	2.97	3.45	3.09	3.72	3.63
females	9.79	11.84	9.87	11.68	13.25	12.08	11.68	11.93
	2.66	3.69	2.64	3.16	3.80	3.31	3.70	4.11

Table 8.2 Test-retest correlation of P300 amplitude for targets and nontargets on electrode positions: C3, Cz, C4, P3, Pz, P4, O1 and O2. Number of twins = 176. Twin A = eldest twin and Twin B = youngest twin.

Scalp positions	C3	Cz	C4	P3	Pz	P4	O1	O2	Mean
Targets									
Twin A	.56	.58	.51	.60	.59	.54	.60	.56	.57
Twin B	.52	.60	.58	.54	.55	.57	.62	.53	.56
Nontargets									
Twin A	.53	.54	.60	.67	.65	.61	.65	.67	.62
Twin B	.58	.67	.54	.64	.72	.66	.67	.70	.66

Table 8.3 Split-half correlation of P300 amplitude of measurement 2 for targets and nontargets on electrode positions: C3, Cz, C4, P3, Pz, P4, O1 and O2. Number of twins = 179. Twin A = eldest twin and Twin B = youngest twin. Split-half correlations were adjusted for test length by the Spearman-Brown prophecy formula.

Scalp positions	C3	Cz	C4	P3	Pz	P4	O1	O2	Mean
Targets									
Twin A	.77	.68	.69	.77	.71	.67	.77	.74	.72
Twin B	.72	.79	.71	.77	.75	.73	.76	.72	.74
Nontargets									
Twin A	.73	.71	.74	.80	.82	.80	.82	.88	.79
Twin B	.80	.84	.75	.78	.81	.82	.85	.84	.81

Table 8.4 *Measurement 1 and 2*. Twin correlations (MZM, DZM, MZF, DZF and DOS twins) of the P300 amplitude for targets and nontargets on electrode positions: C3, Cz, Cz, P3, Pz, P4, O1 and O2.

Measurement 1								
	C3	Cz	C4	P3	Pz	P4	O1	O2
Targets								
MZM (37)	.34	.10	.42	.45	.47	.52	.54	.51
DZM (35)	.33	.32	.16	.03	.10	.21	.21	.26
MZF (48)	.22	.25	.25	.33	.52	.50	.50	.58
DZF (37)	.44	.55	.64	.54	.56	.56	.55	.56
OS (47)	.11	.15	.11	-.23	.03	-.07	-.08	.04
Twin correlations pooled over males and females:								
MZ (85)	.27	.19	.29	.38	.49	.48	.52	.54
DZ (119)	.27	.33	.31	.12	.24	.23	.21	.27
Nontargets								
MZM (37)	.24	.57	.56	.56	.54	.47	.55	.67
DZM (35)	.35	.17	.45	.19	.30	.32	.15	.28
MZF (48)	.40	.42	.53	.37	.53	.42	.47	.54
DZF (37)	.08	.33	.33	.24	.26	.42	.55	.58
OS (47)	.31	.15	.32	.08	.17	.11	.20	.09
Twin correlations pooled over males and females:								
MZ (85)	.34	.48	.54	.45	.54	.43	.51	.61
DZ (119)	.26	.22	.36	.16	.22	.24	.29	.29
Measurement 2								
	C3	Cz	C4	P3	Pz	P4	O1	O2
Targets								
MZM (36)	.29	.42	.50	.34	.43	.43	.31	.28
DZM (29)	.26	.44	.29	.09	.21	.04	.37	.25
MZF (44)	.39	.50	.51	.52	.62	.56	.64	.57
DZF (32)	.36	.26	.40	.49	.43	.35	.51	.65
OS (42)	.00	.00	-.04	-.12	-.13	.02	-.10	.14
Twin correlations pooled over males and females:								
MZ (80)	.34	.47	.50	.43	.53	.51	.46	.42
DZ (103)	.20	.24	.23	.20	.20	.17	.23	.32
Nontargets								
MZM (36)	.43	.61	.57	.49	.46	.45	.44	.49
DZM (29)	.16	.10	.26	.35	.38	.44	.14	.40
MZF (44)	.41	.38	.45	.53	.63	.55	.37	.59
DZF (32)	.17	.10	.20	.32	.27	.33	.47	.52
OS (42)	-.16	.14	.08	.16	.16	.17	.17	.21
Twin correlations pooled over males and females:								
MZ (80)	.42	.48	.48	.51	.52	.48	.39	.55
DZ (103)	.05	.12	.17	.26	.26	.31	.28	.38

Table 8.5 *Measurement 1*: Mean values of EEG power (uV²) for 14 electrode positions (Fp1, Fp2, F3 and so on) and 4 frequency bands (delta, theta, alpha, beta). The mean values were calculated over untransformed EEG power values and averaged over oldest and youngest twin (Number of males = 190 and females = 224).

Electrode positions							
	Fp1	F3	F7	C3	P3	O1	T5
Frequency band							
DELTA							
males	16.16	23.32	13.09	25.12	33.12	38.68	20.58
females	16.46	21.96	12.05	23.72	31.56	37.31	20.87
THETA							
males	6.85	14.73	6.16	19.21	26.77	31.05	16.72
females	7.58	16.00	6.50	20.39	29.00	34.57	19.93
ALPHA							
males	6.44	12.38	6.03	22.87	53.84	117.47	37.68
females	7.29	14.12	6.51	23.06	55.21	110.57	37.18
BETA							
males	3.24	5.95	3.21	7.15	9.50	13.48	6.90
females	3.71	6.06	3.05	7.51	10.18	15.19	7.70

Electrode positions							
	Fp2	F4	F8	C4	P4	O2	T6
Frequency band							
DELTA							
males	17.96	25.74	13.68	27.40	37.00	38.64	26.70
females	18.17	24.05	12.75	25.62	34.10	37.66	26.41
THETA							
males	8.41	17.08	7.19	20.71	29.43	31.50	22.10
females	8.76	17.87	7.37	22.14	31.01	34.90	24.97
ALPHA							
males	7.52	14.02	6.84	24.87	66.02	124.42	56.99
females	8.21	15.76	7.31	25.27	65.38	119.08	55.44
BETA							
males	4.24	7.08	3.86	8.01	10.24	13.49	7.86
females	4.62	7.08	3.59	8.21	10.86	15.54	9.13

Table 8.6 *Measurement 2*: Mean values of EEG power (uV²) for 14 electrode positions (Fp1, Fp2, F3 and so on) and 4 frequency bands (delta, theta, alpha, beta). The mean values were calculated over untransformed EEG power values and averaged over oldest and youngest twin (Number of males = 167, and females = 203).

Electrode positions							
	Fp1	F3	F7	C3	P3	O1	T5
Frequency band							
DELTA							
males	12.92	17.68	9.55	19.32	24.45	29.67	15.92
females	13.87	19.41	10.23	21.53	26.97	31.42	17.82
THETA							
males	5.84	11.70	4.95	14.85	20.52	25.16	13.53
females	7.11	14.58	5.92	19.21	26.56	31.25	17.34
ALPHA							
males	5.99	10.51	5.17	19.40	48.10	103.70	36.05
females	7.45	13.63	6.33	22.56	55.77	116.17	40.90
BETA							
males	2.86	4.98	2.70	6.11	8.14	12.37	6.27
females	3.06	5.94	2.93	7.58	10.10	15.66	7.94

Electrode positions							
	Fp2	F4	F8	C4	P4	O2	T6
Frequency band							
DELTA							
males	13.82	19.16	10.03	20.33	26.20	29.27	18.96
females	15.25	20.50	10.58	22.33	28.11	32.41	21.12
THETA							
males	6.89	13.15	5.57	15.91	22.37	26.20	16.44
females	7.99	15.82	6.47	20.18	27.71	32.60	20.62
ALPHA							
males	6.75	11.55	5.63	20.47	55.39	112.36	48.09
females	8.15	14.68	6.87	23.12	62.12	125.88	54.17
BETA							
males	3.52	5.69	3.09	6.63	8.54	12.60	6.65
females	4.42	6.62	3.30	7.90	10.53	16.22	8.59

Table 8.7 *Measurement 1*: Estimated log-transformed means and their standard deviations of EEG power for males and females. The EEG power is given for all electrode positions (Fp1, Fp2, F3 and so on) and for each frequency band (delta, theta, alpha and beta). (Number of males =190, number of females =224)

Electrode positions	Fp1	F3	F7	C3	P3	O1	T5
Frequency band							
DELTA							
males	1.18	1.34	1.08	1.37	1.47	1.52	1.26
	.18	.16	.19	.17	.21	.25	.23
females	1.17	1.31	1.04	1.35	1.45	1.48	1.24
	.19	.15	.18	.16	.19	.25	.22
THETA							
males	.81	1.14	.75	1.24	1.34	1.37	1.13
	.19	.20	.21	.23	.30	.35	.32
females	.81	1.13	.74	1.23	1.34	1.36	1.13
	.21	.21	.22	.23	.30	.36	.33
ALPHA							
males	.74	1.02	.70	1.24	1.56	1.85	1.38
	.28	.28	.29	.34	.41	.49	.44
females	.77	1.05	.71	1.24	1.57	1.83	1.38
	.28	.29	.30	.32	.41	.46	.43
BETA							
males	.48	.72	.46	.79	.90	1.02	.76
	.15	.21	.20	.23	.26	.31	.27
females	.54	.74	.45	.82	.95	1.10	.82
	.15	.18	.17	.21	.22	.27	.23

	Fp2	F4	F8	C4	P4	O2	T6
Frequency band							
DELTA							
males	1.22	1.38	1.10	1.41	1.51	1.52	1.35
	.18	.17	.20	.18	.23	.26	.27
females	1.21	1.35	1.06	1.38	1.48	1.48	1.33
	.19	.16	.20	.16	.20	.25	.25
THETA							
males	.89	1.19	.81	1.27	1.37	1.37	1.22
	.20	.21	.23	.24	.31	.36	.35
females	.87	1.18	.79	1.26	1.37	1.37	1.22
	.22	.22	.24	.24	.30	.35	.35
ALPHA							
males	.81	1.07	.75	1.29	1.64	1.88	1.56
	.26	.28	.29	.34	.42	.48	.45
females	.82	1.10	.75	1.27	1.64	1.87	1.57
	.27	.29	.30	.33	.41	.45	.44
BETA							
males	.58	.78	.53	.84	.93	1.01	.81
	.18	.22	.23	.24	.26	.32	.28
females	.63	.80	.51	.86	.98	1.11	.89
	.17	.20	.19	.21	.22	.26	.25

Table 8.8 *Measurement 2*: Estimated log-transformed means and their standard deviations of the EEG power for males and females. The power is given for all electrode positions (Fp1, Fp2, F3 and so on) and for each frequency band (delta, theta, alpha and beta). (Number of males = 167 and number of females = 203)

Electrode positions	Fp1	F3	F7	C3	P3	O1	T5
Frequency band							
DELTA							
males	1.08	1.22	.95	1.26	1.35	1.41	1.15
	.18	.15	.17	.15	.18	.24	.20
females	1.11	1.26	.98	1.31	1.40	1.44	1.21
	.16	.14	.17	.14	.17	.22	.19
THETA							
males	.74	1.03	.66	1.13	1.23	1.28	1.03
	.18	.19	.19	.22	.28	.34	.30
females	.80	1.11	.72	1.22	1.32	1.37	1.13
	.20	.20	.20	.23	.28	.33	.30
ALPHA							
males	.70	.94	.64	1.17	1.50	1.79	1.34
	.26	.26	.26	.32	.40	.47	.44
females	.79	1.05	.71	1.25	1.59	1.88	1.44
	.27	.27	.28	.31	.40	.45	.42
BETA							
males	.42	.65	.39	.72	.83	.98	.71
	.16	.19	.18	.23	.25	.31	.27
females	.53	.73	.43	.82	.95	1.12	.83
	.15	.18	.16	.21	.22	.26	.24
	Fp2	F4	F8	C4	P4	O2	T6
Frequency band							
DELTA							
males	1.11	1.25	.97	1.28	1.37	1.40	1.21
	.17	.16	.17	.15	.19	.24	.23
females	1.15	1.29	.99	1.32	1.42	1.45	1.28
	.16	.15	.17	.14	.17	.22	.21
THETA							
males	.81	1.08	.71	1.15	1.26	1.29	1.09
	.19	.20	.20	.23	.29	.35	.34
females	.85	1.14	.75	1.23	1.34	1.38	1.19
	.20	.21	.21	.24	.29	.34	.33
ALPHA							
males	.76	.99	.67	1.20	1.56	1.82	1.47
	.26	.26	.27	.31	.41	.47	.44
females	.83	1.08	.74	1.26	1.64	1.92	1.57
	.26	.28	.28	.31	.40	.45	.43
BETA							
males	.51	.69	.44	.75	.85	.98	.72
	.17	.21	.19	.23	.25	.32	.28
females	.61	.77	.48	.84	.97	1.13	.87
	.16	.20	.18	.21	.22	.26	.24

Table 8.9 Test-retest correlations of the log-transformed EEG power for each electrode position (Fp1, Fp2, F3 and so on) and frequency band (delta, theta, alpha, beta). The correlation is given for oldest (twin A) and youngest twin (twin B). Number of subjects = 181.

Electrode positions														
	Fp1	Fp2	F3	F4	F7	F8	C3	C4	P3	P4	O1	O2	T5	T6
Frequency band														
DELTA														
twin A	.63	.64	.73	.68	.51	.61	.76	.77	.85	.85	.83	.82	.80	.82
twin B	.55	.63	.73	.69	.46	.58	.75	.77	.85	.88	.82	.84	.81	.84
THETA														
twin A	.74	.83	.83	.84	.78	.80	.85	.85	.88	.88	.87	.86	.86	.86
twin B	.78	.83	.86	.86	.79	.82	.87	.90	.90	.91	.88	.89	.89	.89
ALPHA														
twin A	.79	.83	.81	.82	.81	.81	.87	.85	.88	.88	.88	.87	.85	.86
twin B	.82	.84	.85	.87	.84	.85	.89	.91	.91	.91	.89	.88	.89	.88
BETA														
twin A	.74	.80	.83	.84	.68	.66	.88	.85	.90	.89	.90	.89	.86	.88
twin B	.68	.76	.85	.86	.70	.76	.88	.90	.90	.90	.89	.88	.87	.86

Table 8.10 Split-half correlations of the log-transformed EEG power measured on time 2. For each lead (Fp1, Fp2, F3 and so on) and frequency band (delta, theta, alpha, and beta). The correlations are depicted for oldest (twin A) and youngest twin (twin B) (Number of subject = 181).

Electrode positions														
	Fp1	Fp2	F3	F4	F7	F8	C3	C4	P3	P4	O1	O2	T5	T6
Power bands														
DELTA														
twin A	.90	.89	.93	.94	.92	.89	.94	.94	.95	.95	.97	.97	.97	.96
twin B	.91	.90	.92	.93	.90	.91	.92	.93	.95	.95	.97	.96	.96	.96
THETA														
twin A	.96	.96	.97	.97	.97	.97	.98	.98	.98	.99	.99	.99	.99	.99
twin B	.95	.95	.97	.97	.97	.97	.98	.98	.99	.99	.99	.99	.99	.99
ALPHA														
twin A	.98	.98	.98	.98	.98	.98	.99	.99	.99	.99	.99	.99	.99	.99
twin B	.98	.98	.98	.98	.99	.98	.99	.97	.99	.99	.99	.99	.99	.99
BETA														
twin A	.98	.98	.98	.99	.98	.97	.99	.99	.98	.99	.99	.99	.99	.99
twin B	.98	.99	.99	.99	.98	.97	.99	.99	.99	.99	.99	.99	.99	.99

Table 8.11 *Measurement 1*: Twin correlations of the log-transformed EEG for each electrode positions (Fp1, Fp2, F3 and so on) and frequency band (delta, theta, alpha and beta).

DELTA	Electrode positions													
	Fp1	Fp2	F3	F4	F7	F8	C3	C4	P3	P4	O1	O2	T5	T6
MZM (38)	.66	.76	.82	.86	.80	.70	.88	.86	.90	.93	.78	.76	.76	.87
DZM (36)	.38	.39	.29	.25	.14	.33	.34	.33	.32	.38	.40	.35	.35	.51
MZF (52)	.50	.60	.70	.63	.53	.65	.68	.83	.74	.86	.76	.74	.74	.84
DZF (38)	.25	.28	.64	.43	.26	.19	.59	.48	.52	.54	.62	.43	.43	.57
DOS (45)	.34	.31	.44	.44	.30	.26	.47	.48	.31	.34	.35	.32	.32	.45

THETA	Electrode positions													
	Fp1	Fp2	F3	F4	F7	F8	C3	C4	P3	P4	O1	O2	T5	T6
MZM (38)	.89	.91	.91	.94	.91	.90	.93	.94	.93	.94	.91	.90	.85	.87
DZM (36)	.55	.48	.43	.35	.39	.47	.46	.41	.53	.48	.57	.54	.54	.53
MZF (52)	.88	.88	.89	.89	.88	.87	.86	.88	.87	.91	.86	.89	.88	.89
DZF (38)	.55	.52	.54	.51	.58	.50	.50	.45	.52	.53	.58	.60	.54	.55
DOS (45)	.54	.57	.53	.53	.48	.55	.50	.47	.39	.38	.41	.44	.38	.37

ALPHA	Electrode positions													
	Fp1	Fp2	F3	F4	F7	F8	C3	C4	P3	P4	O1	O2	T5	T6
MZM (38)	.89	.88	.91	.91	.92	.90	.93	.95	.94	.93	.93	.92	.92	.84
DZM (36)	.47	.43	.51	.41	.41	.37	.49	.43	.46	.38	.46	.42	.42	.32
MZF (52)	.87	.87	.87	.88	.88	.88	.90	.92	.90	.93	.90	.88	.86	.90
DZF (38)	.50	.50	.51	.47	.57	.56	.45	.35	.40	.38	.55	.49	.43	.43
DOS (45)	.57	.56	.60	.55	.56	.53	.60	.56	.37	.37	.39	.34	.43	.43

BETA	Electrode positions													
	Fp1	Fp2	F3	F4	F7	F8	C3	C4	P3	P4	O1	O2	T5	T6
MZM (38)	.87	.86	.93	.94	.81	.69	.91	.92	.97	.94	.88	.90	.90	.80
DZM (36)	.31	.34	.43	.38	.48	.37	.42	.37	.33	.34	.42	.39	.36	.43
MZF (52)	.64	.76	.90	.90	.77	.74	.93	.93	.93	.93	.86	.87	.85	.87
DZF (38)	.36	.41	.25	.13	.41	.24	.19	.12	.14	.11	.42	.36	.21	.23
DOS (45)	.36	.24	.36	.32	.25	.35	.41	.52	.33	.44	.40	.43	.26	.38

Table 8.12 *Measurement 2*: Twin correlations of the log-transformed EEG power for each electrode position (Fp1, Fp2, F3 and so on) and frequency band (delta, theta, alpha and beta).

DELTA	Electrode positions													
	Fp1	Fp2	F3	F4	F7	F8	C3	C4	P3	P4	O1	O2	T5	T6
MZM (32)	.43	.47	.53	.70	.24	.43	.61	.77	.80	.91	.85	.81	.71	.87
DZM (29)	.49	.36	.46	.59	.63	.13	.42	.41	.29	.31	.27	.23	.34	.45
MZF (44)	.60	.56	.76	.71	.57	.66	.83	.83	.84	.90	.86	.84	.80	.85
DZF (35)	.02	.04	.28	.20	.13	.03	.36	.34	.40	.43	.47	.55	.40	.56
OS (41)	.56	.50	.47	.50	.51	.62	.44	.47	.31	.39	.41	.46	.24	.51
THETA	Electrode positions													
	Fp1	Fp2	F3	F4	F7	F8	C3	C4	P3	P4	O1	O2	T5	T6
MZM (32)	.69	.75	.86	.85	.76	.80	.89	.89	.90	.93	.90	.94	.85	.92
DZM (29)	.47	.52	.46	.56	.60	.50	.44	.46	.45	.44	.48	.48	.47	.54
MZF (44)	.82	.87	.85	.88	.82	.88	.89	.91	.90	.93	.89	.91	.87	.91
DZF (35)	.24	.28	.37	.36	.31	.37	.43	.45	.47	.52	.40	.43	.44	.50
OS (41)	.61	.63	.52	.54	.52	.54	.53	.51	.42	.40	.40	.42	.32	.53
ALPHA	Electrode positions													
	Fp1	Fp2	F3	F4	F7	F8	C3	C4	P3	P4	O1	O2	T5	T6
MZM (32)	.86	.91	.92	.92	.91	.94	.94	.94	.94	.95	.94	.93	.91	.92
DZM (29)	.37	.35	.43	.37	.42	.35	.50	.43	.52	.48	.47	.38	.45	.53
MZF (44)	.82	.85	.83	.83	.81	.82	.80	.85	.85	.87	.82	.78	.76	.86
DZF (35)	.37	.30	.35	.28	.31	.31	.38	.39	.40	.45	.40	.42	.33	.44
OS (41)	.50	.50	.53	.51	.54	.52	.57	.57	.26	.32	.30	.28	.32	.48
BETA	Electrode positions													
	Fp1	Fp2	F3	F4	F7	F8	C3	C4	P3	P4	O1	O2	T5	T6
MZM (32)	.70	.84	.79	.90	.55	.66	.84	.90	.94	.94	.90	.90	.81	.90
DZM (29)	.37	.34	.42	.40	.51	.48	.43	.38	.45	.48	.50	.48	.42	.57
MZF (44)	.71	.74	.91	.84	.76	.74	.91	.91	.89	.91	.83	.85	.78	.84
DZF (35)	.31	.38	.31	.25	.23	.20	.23	.29	.34	.44	.37	.43	.39	.45
OS (41)	.34	.29	.30	.35	.07	.26	.34	.40	.24	.35	.33	.35	.09	.44

Table 8.13 *Measurement 1*: Estimated means and standard deviations of the transformed and untransformed EEG coherences of all combinations of electrode pairs in the left and right hemisphere for frequency band delta and theta. In the first 4 columns the means of the untransformed EEG coherences for males and females in the next 4 columns the means and standard deviations of the transformed EEG coherence for males and females are depicted.

DELTA		Untransformed				Transformed			
		Males		Females		Males		Females	
		left	right	left	right	left	right	left	right
Fp-O	mean	.03	.03	.03	.03	-1.58	-1.60	-1.60	-1.62
	s.d					.27	.27	.30	.31
Fp-P	mean	.06	.05	.06	.06	-1.31	-1.34	-1.35	-1.34
	s.d					.30	.31	.33	.33
F-O	mean	.06	.06	.07	.07	-1.32	-1.30	-1.23	-1.21
	s.d					.33	.31	.37	.34
Fp-C	mean	.17	.19	.18	.20	-.72	-.65	-.68	-.64
	s.d					.24	.21	.24	.22
C-O	mean	.22	.22	.27	.26	-.58	-.59	-.48	-.48
	s.d					.25	.26	.27	.28
Fp-F	mean	.50	.51	.51	.52	.01	.02	.02	.04
	s.d					.16	.16	.17	.17
F-C	mean	.61	.61	.65	.66	.20	.21	.29	.29
	s.d					.12	.14	.13	.13
C-P	mean	.66	.62	.67	.65	.29	.21	.32	.27
	s.d					.13	.16	.14	.16
P-O	mean	.59	.62	.67	.69	.16	.22	.32	.36
	s.d					.19	.17	.19	.19

THETA		Untransformed				Transformed			
		Males		Females		Males		Females	
		left	right	left	right	left	right	left	right
Fp-O	mean	.03	.03	.03	.03	-1.55	-1.57	-1.54	-1.55
	s.d					.30	.28	.27	.30
Fp-P	mean	.05	.05	.05	.05	-1.37	-1.37	-1.31	-1.30
	s.d					.29	.28	.28	.27
F-O	mean	.05	.05	.06	.06	-1.37	-1.36	-1.28	-1.29
	s.d					.25	.23	.26	.26
Fp-C	mean	.17	.20	.20	.22	-.72	-.64	-.63	-.58
	s.d					.24	.21	.23	.21
C-O	mean	.18	.17	.21	.20	-.70	-.73	-.60	-.64
	s.d					.23	.23	.23	.23
Fp-F	mean	.53	.56	.54	.57	.05	.11	.08	.13
	s.d					.16	.14	.16	.16
F-C	mean	.58	.58	.64	.63	.15	.15	.25	.24
	s.d					.13	.14	.13	.13
C-P	mean	.63	.59	.65	.62	.24	.16	.28	.21
	s.d					.13	.15	.12	.14
P-O	mean	.54	.57	.61	.63	.08	.13	.20	.24
	s.d					.16	.15	.15	.15

Table 8.14 *Measurement 2*: Estimated means and standard deviations of the transformed and untransformed EEG coherences of all combinations of electrode pairs in the left and right hemisphere for frequency band delta and theta. In the first 4 columns the means of the untransformed EEG coherences for males and females in the next 4 columns the means and standard deviations of the transformed EEG coherence for males and females are depicted.

DELTA		Untransformed				Transformed			
		Males		Females		Males		Females	
		left	right	left	right	left	right	left	right
Fp-O	mean	.03	.03	.03	.03	-1.63	-1.64	-1.65	-1.65
	s.d					.30	.29	.28	.26
Fp-P	mean	.07	.07	.06	.06	-1.22	-1.24	-1.25	-1.26
	s.d					.33	.34	.30	.30
F-O	mean	.09	.08	.09	.09	-1.13	-1.18	-1.08	-1.12
	s.d					.34	.32	.34	.35
Fp-C	mean	.20	.22	.20	.21	-.63	-.59	-.62	-.59
	s.d					.24	.23	.20	.18
C-O	mean	.30	.28	.32	.30	-.40	.-43	-.36	-.40
	s.d					.25	.23	.25	.24
Fp-F	mean	.53	.55	.53	.54	.05	.09	.06	.07
	s.d					.17	.16	.15	.14
F-C	mean	.65	.65	.68	.68	.27	.27	.34	.33
	s.d					.14	.14	.12	.11
C-P	mean	.71	.68	.71	.68	.39	.33	.39	.35
	s.d					.16	.16	.13	.14
P-O	mean	.67	.67	.72	.71	.31	.33	.42	.41
	s.d					.20	.17	.18	.18

THETA		Untransformed				Transformed			
		Males		Females		Males		Females	
		left	right	left	right	left	right	left	right
Fp-O	mean	.03	.03	.03	.03	-1.53	-1.54	-1.58	-1.57
	s.d					.27	.26	.28	.28
Fp-P	mean	.06	.06	.07	.07	-1.29	-1.29	-1.23	-1.22
	s.d					.27	.27	.28	.27
F-O	mean	.06	.06	.07	.06	-1.27	-1.31	-1.19	-1.25
	s.d					.30	.29	.29	.28
Fp-C	mean	.20	.22	.22	.24	-.64	-.58	-.56	-.51
	s.d					.22	.19	.21	.18
C-O	mean	.23	.21	.25	.22	-.54	-.60	-.50	-.57
	s.d					.22	.23	.22	.22
Fp-F	mean	.56	.60	.57	.60	.11	.18	.13	.18
	s.d					.16	.14	.15	.13
F-C	mean	.61	.66	.66	.66	.20	.20	.30	.30
	s.d					.14	.13	.13	.11
C-P	mean	.67	.64	.68	.65	.31	.26	.33	.28
	s.d					.13	.14	.12	.13
P-O	mean	.62	.62	.66	.65	.22	.22	.29	.28
	s.d					.16	.16	.15	.14

Table 8.15 *Measurement 1*: Estimated means and standard deviations of the transformed and untransformed EEG coherences of all combinations of electrode pairs in the left and right hemisphere for frequency band alpha and beta. In the first 4 columns the means of the untransformed EEG coherences for males and females in the next 4 columns the means and standard deviations of the transformed EEG coherence for males and females are depicted.

ALPHA		Untransformed				Transformed			
		Males		Females		Males		Females	
		left	right	left	right	left	right	left	right
Fp-O	mean	.15	.15	.15	.14	-.86	-.85	-.87	-.89
	s.d					.39	.38	.38	.38
Fp-P	mean	.08	.08	.08	.08	-1.16	-1.14	-1.16	-1.16
	s.d					.34	.33	.30	.30
F-O	mean	.09	.10	.09	.09	-1.11	-1.08	-1.09	-1.10
	s.d					.37	.38	.34	.34
Fp-C	mean	.21	.22	.25	.25	-.63	-.61	-.54	-.53
	s.d					.32	.31	.33	.31
C-O	mean	.12	.12	.14	.13	-.95	-.96	.85	.86
	s.d					.29	.31	.27	.26
Fp-F	mean	.62	.64	.64	.66	.22	.26	.26	.30
	s.d					.20	.18	.23	.21
F-C	mean	.52	.51	.58	.56	.04	.02	.14	.11
	s.d					.23	.23	.22	.22
C-P	mean	.51	.46	.52	.48	.02	-.08	.04	-.04
	s.d					.20	.23	.18	.19
P-O	mean	.54	.59	.60	.64	.08	.16	.18	.26
	s.d					.23	.21	.18	.18

BETA		Untransformed				Transformed			
		Males		Females		Males		Females	
		left	right	left	right	left	right	left	right
Fp-O	mean	.03	.03	.03	.03	-1.57	-1.60	-1.55	-1.57
	s.d					.26	.24	.26	.24
Fp-P	mean	.04	.04	.04	.04	-1.54	-1.53	-1.47	-1.49
	s.d					.25	.23	.24	.23
F-O	mean	.03	.03	.03	.03	-1.62	1.62	-1.58	-1.60
	s.d					.21	.22	.20	.20
Fp-C	mean	.13	.13	.15	.16	-.88	-.84	-.79	-.75
	s.d					.21	.19	.22	.20
C-O	mean	.10	.09	.11	.10	-.99	-1.04	-.94	-.99
	s.d					.22	.23	.21	.22
Fp-F	mean	.39	.42	.41	.44	-.20	-.14	-.16	-.11
	s.d					.15	.13	.18	.16
F-C	mean	.48	.47	.53	.52	-.04	-.06	.06	.04
	s.d					.13	.13	.15	.15
C-P	mean	.48	.44	.50	.47	-.03	-.10	.004	-.06
	s.d					.13	.14	.12	.13
P-O	mean	.48	.50	.53	.55	-.03	-.003	.06	.09
	s.d					.13	.14	.12	.12

Table 8.16 *Measurement 2*: Estimated means and standard deviations of the transformed and untransformed EEG coherences of all combinations of electrode pairs in the left and right hemisphere for frequency band delta and theta. In the first 4 columns the means of the untransformed EEG coherences for males and females in the next 4 columns the means and standard deviations of the transformed EEG coherence for males and females are depicted.

ALPHA		Untransformed				Transformed			
		Males		Females		Males		Females	
		left	right	left	right	left	right	left	right
Fp-O	mean	.15	.16	.14	.14	-.86	-.83	-89	-.88
	s.d					.38	.37	.39	.38
Fp-P	mean	.09	.09	.08	.08	-1.13	-1.12	-1.12	-1.13
	s.d					.34	.35	.32	.31
F-O	mean	.09	.10	.09	.09	-1.11	-1.10	-1.09	-1.10
	s.d					.33	.36	.32	.33
Fp-C	mean	.22	.22	.26	.25	-.62	-.61	-.51	-.51
	s.d					.32	.31	.31	.30
C-O	mean	.16	.16	.17	.16	-.77	-.79	.74	.77
	s.d					.28	.28	.29	.29
Fp-F	mean	.65	.67	.67	.68	.28	.31	.32	.35
	s.d					.20	.19	.21	.21
F-C	mean	.52	.51	.57	.56	.04	.02	.14	.11
	s.d					.25	.25	.23	.22
C-P	mean	.56	.52	.55	.52	.11	.04	.09	.04
	s.d					.20	.20	.19	.19
P-O	mean	.63	.64	.66	.67	.23	.27	.30	.32
	s.d					.18	.20	.17	.19

BETA		Untransformed				Transformed			
		Males		Females		Males		Females	
		left	right	left	right	left	right	left	right
Fp-O	mean	.03	.03	.03	.03	-1.55	-1.56	-1.61	-1.60
	s.d					.22	.24	.24	.23
Fp-P	mean	.04	.04	.04	.04	-1.48	-1.49	-1.39	-1.41
	s.d					.25	.24	.24	.23
F-O	mean	.03	.03	.03	.03	-1.55	-1.58	-1.54	-1.59
	s.d					.21	.22	.20	.20
Fp-C	mean	.15	.15	.18	.18	-.79	-.77	-.70	-.69
	s.d					.21	.18	.22	.19
C-O	mean	.13	.12	.14	.12	-.84	-.92	-.83	-.91
	s.d					.20	.22	.19	.20
Fp-F	mean	.44	.46	.46	.48	-.10	-.07	-.07	-.04
	s.d					.14	.13	.17	.15
F-C	mean	.50	.49	.55	.53	-.01	-.02	.01	.06
	s.d					.14	.15	.15	.15
C-P	mean	.52	.49	.53	.51	.04	-.01	.05	.01
	s.d					.12	.13	.11	.11
P-O	mean	.56	.55	.59	.57	.10	.09	.16	13
	s.d					.12	.13	.11	.11

Table 8.17 *Measurement 1:* Twin correlations of the log-transformed EEG coherence for all electrode combinations in the left and right hemisphere for each frequency band (delta, theta, alpha and beta). Above each column the number of twins is given.

DELTA	35		34		50		36		44	
	mzm		dzm		mzf		dzf		dos	
	left	right	left	right	left	right	left	right	left	right
Fp-O	.21	.30	.39	.31	.29	.31	.29	.19	.10	-.01
Fp-P	.39	.53	.05	.17	.31	.39	.20	.09	.08	.35
F-O	.60	.51	.14	.28	.34	.36	.46	.36	.12	.05
Fp-C	.70	.51	.14	.22	.50	.49	.22	.13	.13	.21
C-O	.67	.58	.10	.05	.43	.47	.34	.41	.37	.36
Fp-F	.51	.50	.32	.29	.56	.55	.28	.39	.15	.53
F-C	.70	.60	.31	.17	.36	.57	.04	.30	.32	.32
C-P	.72	.60	.14	.10	.39	.51	.02	.25	.27	.12
P-O	.63	.58	-.01	.10	.45	.46	.36	.25	.41	.26
THETA	37		35		51		36		45	
	mzm		dzm		mzf		dzf		dos	
	left	right	left	right	left	right	left	right	left	right
Fp-O	.79	.74	.26	.02	.62	.64	.34	.28	.24	.24
Fp-P	.36	.38	.53	.31	.55	.54	.27	-.04	.23	.28
F-O	.58	.62	-.04	.02	.59	.54	.26	.-.07	.10	.18
Fp-C	.59	.64	.58	.35	.76	.78	.23	.16	.40	.48
C-O	.73	.75	.20	.11	.58	.64	.38	.39	.37	.49
Fp-F	.66	.62	.58	.47	.76	.74	.41	.44	.41	.48
F-C	.60	.68	.49	.24	.56	.56	.01	.20	.11	.39
C-P	.76	.71	.35	.33	.55	.62	.19	.22	.27	.20
P-O	.61	.58	.20	.28	.50	.51	.28	.48	.26	.36
ALPHA	37		35		20		37		46	
	mzm		dzm		mzf		dzf		dos	
	left	right	left	right	left	right	left	right	left	right
Fp-O	.76	.89	.25	.25	.73	.72	.33	.29	.24	.34
Fp-P	.80	.81	.12	.15	.64	.60	.47	.38	.08	.02
F-O	.70	.86	.19	.19	.71	.73	.36	.41	.25	.32
Fp-C	.71	.68	.23	.12	.69	.82	.32	.37	.45	.53
C-O	.59	.59	.03	.10	.54	.63	.07	.05	.00	.15
Fp-F	.71	.71	.26	.19	.80	.88	.30	.47	.43	.44
F-C	.83	.69	.43	.11	.64	.68	.20	.24	.40	.39
C-P	.61	.65	.29	.32	.58	.57	.36	.21	.31	.07
P-O	.67	.73	.41	.21	.52	.48	.21	.23	.01	.27
BETA	34		33		50		36		42	
	mzm		dzm		mzf		dzf		dos	
	left	right	left	right	left	right	left	right	left	right
Fp-O	.49	.61	.36	.27	.66	.69	.53	.34	.28	.36
Fp-P	.72	.72	.35	-.04	.54	.51	.44	.48	.23	.14
F-O	.51	.53	.11	.12	.59	.44	.09	.04	.17	.06
Fp-C	.70	.69	.46	.06	.68	.67	.49	.61	.21	.20
C-O	.57	.61	.29	.35	.64	.59	.55	.37	.22	.39
Fp-F	.51	.75	.26	-.13	.59	.65	.43	.31	.11	.05
F-C	.60	.60	.28	.09	.64	.58	.38	.40	.38	.25
C-P	.65	.64	.17	.38	.68	.65	.58	.30	.21	.26
P-O	.52	.57	.25	.43	.55	.51	.14	.29	.17	.31

Table 8.18 *Measurement 2*: Twin correlations of the log-transformed EEG coherence for all electrode combinations in the left and right hemisphere for each frequency band (delta, theta, alpha, beta). Above each column the number of twins is given.

DELTA	31		26		44		36		42	
	mzm		dzm		mzf		dzf		dos	
	left	right	left	right	left	right	left	right	left	right
Fp-O	.04	.12	.17	.07	.19	-.01	.05	-.01	-.09	.33
Fp-P	.34	.37	.12	-.04	.47	.30	.17	.17	.32	.28
F-O	.54	.49	.30	.32	.41	.37	.26	.31	.18	.44
Fp-C	.53	.44	.22	.10	.47	.32	.13	.01	.41	.30
C-O	.54	.71	.18	.09	.52	.28	.29	.12	.33	.47
Fp-F	.50	.33	.40	.34	.37	.49	.06	-.16	.33	.20
F-C	.59	.64	.09	.01	.57	.46	.20	.28	.38	.47
C-P	.51	.70	.11	.12	.31	.38	.01	.20	.34	.39
P-O	.52	.66	-.08	-.07	.48	.31	.52	.23	.27	.16

THETA	32		29		44		36		42	
	mzm		dzm		mzf		dzf		dos	
	left	right	left	right	left	right	left	right	left	right
Fp-O	.66	.62	-.05	-.02	.31	.32	.14	-.14	.02	-.11
Fp-P	.20	.31	.07	.28	.32	.33	.07	.15	.36	.14
F-O	.66	.62	.12	.19	.49	.56	.08	.07	.25	.23
Fp-C	.39	.47	.29	.41	.57	.50	.04	.17	.45	.42
C-O	.71	.77	.30	.22	.50	.43	.20	.18	.32	.30
Fp-F	.49	.40	.27	.56	.53	.50	.08	.05	.29	.13
F-C	.67	.79	.40	.30	.63	.60	.03	.09	.18	.14
C-P	.67	.69	.14	.30	.24	.49	.01	.05	.14	.17
P-O	.77	.61	-.08	.13	.49	.34	.43	.31	.27	.07

ALPHA	32		29		44		36		44	
	mzm		dzm		mzf		dzf		dos	
	left	right	left	right	left	right	left	right	left	right
Fp-O	.67	.78	.40	.30	.83	.79	.37	.30	.14	.08
Fp-P	.70	.77	.24	.14	.57	.52	.36	.25	-.10	-.13
F-O	.62	.71	.40	.30	.66	.72	.30	.37	.08	.09
Fp-C	.74	.76	.26	.29	.74	.78	.30	.21	.28	.37
C-O	.57	.69	-.03	.09	.59	.60	.00	.07	.23	.32
Fp-F	.58	.63	.22	.26	.79	.81	.22	.21	.39	.21
F-C	.81	.82	.30	.38	.73	.68	.16	.13	.22	.16
C-P	.63	.65	-.18	.03	.54	.59	.04	.08	.39	.34
P-O	.66	.68	.17	.41	.52	.55	.39	.38	-.02	.07

BETA	31		28		41		34		41	
	mzm		dzm		mzf		dzf		dos	
	left	right	left	right	left	right	left	right	left	right
Fp-O	.15	.41	.43	.42	.54	.69	.40	.34	.07	-.01
Fp-P	.52	.48	.00	.20	.52	.64	.30	.12	.29	.10
F-O	.74	.79	.42	.28	.43	.44	.24	-.12	-.04	.16
Fp-C	.44	.50	-.10	-.08	.61	.72	.36	.45	.33	.22
C-O	.74	.70	.22	.19	.58	.63	.58	.60	.37	.44
Fp-F	.60	.56	.01	.08	.66	.62	.32	.18	.28	.19
F-C	.53	.56	.10	.32	.66	.73	.12	.30	.16	.31
C-P	.68	.56	.09	.15	.59	.77	.33	.38	.20	.09
P-O	.68	.69	.08	.24	.45	.33	.55	.53	.26	.38

Table 8.19 Test-retest and split-half correlations of the EEG coherence for combinations of electrode pairs in the left and right hemisphere. In the first 4 columns the test-retest correlations for the oldest (twin 1) and in the second column the correlations of the youngest twin (twin 2). In the next 4 columns the split-half correlation is given of oldest and youngest twin, respectively. The split-half correlation could adjusted by the spearman brown formula for the halving of the number of trials. Above each column the number of subjects is given.

	test-retest				***split-half***			
DELTA	170		170		179		179	
	twin 1		twin 2		twin 1		twin 2	
	left	right	left	right	left	right	left	right
Fp-O	.05	.06	.09	.15	.45	.31	.49	.43
Fp-P	.40	.36	.46	.46	.62	.63	.65	.67
F-O	.57	.48	.55	.58	.72	.74	.72	.79
Fp-C	.49	.49	.37	.45	.70	.67	.74	.74
C-O	.65	.56	.64	.72	.87	.85	.86	.87
Fp-F	.51	.42	.41	.55	.77	.80	.80	.80
F-C	.59	.55	.52	.61	.81	.79	.82	.81
C-P	.58	.63	.64	.66	.86	.86	.84	.87
P-O	.56	.45	.55	.56	.92	.87	.89	.87
THETA	177		177		183		183	
	tw1		tw2		tw1		tw2	
	left	right	left	right	left	right	left	right
Fp-O	.55	.49	.46	.54	.55	.56	.61	.64
Fp-P	.54	.55	.50	.49	.69	.77	.74	.68
F-O	.54	.49	.63	.59	.72	.74	.76	.76
Fp-C	.61	.58	.52	.61	.84	.81	.87	.81
C-O	.65	.66	.69	.75	.87	.88	.86	.89
Fp-F	.56	.44	.50	.64	.88	.85	.90	.88
F-C	.66	.63	.74	.68	.89	.86	.89	.87
C-P	.62	.69	.71	.70	.84	.87	.88	.88
P-O	.63	.61	.70	.60	.91	.90	.89	.90
ALPHA	180		180		184		184	
	tw1		tw2		tw1		tw2	
	left	right	left	right	left	right	left	right
Fp-O	.81	.80	.82	.85	.92	.93	.94	.94
Fp-P	.71	.74	.67	.71	.87	.87	.90	.87
F-O	.70	.74	.74	.77	.86	.88	.86	.88
Fp-C	.76	.76	.70	.72	.94	.93	.94	.93
C-O	.71	.69	.69	.73	.91	.89	.89	.89
Fp-F	.70	.69	.72	.76	.94	.94	.94	.94
F-C	.81	.80	.77	.74	.96	.96	.96	.94
C-P	.78	.76	.73	.71	.94	.91	.93	.94
P-O	.79	.79	.78	.76	.94	.95	.93	.95
BETA	163		163		175		175	
	tw1		tw2		tw1		tw2	
	left	right	left	right	left	right	left	right
Fp-O	.64	.65	.58	.61	.73	.81	.76	.82
Fp-P	.67	.64	.60	.55	.80	.82	.83	.78
F-O	.51	.56	.51	.54	.70	.75	.72	.73
Fp-C	.74	.71	.68	.69	.90	.91	.91	.91
C-O	.69	.64	.70	.72	.89	.88	.89	.91
Fp-F	.67	.59	.55	.64	.91	.91	.95	.94
F-C	.68	.68	.71	.63	.95	.96	.96	.94
C-P	.72	.70	.66	.66	.94	.91	.93	.94
P-O	.73	.68	.67	.67	.94	.93	.93	.94

9

Samenvatting

Tot nu toe was weinig bekend over de genetische en omgevingsinvloeden van individuele verschillen van het centraal zenuwstelsel (CZS). In dit proefschrift wordt beschreven in hoeverre genetische en omgevingsfactoren van invloed zijn op individuele verschillen in het functioneren van het CZS. Om een indicatie van het functioneren van het centraal zenuwstelsel (CZS) te krijgen is met behulp van een electroencephalogram (EEG) de elektrische hersenaktiviteit aan de buitenkant van het hoofd gemeten. De EEG-registraties zijn gemaakt tijdens rust en tijdens het uitvoeren van een eenvoudige taak, een oddball-taak. Van het EEG zijn drie electrofysiologische maten afgeleid: EEG-power, EEG-coherentie en de P300. EEG-power geeft de globale hersenactiviteit weer en geeft informatie over de verschillende frequenties (delta, theta, alpha en beta) waaruit het EEG-signaal is opgebouwd. EEG-coherentie is gebruikt om de samenhang van de hersenactiviteit tussen de verschillende gebieden weer te geven. De P300 geeft de hersenaktiviteit tijdens de taak weer. Het is een component van een 'Event Related Potential ' (ERP). Een ERP is een verandering van de elektrische hersenaktiviteit die samenhangt met de verwerking van een stimulus.
Kennis over de genetische en omgevingsinvloeden op individuele verschillen in CZS kan bijdragen tot meer inzicht in de genetische determinanten van complex gedrag. Voor een groot aantal eigenschappen, zoals cognitieve vaardigheden, persoonlijkheidseigenschappen en psychopathologisch gedrag (Plomin et al. 1990), is bekend dat genetische factoren een belangrijke rol spelen. Het is echter moeilijk om de genetische determinanten te bepalen omdat deze eigenschappen waarschijnlijk beïnvloed worden door meer dan één gen en tot stand komen in interactie met de omgeving. Omdat de hersenen een mediërende rol spelen bij dit soort complexe gedragingen, kan de bestudering van het CZS mogelijk een bijdrage leveren aan het bepalen van de genetische determinanten van complex gedrag.
Om de bijdrage van genetische en omgevingsfactoren te bepalen is de tweelingmethode gebruikt. Deze methode vergelijkt de overeenkomst voor een bepaalde eigenschap, zoals bijvoorbeeld de hersenacktiviteit tussen monozygote (MZ) tweelingen en dizygote tweelingnen (DZ) om een schatting van de erfelijkheid te krijgen. MZ tweelingen zijn genetisch identiek en verschillen tussen twee leden van een tweelingpaar moeten dus veroorzaakt worden door unieke

omgevingsfactoren. Bij DZ tweelingen is het erfelijk materiaal gemiddeld 50% gelijk. Indien de overeenkomst voor bijvoorbeeld hersenaktiviteit groter is in MZ- dan DZ-tweelingen dan is dit een eerste indicatie dat erfelijke factoren een rol spelen. Als de mate van overeenkomst in MZ- en DZ-tweelingen gelijk is dan spelen gemeenschappelijke omgevingsfactoren een rol.
Na een algemene introductie in hoofstuk 1, wordt in hoofdstuk 2 een overzicht gegeven van tweeling- en familiestudies die de oorzaken van individuele verschillen in EEG en ERPs onderzocht hebben. Hoewel de meeste studies weinig proefpersonen gebruikten, kan geconcludeerd worden dat genetische factoren de belangrijkste determinanten zijn van individuele verschillen in het EEG. De invloed van erfelijke factoren op ERPs is minder duidelijk, maar waarschijnlijk speelt een geringer betrouwbaarheid van een ERP-meting hierin een rol. In de meeste tweelingstudies over EEG en ERPs zijn correlaties tussen familieleden gebruikt om een schatting van de erfelijkheid te geven. Weinig onderzoeken hebben gebruik gemaakt van de meer geavanceerde methode van 'model fitting'. Hoewel er duidelijke verschillen zijn in de structuur en functie van verschillende hersengebieden, hebben weinig onderzoeken de invloed van dezelfde genetische factoren op meerdere gebieden onderzocht. Hetzelfde geldt voor verschillen tussen jongens en meisjes, niet eerder zijn sekse verschillen in de genetisch architectuur van het CZS onderzocht. In dit proefschrift is model fitting toegepast voor alle drie electrofysiologische maten, zijn sekseverschillen in genetische architectuur onderzocht en is bekeken in hoeverre dezelfde genetische factoren van invloed zijn op verschillende hersengebieden.
Op twee tijdstippen is de hersenactiviteit gemeten in 213 tweeling paren, eenmaal op 16-jarige leeftijd en de tweede keer op 17.5-jarige leeftijd. Om sekse-afhankelijke effecten te onderzoeken zijn naast MZ en DZ tweelingen van gelijk geslacht ook DZ tweelingen van ongelijk geslacht opgenomen in het onderzoek. Sekseverschillen kunnen tot uiting komen in zowel de grootte van de effecten (verschillende mate van erfelijkheid voor jongens en meisjes) als in de aard van de effecten (andere genetische en/of omgevingsfactoren). De hersenactiviteit is geregistreerd over meerdere hersengebieden. Bovendien zijn dezelfde tweelingen herhaald gemeten, zodat ook de stabiliteit van de genetische en omgevingsinvloeden onderzocht kan worden. In de appendix zijn gegevens over de betrouwbaarheid en stabiliteit van beide metingen weergegeven.
In hoofdstuk 3 worden de resultaten besproken van de genetische analyses van de EEG-power gemeten in 16-jarige jongens en meisjes. De karakteristieken van de EEG-power zijn afhankelijk van de gedragstoestand waarin de persoon zich bevindt en van het hersengebied waarin wordt gemeten. Uit de resultaten blijkt dat de bijdrage van genetische factoren aan individuele verschillen in de EEG-power in alle hersengebieden hoog is, gemiddeld 80% van de variantie wordt verklaard door genetische factoren. De invloed van erfelijke factoren was iets kleiner voor de

delta-frequentie (lage frequenties) in de frontale hersengebieden, mogelijk veroorzaakt door interferentie met de oogbewegingen. Er zijn bijna geen sekseverschillen gevonden in genetische architectuur van de EEG-power. Slechts voor enkele hersengebieden van delta, theta en beta (enkele banden van frequencies van de EEG-power) was de proportie door genetische factoren verklaarde variantie groter in jongens dan meisjes, deze verschillen waren echter erg klein.
Dus, in tegenstelling tot de anatomische en functionele verschillen van de hersengebieden, is de erfelijkheid van de EEG power bijna even hoog in de verschillende gebieden van de cortex. Hoewel er aanwijzingen zijn dat de morfologische variatie groter is (en de erfelijkheid lager) in de jongere, frontale hersengebieden (Meshkova & Ravich-Shcherbo, 1982; Markowitsh, 1988) wordt dit niet weerspiegeld in de genetische factoren die EEG-power beïnvloeden.
Met behulp van multivariate genetische modellen is het mogelijk om te te kijken naar de oorzaken van de covariantie tussen de verschillende hersengebieden en kan de vraag beantwoord worden in hoeverre de covariantie tussen de verschillende hersengebieden beïnvloed wordt door dezelfde genetische factoren en/of omgevingsfactoren. Een hoge genetische correlatie ontstaat wanneer de genetische factoren die de afzonderlijke variabelen beïnvloeden gecorreleerd zijn. Dit suggereert dat dezelfde genen een rol spelen. Multivariate modellen zijn gebruikt om na te gaan of de dezelfde genetische factoren de covariantie tussen hersengebieden in de linker en rechter hersenhelft verklaren. Uit de resultaten blijkt dat de covariantie tussen de twee hersenhelften voornamelijk wordt bepaald door dezelfde genen, dit geldt voor alle hersengebieden (behalve Fp1-Fp2) van alle frequentiebanden. Vervolgens is per hersenhelft gekeken of de covariantie tussen de verschillende hersengebieden bepaald wordt door dezelfde genetische factoren. Voor de alpha-frequentie waren de genetische correlaties tussen de verschillende schedellocaties binnen een hersenhelft erg hoog. Voor de overige frequentie-banden zijn de fenotypische (geobserveerde) correlaties tussen de verschillende hersengebieden ook hoog. Waarschijnlijk worden de verschillende hersengebieden van deze frequentie-banden beïnvloed door dezelfde genetische factoren.
In hoofdstuk 4 zijn de resultaten van de P300 besproken. Tijdens een 'oddball' taak is de hersenenactiviteit gemeten. In deze taak werden series plaatjes aangeboden, waarbij de 'targets' minder frequent worden aangeboden dan de 'nontargets'. Bovendien moesten de targets geteld worden. De P300 treedt met name op als hersenrespons op de targets. De P300 wordt meestal geïnterpreteerd als een index van stimulusevaluatie en/of hoeveelheid informatie die wordt verwerkt. De hersenaktiviteit is over meerdere gebieden gemeten en sekseverschillen in de genetische architectuur zijn onderzocht. De resultaten van de genetische analyses zijn echter minder eenduidig dan de resultaten van de EEG-power. Hoewel er een duidelijke familiale overeenkomst werd gevonden binnen tweelingparen, was het

niet mogelijk om te bepalen of deze overeenkomst veroorzaakt werd door genetische verwantschap of door het feit dat ze opgroeien en leven in hetzelfde gezin. Waarschijnlijk is dit probleem ontstaan door een gebrek aan voldoende statistische power. Bovendien was de proportie door erfelijke/gemeenschappelijke omgevingsfactoren verklaarde variantie van de P300 kleiner (varieert van 25% tot 40%) dan de proportie verklaarde variantie van de EEG-power (gemiddeld 80%).
De relatieve bijdrage van de familiale factoren was verschillend in jongens en meisjes. Echter, een interpretatie van deze sekseverschillen in termen van verschillende genetische of omgevingsinvloeden is moeilijk te geven in verband met het gebrek statistische power.
De proportie verklaarde variantie door familiale factoren voor de verschillende hersengebieden was iets lager in de centrale en parietale gebieden dan in de occipitale gebieden. Uit de multivariate genetische analyse blijkt dat dezelfde genetische/om-gevingsfactoren een rol spelen in de verschillende gebieden. Dit geldt zowel voor de targets als de nontargets. Daarnaast was er een tweede factor die hoog laadde op de occipitale gebieden. Deze factor zou een mogelijke aanwijzing kunnen zijn voor meer dan één neurale generator van de P300. Vervolgens werd bekeken of de covariantie tussen beide soorten stimuli beïnvloed werd door dezelfde genetische en/of omgevingsfactoren. Gevonden werd dat dezelfde genetische/omgevingsfactor de targets en nontargets beïnvloedde, maar daarnaast werd er een tweede genetisch/omgevingsfactor gevonden die alleen invloed had op de nontargets. Dit impliceert een interactie tussen de psychologische test conditie en de genetische/omgevings factoren: de mate van beïnvloeding door genetische/ omgevingsfactoren is afhankelijk van informatieverwerkende processen.
In hoofdstuk 5 is een beschrijving gegeven van de uitkomsten van de genetische analyses van de EEG-coherentie. EEG-coherentie is een EEG-index welke is toegesneden op de meting van de samenhang in hersenaktiviteit tussen verschillende hersengebieden. Korte en lange cortico-corticale verbindingen zouden ten grondslag liggen aan de coherente activiteit van de verschillende hersengebieden. Een hoge EEG-coherentie tussen twee hersengebieden zou de mate van 'verbindingen' reflecteren. Omdat dit het eerste onderzoek is naar de genetische beïnvloeding van EEG-coherentie, is er een inventarisatie gemaakt van genetische/omgevingsinvloeden over paren van electrode-combinaties over langere en korter afstanden in verschillende frequenties.
Uit de resultaten blijkt dat 40 tot 60% van de variantie in EEG-coherentie verklaard wordt door genetische factoren. De grootste invloed van genetische factoren werd gevonden voor de electrode-combinaties van de alpha-frequentie. De laagste genetische invloed werd voor delta-frequentie over de langere afstanden gevonden.

Voor alle frequenties werd op fenotypisch niveau een significant hoofdeffect van sekse gevonden. Voor de meeste combinaties van electrodenparen was de EEG-coherentie hoger in meisjes dan jongens. Een sekseverschil werd niet teruggevonden in de genetische beïnvloeding.

In hoofdstuk 6 wordt naast de samenvatting ook de statistische power, de betrouwbaarheid en de fenotypische en genetische stabiliteit besproken.

Statistische power. De statistische power van een tweelingonderzoek is afhankelijk van een aantal factoren, zoals het aantal tweelingen en de grootte van de werkelijke genetische invloed in de populatie. Indien de variantie in een bepaalde eigenschap voor 80% wordt bepaald door genetische factoren dan zijn ongeveer 50 tweelingen (25 MZ en 25 DZ tweeling paren) voldoende om een statistische power van 80% te bereiken. Echter, om kleinere genetische effecten te detecteren is een groter aantal tweelingen nodig, bijvoorbeeld bij een erfelijkheid (h^2) van 60% zijn er 180 tweelingen nodig, bij een h^2 van 40% zijn er 597 tweelingen nodig. Voor de P300 amplitude was de hoeveelheid variantie verklaard door familiale overeenkomst ongeveer 40%. Er was niet voldoende statistische power om de overeenkomst binnen tweelingparen toe te wijzen aan genetische of aan gemeenschappelijke omgevingsfactoren. Hiervoor zou een grotere steekproef nodig zijn. Een alternatieve oplossing om de statistische power te vergroten is om de meetfout te betrekken in de genetische analyse.

Betrouwbaarheid. De betrouwbaarheid van een meting vormt de bovengrens van de grootte van de erfelijkheid (Falconer, 1981). Erfelijkheid wordt berekend als de variantie verklaard door genetische factoren gedeeld door de totale variantie (is de som van erfelijke en unieke omgevingsfactoren). Het gedeelte van de unieke omgevingsvariantie bestaat uit individu specifieke omgevingsinvloeden en mogelijke meetfout. Een hoge meetfout zal daarom een vertekend beeld van de erfelijkheid opleveren. In dit proefschrift is de erfelijkheid van de EEG-power, EEG-coherentie en P300-amplitude geschat met traditionele genetische modellen, waarin de meetfout is inbegrepen in de variantie van de unieke omgevingsfactor. Het opnemen van de betrouwbaarheid in het genetische model zou het mogelijk maken om de meetfout van de werkelijke unieke omgevingsinvloeden te scheiden en mogelijk een hogere schatting van de genetische factoren opleveren. De split-half correlaties van de EEG/ERP maten geven een indicatie van de betrouwbaarheid (zie appendix). Een hoge split-half correlatie wijst op een lage meetfout. De meetfout is hoger voor de P300-amplitude en EEG-coherentie, daardoor is het mogelijk dat voor deze maten de erfelijkheid is onderschat.

Stabiliteit van de fenotypische waarden. De stabiliteit wordt weergegeven door de test-hertest correlaties, die berekend zijn tussen twee metingen met een tussenliggende periode van anderhalf jaar. Een lage stabiliteit is een indicatie voor veranderingen die optreden als het gevolg van maturatie van het brein. Uit

test-hertest correlaties van alle EEG/ERP maten blijkt er weinig evidentie voor maturatie.
Stabiliteit van genetische invloeden. De invloed van erfelijke factoren heeft geen constante waarde maar kan tijdens het leven veranderen. De relatieve bijdrage van erfelijke factoren kunnen bij het ouder worden toenemen (zoals b.v. bij het IQ) of afnemen (zoals in het geval van de bloeddruk). Dit hoeft geen verandering op moleculair niveau te zijn, maar kan een gevolg zijn van een kleinere of grotere invloed van omgevingsfactoren. Daarentegen kan de erfelijkheid gelijk blijven, maar kunnen verschillende genen een rol gaan spelen. In de appendix zijn de tweelingcorrelaties van twee metingen weergegeven om een eerste indruk te geven van de stabiliteit van genetische/omgevingsfactoren. Op het eerste gezicht vertonen de tweelingcorrelaties van de drie electrofysiologische maten geen grote verschillen tussen de meting op 16- en 17.5 jarige leeftijd. Alle drie electrofysiologische maten vertoonden een hoge genetische stabiliteit.

In het proefschrift werd de nadruk gelegd op de genetische analyse van EEG/ERP maten gemeten in 16 jaar oude tweelingen. Uit de resultaten blijkt dat de individuele verschillen in EEG maten voornamelijk beïnvloed worden door genetische factoren, met name EEG-power is erg erfelijk. Met een erfelijkheid van 80% is de EEG-power een van de meest erfelijke eigenschappen. Dit vertelt uiteraard niets over welke genen een rol spelen bij hersenfuncties. Om genen te identificeren zijn 'linkage' (=koppeling) onderzoeken nodig, die gebruik maken van zowel de recente ontwikkelingen in de moleculaire genetica en DNA technologie alswel de recente ontwikkelingen in statistische technieken om linkage technieken toe te passen op complexe eigenschappen. In het algemeen zijn er grote aantallen (DZ) tweelingen nodig om 'linkage' te detecteren tussen een quantitative trait locus (QTL = plaatsen op het chromosoom die een bepaalde eigenschap beïnvloeden) en een DNA marker, vooral als de erfelijkheid klein is. De kans op 'linkage' kan vergroot worden door multivariate fenotypen te gebruiken of door individuele genotypische waarden te schatten (Boomsma, 1996). Omdat in het onderzoek, beschreven in dit proefschrift, zowel multivariate fenotypen geanalyseerd zijn als een hoge erfelijkheid van het EEG is gevonden, is de uitgangspositie om te zoeken naar genen die de hersenactiviteit beïnvloeden gunstig en daardoor mogelijk ook een veelbelovend uitgangspositie voor het onderzoek naar de genetische determinanten van complexe gedragingen.

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