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Summary and Discussion

The four papers in this thesis were based on a large longitudinal study of 209 twin pairs. These 418 children underwent extensive electrophysiological testing at the Vrije Universiteit in Amsterdam when they were 5 years old and again when they were 7 years. The main goal of this thesis was to examine the architecture of individual differences in a set of electrophysiological parameters that have been cited extensively in the psychophysiological literature as indices of brain maturation, and as correlates of behavioral and cognitive traits. The first aim was to establish the relative influences of genetic and environmental factors on individual differences in brain function at age 5. The twin method is a powerful method to this end. Using MZ and DZ twins allows the simultaneous assessment of genetic and shared (family) environmental influences. Thus, rather than arguing about the importance of nature and nurture for the preschool child's development, this twin study provides a solid quantification of such influences. As might have been expected, the contribution of both environment and genes was important. Nonetheless, most of the evidence implicates genes as the main source of interindividual differences in childhood EEG indices of neural functioning. In the first part of this discussion the main findings on heritabilities of EEG indices will be summarized.

In addition to the examination of the relative influences of genes and environment at age 5, an important goal was to detect changes in these influences from age 5 to age 7. In this period children enter the formal schooling system in the Netherlands, which may have a clear impact on both shared and unique environmental sources. It is also an age at which vital changes in grey and white brain matter are at their peak (Huttenlocher, 1979; 1994; Huttenlocher et al., 1982; Chugani et al., 1987; Chugani, 1994; Jernigan, 1991; Pfefferbaum et al., 1994). These changes strongly depend on proteins affecting neural growth factors, myelination, and neurotransmission. The regulation of these proteins, in turn, depends on the individuals genotype. It is not surprising, therefore, that this age has been characterized as the beginning of a gradual increase in genetic influences on individual differences in cognitive abilities (Cherny & Cardon, 1994; Boomsma & Van Baal, in press). Also, this age period is known for a clear change in the quality of cognition, that has been best described by Piaget and Inhelder (1969). Around age 6 children make a transition from a pre-operational to an operational phase, that is, they learn to notice that the quantity of something remains the same, despite transformations in its appearance. Thus, the age range of 5 to 7 is a period of change in both qualitative and quantitative differences in cognition. If changes in cognition coincide with changes in brain function, which is the central axiom of psychophysiology, then this period seems optimal for detecting changes in the genetic and environmental determinants of EEG parameters. The second part of this discussion deals with these changes across time.

Heritability of EEG parameters in children

The recent surge in output from the field of behavior genetics has established beyond doubt that a wide range of human behaviors are influenced by genetic factors (e.g., Rose, 1995; Plomin et al., 1994; Boomsma, 1993; Heath et al., 1995; Eaves et al., 1989). This includes various measures of cognitive ability, motor skills, personality, and susceptibility for problem behavior and life style. To explain how genetic variation can account for behavioral variation, it is desirable to study intermediate phenotypes, like the functional organization of the brain (Lander, 1988). Brain functioning can be indexed by the electroencephalogram (EEG), which measures electrical activity of the brain. The EEG can be measured at rest as well as in response to a standardized stimulus, the so-called event related potentials or ERPs. If EEG is measured at different locations on the scalp, coherence of EEG between various scalp regions can be used to estimate the functional connectivity of these regions. Although some earlier studies have addressed heritability of some of these EEG phenotypes, only a small number of children were studied before we commenced this study in Dutch twins. Our study, therefore, presents the first firm data on the genetic architecture of EEG power, ERP-P3, and EEG coherence in children.

EEG Power

In studies of children, EEG power has been used as the major index for brain maturation. Around 1970, a Swedish group of researchers reported on electroencephalographic data of 561 children aged 1 to 21 years (Petersén & Eeg-Olofsson, 1971; Matoušek & Petersén, 1973). This study provided important data on development of children's EEG. It was shown that during development EEG changed from a signal containing mainly slow waves to a signal with substantially less delta and theta activity, but more alpha and beta activity. The dominant EEG frequency in adults lies in the alpha range (around 10 Hz), but is lower in young children (around 7 Hz). Relative power (the ratio of power in a certain band over total power in the signal) or the theta/alpha ratio is often used to reflect these shifts in the dominant EEG frequency components. In chapter 2 of this thesis it was shown that absolute and relative EEG power in all broad bands (delta, theta, alpha1, alpha2, beta1 and beta2) were highly heritable at age 5 (with h^2 = 70% on average). In fact, these traits are among the most heritable polygenic traits found in children. This suggests that the individual differences in rhythmic activity of cortical pyramidal cells are under strong genetic control in childhood. At first sight, this finding shows great promise to bridge the gap between genes and behavior. If the theta/alpha ratio tells us something about brain maturation, then finding specific genes influencing this ratio may help us to determine which processes are involved in the

development of the subcortical and cortical generators of these rhythms. Deviations in these processes may be reflected in behavior. With his "neurometrics" approach, John (e.g., John, Prichep, Fridman & Easton, 1988) was able to discriminate between dementia, alcoholism, unipolar and bipolar depression, based on quantitative EEG data only. However, the direct association of EEG power with behavior has not been unequivocal (Gale & Edwards, 1986). The relationship between EEG power and cognitive abilities is even less clear (Vogel et al., 1968). In fact, it has been argued (Van der Molen & Molenaar, 1994) that there is no merit in investigating EEG when the child is committed to idle contemplation bearing little or no relationship to cognition. Thus, notwithstanding the fact that EEG power does seem to track individual differences in the stage of maturation of the brain, it is unlikely that individual differences in normal behavior or cognition are well indexed by background EEG.

ERP-P3

To index brain processes underlying cognition, psychophysiological researchers have increasingly turned to the event related potentials. The P3 (also known as P300) showed particular promise for this purpose. It can be reliably evoked, even in young children, in a simple oddball paradigm. The latency of the P3 (i.e., the timing of its peak) provides a measure of mental processing speed that is independent of behavioral responding (Donchin et al., 1986). Latency gradually decreases with age until young adulthood (Courchesne, 1977; 1978; 1990; Polich et al., 1990; Friedman, 1992). Individual differences in P3 latency have been suggested to be related to faster processing speed in various tests of cognitive function (Ladish & Polich, 1990; Emmerson et al., 1990). P3 amplitude is sensitive to task relevance and (subjective) probability of the stimulus and is suggested to be proportional to attentional resources invested in the maintenance and updating of working memory (Polich, 1996). Indeed, larger P3 amplitude has been associated with superior memory performance (Fabiani et al., 1990; Noldy et al., 1990). P3 latency has been used to index individual differences in cognition, whereas P3 amplitude has been used as an indicator of clinical disorders, for example attention deficit hyperactivity disorder (Robaey et al., 1992), autism (Kemner et al., 1992) and alcoholism (Begleiter et al., 1988; Polich et al., 1994). This may indicate that P3 amplitude has a predictive value as an index of susceptibility for deviant behavior. This thesis tested the extent to which this psychophysiological marker, is of a genetic nature.

During data reduction and analysis we were confronted with a very large intraindividual variability in the P3 wave form. This was particularly problematic for targets, of which only 25 trials were available to compute the average latency and amplitude. Even after

latency correction with a Woody filter (Woody, 1967), data from all frontal and temporal leads had to be discarded because of the bad signal to noise ratio. In addition, occipital leads had to be dropped, because of the strong interference of the dominant 4-8 Hz rhythmic activity on the P3. Because of the low reliability of the P3, structural model fitting on the remaining electrodes yielded badly fitting models that explained all observed variance by unique environmental factors. Therefore, a multivariate approach was employed that allowed a distinction between reliable genetic or environmental variances and measurement error. This was done by computing two separate P3 latencies and two separate P3 amplitudes on the odd and even nontarget trials. The odd and even trials were used to estimate the measurement error on nontarget P3 and it was assumed that this measurement error was similar to that on target trials. The fit of the structural models greatly improved for both targets and nontargets, when measurement error was modeled in this way. Latency of P3 appeared to be a heritable trait in 5 year olds (h^2 = 34%). This is well in accordance with twin data from adolescents and adults. In these studies, measurement error was not accounted for, but wave forms in older subjects are generally more reliable. Taken together, adult and child twin data suggest that genetic contribution to individual differences in speed of stimulus processing is present from an early age onwards. This does not, however, preclude the possibility that different genes influence P3 latency at different ages.

Heritability of P3 latency is quite comparable to that of reaction time (Rijsdijk, 1997). Both have been associated with IQ (Chalke & Ertl, 1965; Barrett & Eysenck, 1992; Vernon, 1987). Vernon and colleagues (1993) have proposed a neural efficiency hypothesis to explain the significant relationship between reaction time and IQ: the faster the stimulus processing is completed, the more time for stimulus elaboration or processing of other stimuli is available in working memory. Similar arguments can be put forward to explain the relationship between P3 latency and IQ. In our data, low but significant correlations (.19) were found between IQ and P3 latencies. It was not tested, however, whether the genetic factor influencing IQ was the same as that influencing P3 latency. A future application of the approach in the present study is to analyze IQ and P3 latency in a multivariate genetic model.

For P3 amplitude a clear discrepancy between the heritability of targets (which was low) and nontargets (which was moderate to high) was found. The largest part of the individual differences in target P3 amplitude appeared to be explained by unique environmental factors only. Yet, according to model fitting the genetic factor influencing nontargets appeared to be the same as that influencing targets. In the discussion of chapter 3 it is suggested that this genetic factor probably affects individual differences in the first part of stimulus processing of both types of stimuli, that is, everything until the detection

of nonrelevance of stimuli. This genetic factor did not affect individual differences in the part of stimulus processing that is specific to targets. We interpreted this as being caused by the difficulty of standardizing motivational effort and general arousal in these children. However, another possibility must also be considered. Four times more nontarget than target trials were presented, improving signal to noise ratio of nontargets considerable above that of targets. This may have caused underestimation of heritability in target ERPs.

EEG Coherence

Although the P3 has a well-documented relationship to cognition, its sources in terms of neural generators are largely unknown (Johnson, 1993; Polich, 1996). In contrast, EEG coherence can be directly linked to processes like axonal sprouting, synaptogenesis, myelination, and pruning of synaptic connections (Kaiser & Gruzelier, 1996). Thatcher and coworkers (Thatcher et al., 1986; Thatcher et al., 1987; Thatcher, 1994) have suggested that coherent activity between two electrodes measures the number of cortico-cortical connections and synaptic strength of these connections between the brain areas near those electrodes. In their 'two-compartmental' model of EEG coherence, based on the structural properties of the human cortex, compartment A receives input from the short fiber system, that is, from axonal connections of neighboring pyramidal cells, whereas compartment B receives input from the long fiber system, which contains long-distance axonal connections from other parts of the brain that represent the majority of the white matter fibers. Both systems contribute to coherence at the relatively short distances (i.e., to about 14 cm), whereas coherence at the longer distances is influenced by the long fiber system only.

Analyses of coherence data were presented twice in this thesis. In chapter 4, heritability estimates on coherence at age 5 were presented. A substantial difference in measurement error of the various electrode combinations was noted, such that reliability decreased with distance. In chapter 5, reliability was accounted for in the structural model fitting. This yielded heritability estimates between 37% to 75%, depending on electrode location. In this reanalysis, the difference found in the first analyses between additive genetic factors for short distance coherence versus dominance effects in long distances was not confirmed. We did, more importantly, confirm our original finding that heritabilities of long distance coherences were higher compared to heritabilities of short distance coherences. Therefore, the heritability estimates provide support for a two compartment model. Furthermore, the increase in heritability with increasing distance appeared to be most pronounced in the anterior to posterior direction. In the anterior to posterior direction heritabilities increased with increasing distance, whereas in the

posterior to anterior direction heritabilities were very much alike. The fact that heritability was sensitive to the direction of cortico-cortical connectivity supports Thatcher's claim that individual differences in coherence reflect axonal connectivity of the brain, rather than simple volume conduction (Thatcher et al., 1986). Nonetheless, recent reports did show that volume conduction and linked ear reference, as used in the present study, may inflate coherence (Lagerlund et al., 1995) and introduce spurious individual differences. In future analyses we might, therefore, recompute coherence after a Laplacian transform of the raw EEG data. This transform reduces the effects of volume conduction.

Based on studies of dementia and callosal disconnection patients (Dunkin et al., 1994; 1995), in adults, a decrease in coherence is thought to reflect a loss of functional connectivity. In children the reverse picture is seen. Gasser et al. (1987) showed that 10 to 13 year old mildly retarded children had higher coherences than controls. Higher short distance coherences were also found in dyslectics (Leisman & Ashkenazi, 1980) and in Down's syndrome (Schmid et al., 1992). In a population of normal children, Thatcher et al. (1983) showed that a negative correlation exists between full-scale IQ and short-distance coherences. A possible explanation for these paradoxical interpretations of coherence in adults and children was provided by Kaiser and Gruzelier (1996). They proposed that coherence in childhood may increase during the formation of new connections and decrease through pruning of the non-functional part of those synapses. Decreases in short distance coherence in childhood, reflecting pruning, may thus actually improve brain function. After the last growth cycle in adolescence, during which the connections from the prefrontal regions to the rest of the brain are fully matured (Kaiser & Gruzelier, 1996), all further decreases in coherence reflect inadverted pruning of functional connections, and thus damage to normal brain function. However, caution is needed in assuming that changes in coherence solely reflect changes in synaptic density. Apart from synaptic growth, increases in coherence during childhood may reflect improved brain function through a gradual increase in myelination of the axons in cortico-cortical tracts. This process is known to continue up until young adulthood, and is at its peak in young childhood. Increases in coherence in childhood may thus reflect a double growth effect: formation of new synapses and increased myelination. If one accepts a crucial role for genes in these processes, it is not surprising that the present study has clearly established this intriguing phenotype as a genetic trait.

In summary, the study described in this thesis provides information not previously available on the determinants of individual differences in brain function in a large, normative sample of young children. For most EEG indices (P3 amplitude to targets being the major exception) the main cause of individual differences were genetic

differences between children. More distant behavioral traits need not show the same high degree of heritability. In this same group of children, for instance, IQ at age 5, assessed by the RAKIT, interindividual variance could be explained predominantly by common environmental influences shared by children growing up in the same family (C). No evidence for shared environmental influences was found in any of the EEG and ERP indices. At face value, this may be taken to mean that "biological" traits will not be very useful to explain actual behavior. However, it has been pointed out by Plomin and DeFries (1985) that small genetically-based differences at a young age may be amplified across the life span. For instance, a small advantage in processing speed or frontal to occipital connectivity may have a small impact at age 5, but may start to make a large difference at later ages, when processing becomes more complex and the impact of small advantages in basic neural communication increases. Therefore, further research aimed at finding the actual genes influencing the EEG will contribute to our understanding of complex information processing as well as normal and aberrant behavior. In that mission, detecting linkage between a chromosomal region and EEG phenotypes would be a next logical step.

To detect linkage of a trait to a quantitative trait locus (QTL) on the chromosome, a high heritability is an advantage, because this enhances the possibility of finding a QTL that explains a substantial amount of the observed variance. The traits studied in this thesis are promising in this respect. EEG power is particularly promising, because very high heritabilities were found for this trait. In fact, this probably is the most heritable trait found in young children. A further advantage is, that EEG power is simultaneously assessed at 14 scalp locations, thus yielding the possibility of multivariate analyses, which greatly enhances the power to detect QTLs (Boomsma, 1996). This multivariate advantage also applies to P3 latencies and nontarget P3 amplitudes. Although these are slightly less heritable, they have the additional advantage of being more directly linked to cognition than EEG power. In this thesis it was shown that, prior to linkage, it is essential to account for measurement error in these indices. It also needs to be established whether the difference in heritability of P3 amplitude of targets and nontargets is real, or whether this difference may be a result of the fact that we used fewer target trials to obtain an averaged ERP than for nontargets. When the difference between targets and nontargets is real, we may question the use of target P3 amplitudes as possible genetic markers for alcoholism (Polich et al., 1994).

A disadvantage of using P3 amplitudes and P3 latencies to locate QTLs is, that we do not have a firm idea of which neurophysiological structures are responsible for the generation of the P3 wave and individual differences therein. Differences in EEG coherence, in contrast, can be more easily linked to structural aspects of the brain such

as axonal sprouting, synaptogenesis, expansion of existing synaptic terminals, myelination, pruning of synaptic connections, presynaptic changes in the amount of neurotransmitter or changes in the postsynaptic response to a given neurotransmitter. These aspects, in turn, could provide an indication of the type of protein substrates that an established QTL is coding for during follow-up studies with candidate genes. Because coherence is found to be largely heritable and because it is close to neurophysiological structure it provides an attractive starting point for linkage aimed at QTLs associated with cognitive abilities and behavior. In this regard, the recent development of techniques for evoked changes in coherence (Andrew & Pfurtscheller, 1996) is particularly promising, because it may provide phenotypes more directly linked to cognition and overt behavior than resting coherence.

Stability of genetic influences on the EEG

On average 1 year and 7 months after the first assessment at age 5, 192 of the initial 209 twin pairs returned to the laboratory for a second measurement session. This allowed the study of changes and stability of the influences on the EEG phenotypes during development. Developmental behavior genetics recognizes the importance of shifts in genetic and environmental factors on interindividual differences during development. Therefore, in addition to the questions concerning the relative influences of genetic and environmental factors on interindividual differences in electrophysiological indices of brain functioning, the changes in these influences over time were investigated. This investigation consisted of two parts: firstly, are (existing) genetic influences amplified, that is, does the relative importance of genetic over environmental influences, as expressed by heritability (h^2) change over time? Secondly, do new genetic influences emerge, that is, are different genes expressed at ages 5 and 7?

The 5 to 7 age span was chosen for a number of reasons. In developmental psychology it is well recognized that from infancy to adulthood, human brain and behavior undergo large changes. Part of these changes consists of continuous growth, but in addition, a number of periods during childhood can be identified that express more pronounced development. These periods are commonly indicated as growth spurts. One of these growth spurts is seen between ages 5 and 7 years. In this period remarkable stagewise development in cognition is seen (Piaget, 1966; Piaget & Inhelder, 1969): the transition from pre-operational to concrete-operational stage is made, in which the child learns the concept of conservation. Transition from one stage to another always involves

qualitative changes in the child's cognition, and is not reversible. Therefore, children at age 5 are in a qualitatively different phase than children at age 7.

Biological psychology provides a second perspective on change during childhood. Converging evidence from morphometric, PET and MRI studies (Huttenlocher, 1979, Huttenlocher et al., 1982; Chugani et al., 1987; Jernigan et al., 1991) suggests that early brain development from childhood to adolescence is characterized by a gradual decrease in grey matter and an increase in white matter. The decrease in grey matter, starts at about 4 years (Pfefferbaum et al., 1994), and is thought to reflect a pruning of synaptic contacts, such that only connections incorporated into functional networks survive, whereas random connections are eliminated. The increase in white matter may reflect the ongoing myelination of the many cortico-cortical connections. Both these effects contribute to a better differentiation and integration of functionally distant brain areas.

Finally, research in behavior genetics itself provides an indication of development in the age span of 5 to 7 years. In the longitudinal data from the Colorado Adoption Project (Cherny & Cardon, 1994) heritability of childhood IQ was shown to increase after 4 years of age. More importantly, new genetic factors were emerging somewhere between the ages 4 and 7. This, again, may indicate qualitative differences between young children (4 or 5) and somewhat older children (age 7).

In the physiological realm significant developmental changes can be non-invasively indexed by a number of EEG parameters. Substantial empirical evidence from these maturational EEG indices suggests that, on top of continuous growth, various periods of growth spurts in brain activity can be observed. Growth spurts were particularly demonstrated for EEG mean relative power (Hudspeth & Pribram, 1992) and for EEG coherence and phase (Thatcher, 1991; 1992; 1994a; 1994b; Thatcher et al., 1987). Hudspeth and Pribram (1992), using data of Matoušek and Petersén (1973), showed that, in addition to clear continuous growth, growth spurts in mean relative EEG power of four distinctive brain areas existed. They suggested 5 periods of increased development: around ages 4, 8, 12, 15 and 19 years. Their data show a period of relatively little changes between ages 5 and 7. Growth spurts were also found in EEG coherence and EEG phase by Thatcher and colleagues (Thatcher, 1991; 1992; 1994a; 1994b; Thatcher et al., 1987). Their studies concerned a group of 577 children aged 1 to 17 years, for whom EEG was collected on 19 scalp locations. Figure 6.1 (adapted from Thatcher et al., 1987) shows biennial changes in coherences for left and for right intrahemispheric coherences from prefrontal to more posterior scalp locations. The largest increase in coherence was found around age 6. Other peaks were at 10 and 13 years. This suggests that the large changes in coherences are systematically found after the large changes in relative EEG power. They may be related to the same phenomenon, and both Thatcher

and colleagues and Hudspeth and Pribram suggest that the growth spurts in the EEG are probably related to Piagetian stage transitions.

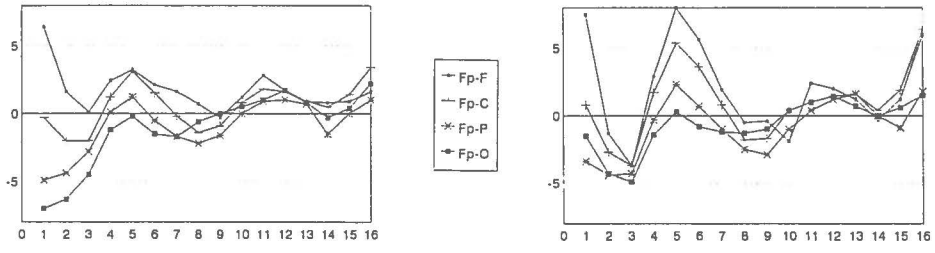

Figure 6.1 *Biennial differences in EEG coherence from ages 1 to 17 years, for left and for right hemispheres, for coherences between prefrontal scalp locations and frontal, central, parietal or occipital scalp locations. Periods with strong increases in coherence are interspersed with periods of less increase, or even decrease in coherence. (Figure adapted from Thatcher et al., 1987).*

In this thesis the development of electrophysiological indices, and possible growth spurts therein, were approached from a behavior genetics viewpoint. Specifically, we tested whether heritability changed over time and whether we could detect discontinuities in the genetic architecture of EEG power, P3 and coherence.

EEG power

Figure 6.2 shows that the power spectra of 7 year old children clearly differ from power spectra of 5 year olds. The alpha peak is more prominent at age 7, and especially delta and theta activity seem to have decreased with age. Although complete analysis of longitudinal EEG power data was not pursued in this thesis, in favor of analyses on ERP and coherence, some preliminary analyses were done for this discussion. Decomposition of variances and covariances into genetic and environmental factors showed that the high heritabilities reported in chapter 2 remained high in 7 year olds. Phenotypic correlations between EEG powers at age 5 and age 7 were about .8 (absolute alpha1-band) and cross-correlations were about twice as high for MZ twins compared to DZ twins, suggesting that the stability between ages 5 and 7 is mainly genetic. No information is yet available about the emergence of new genetic factors.

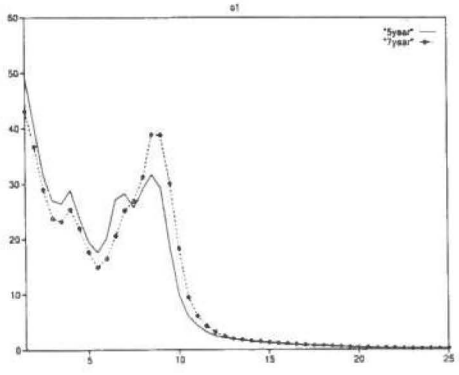

Figure 6.2 *Power spectra averaged over all subjects during rest with eyes closed for left occipital electrode position for 5 year old children and for 7 year old children. The power spectrum of 5 year old children shows more EEG power in the delta and theta frequency bands (.5 to 7.5 Hz), but less EEG power in the alpha frequency bands (8.0 to 12.5 Hz) than the power spectrum of 7 year old children.*

ERP-P3

P3 was chosen as a first target for longitudinal genetic analyses. In chapter 3 the results of genetic and environmental influences on the stability of P3 amplitude and P3 latency were presented. Contrary to our expectations, our results suggest that the maturation of P3 is a continuous process. This is surprising because P3 appears to closely mirror the time-course of development of grey and white matter (Courchesne, 1977; Courchesne et al., 1987). Changes in P3 amplitude are tentatively interpreted as a result of differences in synaptic density, whereas changes in P3 latency are probably related to changes in myelination (Courchesne et al., 1987). Since myelination affects neural speed, a decrease in P3 latency over time might reflect an increase in information processing speed (Reed & Jensen, 1984). Previously, a relationship between P3 latency and IQ had been reported (Chalke & Ertl, 1965; Barrett & Eysenck, 1992). Since new genetic factors emerge for IQ data in the 5 to 7 age range (Cherny & Cardon, 1994), new factors were expected to emerge for P3 latency. Instead, a single genetic factor found at age 5 still had large effects on P3 latency at age 7 on all leads. A significant additional genetic factor emerged only for P3 latency at Cz and P3 scalp locations, but they explained only a small part of the interindividual variance. Therefore, clear emergence of new genetic factors, as had previously been found for IQ in children of this age, was

not found for P3 latency. However, in the same twins as used in this study, Boomsma and Van Baal (1997) showed that interindividual differences in general intelligence at ages 5 and 7 are also influenced by the same genetic factors. No new genetic influences emerged for IQ at age 7. Thus, the absence of such influences on P3 latency in these twins is less surprising.

A priori, there was good reasons to expect a change in the genetic contribution to P3 amplitude. Previous studies suggested a discontinuity in P3 topography as a function of cognitive developmental stage. Stauder and colleagues (Stauder, 1992; Stauder et al., 1993; 1995) have claimed, using dipole analyses, that different P3 sources are found for children in the Piagetian preoperational phase than for children in the operational phase, a phase transition that occurs somewhere between ages 5 and 7. In this context, our finding of a common set of genes for both ages and no new genetic influences is not consistent, since it is unlikely that a new source of P3 would only be influenced by new environmental effects. It must be noted, however, that the present study did not allow for a detailed topographical analysis due to the unreliable signals at occipital and frontal locations. In the oddball task of Stauder et al. (1995) P3 amplitude of children with the ability of volume conservation differed from children without volume conservation only at lead Fz. It is possible that with the emergence of operational thinking new genetic factors emerge only in the frontal P3 generators.

EEG coherence

For coherence between most electrode combinations, the genetic factor expressed at age 5 accounted for the largest part of genetic variance at age 7, which indicates that no massive changes in genetic sources were found. However, additional new genetic factors were shown to emerge for 10 out of a total of 14 cortico-cortical coherences. These new genetic influences were hypothesized to be caused by changes in the relative importance of synaptic growth and synaptic pruning between age 5 and age 7. In an attempt to distinguish between two qualitatively different periods, a period of synaptic growth and a period of synaptic pruning, we simultaneously looked at changes in heritability as well as changes in total genetic and environmental variance (table 5.5). Changeux and colleagues (Changeux & Danchin, 1976; Changeux and Dehaene, 1989) proposed a theory which stated that, in development, a genetically mediated overabundancy of synaptic contacts is followed by a "pruning" of the non-functional part of these synaptic contacts. The consolidation of some and elimination of others is entirely according to the demands of the environment. Genetic influences affect interindividual differences in a number of anatomical and neurophysiological parameters underlying coherence, like axonal sprouting, synaptogenesis and myelination, whereas environmental

influences are believed to account for the final process of pruning. Changes in total genetic or environmental variances from age 5 to 7 thus may point to changes in the relative importance of these mechanisms. Such changes were clearly observed in this study.

A general decrease in environmental variance was found for almost all cortico-cortical coherences. The decrease in total environmental variance coincided with an increase in heritability in coherences in the posterior to anterior direction, that is, from sensory input channels to executive areas and working memory in frontal and prefrontal cortex. This appears contrary to the expectation that from age 5 to 7 pruning would become more important. This expectation was based on Thatcher (1991), who interpreted his coherence data for children between ages 5 and 7 as representing a qualitative change from a stage of synaptic growth to a stage of pruning. However, heritabilities of coherence in the opposite direction, that is, from executive to sensory direction, remained the same in the right hemisphere, and actually decreased in the left hemisphere due to a decrease in genetic variance. Therefore, although environmental variance was smaller, its *relative* contribution to coherence in the anterior to posterior direction actually increased. If effects of unique environment on coherence indeed represent pruning, this may suggest that from ages 5 to 7 pruning of connections of the prefrontal areas to more posterior areas becomes relatively more important. From a developmental perspective this corroborates the findings that the posterior brain areas mature earlier than the anterior brain areas (Stuss, 1992). The latter may continue to develop at least through adolescence. Furthermore, the selective increase in genetic variance in the right hemisphere compared to the left hemisphere, where it is already high at age 5, is in agreement with the developmental lead of the left hemisphere (Thatcher et al., 1987).

This is the first longitudinal study on changes in genetic and environmental influences on electrophysiological indices of neural development in children. Using models in which the unreliability of the measures at each occasion was taken into account, it was shown that interindividual differences in these indices were largely influenced by genetic factors, and that the stable part of the variance is mainly genetic. EEG power and EEG coherence for long connections were highly heritable, EEG coherence for short connections, P3 latencies and (nontarget) P3 amplitudes were moderately heritable. For EEG powers and P3 amplitude and latency these heritabilities did not change much from age 5 to age 7. For a number of cortico-cortical coherences heritabilities changed significantly from age 5 to age 7. This was shown to be due to changing environmental variances or changes in genetic variances, depending entirely on hemisphere and on the direction of the cortico-cortical connection. Little evidence was found for qualitative differences in brain electrophysiology in this period: Although new

genetic factors emerged at age 7 for a number of cortico-cortical coherences and for P3 latency at Cz and P3, these new genetic factors only accounted for a small part of the genetic variance at age 7.

These findings suggest two important directions of further research attempting to connect brain and behavior: The high heritability of these indices of brain functioning make them promising phenotypes to detect quantitative trait loci (QTLs). Once candidate genes have their role in brain function confirmed, neurophysiological study of the protein and its effect on brain structures can be pursued. A second direction of future research is the use of quantative genetic model fitting to link cognitive abilities, personality and psychopathology of children to EEG power, EEG coherence and P3 amplitudes and latencies. Such modelling allows the assessment of associations between these domains, simultaneously testing whether the association is genetically or environmentally mediated. Two possibilities are directly suggested by the present thesis: because P3 latency has been associated with neural speed and IQ (Chalke & Ertl, 1965; Barrett & Eysenck, 1992), one may try to establish the nature of this association by using the structural model that corrects for measurement error in P3 latency. Secondly, the relation between EEG coherence and Piagetian conservation ability could be directly tested. Since IQ data and conservational ability of the twins who participated in this study are available (Boomsma & Van Baal, in press) these questions will be pursued in the future.