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A Genetic Perspective on the Developing Brain

Electrophysiological Indices of Neural Functioning in Young and Adolescent Twins

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Changes in genetic and environmental influences on electroencephalographic (EEG) and event-related potential (ERP) indices of neural development were studied in two large cohorts of young (N = 418) and adolescent (N = 426) twins. Individual differences in these indices were largely influenced by genetic factors, and throughout development, the stable part of the variance was mainly genetic. Both EEG power (which describes the amount of variability in brain electrical potentials that can be attributed to different frequencies) and long-distance EEG coherence (which is the squared cross-correlation between two EEG signals at different scalp locations and can be regarded as an index for cortico-cortical connectivity) were highly heritable. ERP-P300 latencies and amplitudes were low to moderately heritable. Clear differences between young children and adolescents could be observed in the heritabilities of EEG and ERP indices. The heritabilities of EEG power and EEG coherence were higher in adolescents than in children, whereas the heritabilities of P300 latencies were lower. Both cohorts (young children and adolescents) were measured twice: The children were tested when they were 5 and again at 7 years, the adolescents when they were 16 and again at 18 years. Therefore, within these age ranges a more detailed analysis of age-related changes in heritabilities and in the emergence of new genetic influences could be studied. The heritabilities of EEG powers and P300 amplitudes and latencies did not change much from age 5 to age 7 and from age 16 to 18 years. The heritabilities of a substantial number of connections within the cortex, however, as indexed by EEG coherence, changed significantly from age 5 to age 7, though not from age 16 to 18. The only changes in the heritabilities in adolescents were connections within the prefrontal cortex, which is in agreement with theories of adolescent development. These age-related changes in the heritabilities may reflect a larger impact of maturation on cortico-cortical connectivity in childhood than in adolescence. Evidence was found for qualitative changes in brain electrophysiology in young children: New genetic factors emerged at age 7 for posterior EEG coherences and for P300 latency at some scalp locations. This supports theories of qualitative stage transitions in this age range, as previously suggested using behavioral and EEG data.

Keywords: Genetics, heritability, twins, brain, EEG, ERP, P300, development, age.

Introduction

The recent surge in output from the field of behavioral genetics has established beyond doubt that a wide range of human behaviors are influenced by genetic factors (Plomin, De Fries, McClearn, & McGuffin, 2001). These behaviors include various measures of cognitive ability, motor skills, personality, lifestyle, and problem behaviors. However, very little is known about the specific genes that are involved and the mechanisms of their influences on behavior. Recently, gene expression studies in the mouse brain indicated several candidate genes,

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which may shed light on the genetic mechanisms that lead to the differential behavior between the strains (Sandberg et al., 2000). However, in humans, genetic influences on behavior cannot yet be studied in this manner. One way to study the physiological mechanisms mediating the genetic influences on behavior and cognition is to detect genetic and environmental influences on intermediate phenotypes like the functional organization of the brain. In humans, 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 response to stimuli that is observed in the EEG is called the event related potential (ERP) and is composed of different components, like the P300, which is considered an index for stimulus evaluation. If EEG is measured at different locations on the scalp, coherence between EEG signals of various scalp regions (i. e., the squared cross-correlation between the two EEG time series) can be used to estimate the functional connectivity of these regions (Nunez, 1981). All these EEG parameters show substantial individual variation. This variation can result from genetic and environmental influences. Earlier studies addressed the importance of genetic influences on some of these EEG phenotypes in adults (for a review, see Van Beijsterveldt & Boomsma, 1994), but only a small number of studies looked at younger subjects. Our studies of 5- and 7-year-old children and 16- and 18-year-old adolescents present the first data on the genetic architecture of brain functioning in children and adolescents.

The first aim of these studies was to establish the relative influences of genetic and environmental factors on individual differences in brain functioning at each age. A second important goal was to detect changes in these influences throughout development, specifically from age 5 to age 7 years, and from age 16 to age 18 years.

The age span from 5 to 7 years 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 as expressing 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 & Inhelder, 1969): The transition from preoperational 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.

Biological psychology provides a second perspective on change during childhood. Converging evidence from morphometric (Huttenlocher, 1979), positron emission tomography (PET; Chugani, Phelps, & Mazziotta, 1987) and magnetic resonance imaging studies (MRI; Jernigan et al., 1991) suggests that early brain development from childhood to adolescence is characterized by a gradual decrease in gray matter and an increase in white matter. The decrease in gray matter starts at about 4 years 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. These processes are reflected in developmental patterns of EEG parameters. Substantial empirical evidence from maturational EEG indices suggests that—superimposed on 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, Walker, & Guidice, 1987). In the first study it was shown that, in addition to clear continuous growth, there are growth spurts in mean relative EEG power of four distinctive brain areas. Five periods of increased development were suggested: around the ages of 4, 8, 12, 15, and 19 years. The data showed a period of relatively little changes between ages 5 and 7. The second study depicted growth spurts in EEG coherence and EEG phase. Thatcher's study concerned a group of 577 children aged 1 to 17 years, for whom EEG was collected on 19 scalp locations. Biennial changes were observed for EEG coherences for left and for right intrahemispheric coherences. The largest increase in EEG coherence was found around age 6. Other peaks were at 10 and 13 years and then again in later adolescence, around 17 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.

Regarding the collection of adolescent data, the age range from 16 to 18 years was chosen because this period is recognized as a period of more subtle changes in behavior and cognition. Neo-Piagetians suggest that

there is a fifth period of transitional change in this age range. Moreover, in adolescents the maturation of the brain does not seem to be completely finished (Fisher & Rose, 1994): Even in the period of adolescence and young adulthood there are still processes like the elimination of excess synapses (Goldman-Rakic, 1987) and an increase in the degree of myelination in the prefrontal cortex (Benes, Turtle, Khan, & Farol, 1994). Evidence for development of the frontal lobe in adolescence and young adulthood, has also been found using EEG measures. In reanalyzing the large data set of Matoušek and Petersén (1973), Hudspeth and Pribram (1992) found that from the age of 15 onward 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 the left frontal and temporal regions. In addition, EEG coherence changes with increasing age. In the large cross-sectional study of Thatcher et al. (1987) EEG coherence was used to study the cerebral development of normal children between a few months old to early adulthood, showing large changes in EEG coherence during development. From age 15 to adulthood, frontal lobe connections were primarily involved, with probably a growth spurt at age 17 years.

Both of these periods, 5 to 7 and 16 to 18 years, thus seem optimal for detecting changes in the genetic and environmental determinants of EEG parameters. In adolescents, we primarily expect changes in the prefrontal cortex, whereas in children changes may be more global.

In order to study the genetic architecture of a trait, it is essential to assess data on genetically related subjects. A twin design is a powerful method to this end. Using identical, monozygotic (MZ) and fraternal, dizygotic (DZ) twins allows the simultaneous assessment of shared genetic and shared environmental influences (environment shared by family members). This assessment is based on the fact that MZ twins share all their genes, whereas DZ twins, like ordinary siblings, share on average only 50% of their segregating genes. Thus, rather than arguing about the importance of nature and nurture for development, the classical twin method provides a solid quantification of such influences. Data analysis has been done using structural equation modeling. The path diagram in Figure 1 depicts a univariate example of such an analysis. Each observed phenotype (e.g., EEG power in twin 1) is influenced by different

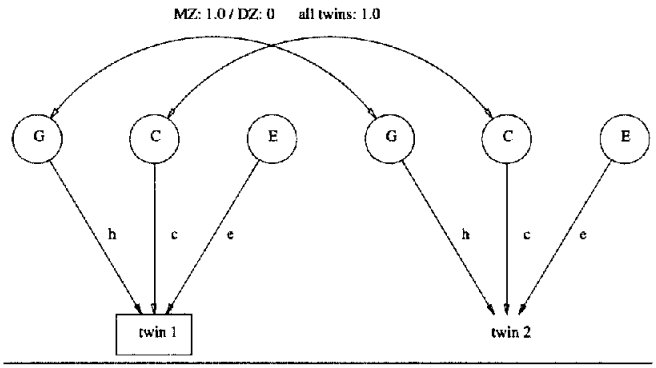

Figure 1
Path diagram of the univariate twin model. Rectangles are observed variables. Two variables are observed: P300 amplitude of twin 1 and P300 amplitude of twin 2. These variables are influenced by latent factors: genetic (G), common environmental (C), and unique environmental (E) factors. Correlations between the G's of twin 1 and twin 2 are 1 for MZ twins, and .5 for DZ twins. Correlations between the C's of twin 1 and twin 2 are 1 for all twins. This model can be extended to different forms of multivariate models (cf. appendix of Plomin et al., 2001; Van Baal et al., 1998b).

factors: genetic (G), common, shared environmental influences, like family environment (C), and unique environmental influences, that cause subjects to be different (E). These factors are correlated within twins, depending on their zygosity (MZ or DZ twins): The correlation between the genetic factors is 1 for MZ twins and 0.5 for DZ twins. The correlation between the common environmental factors is 1 for both types of twins (all reared together). By fitting the data to these models, one can estimate the magnitude of these three influences and test for their significance by excluding them from the model and examining the deterioration in goodness of fit.

The results presented in this paper are based on data from 180 MZ and 241 DZ twin pairs. The influences of genes and environment can vary with age and with sex. We therefore studied 5 young and 5 adolescent gender-by-zygosity groups (MZ male, MZ female, DZ male, DZ female, and DZ opposite sex twin pairs). The number of twin pairs for each group are shown in Table 1. All subjects were screened on neurological complications and had normal or corrected-to-normal vision. Their IQ's tested with RAKIT (Revisie Amsterdamse Kinder Intelligentie Test [Revised Amsterdam Child Intelligence Test]) at ages 5 and 7 years and WAIS at age 18 years (both with population mean 100 and *SD* 15)) showed a normal distribution with means and *SD* of

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Table 1
Number of twin pairs for each age/sex/zygosity group.

Age cohort	MZM	DZM	MZF	DZF	DOS
Young	42	44	47	37	39
Adolescent	39	36	52	38	48

MZM = monozygotic male twins, DZM = dizygotic male twins, MZF = monozygotic female twins, DZF = dizygotic female twins, DOS = Dizygotic opposite sex twins.

102.7 (13.2, age 5 years), 102.3 (14.7, age 7 years) and 113.8 (11.7, age 18 years). At age 16, Raven Standard Progressive Matrices were used as an index of cognitive ability. Mean value was 4.95 (SD = 0.6).

All twins (418 children and 426 adolescents) underwent extensive electrophysiological testing (Van Baal, 1997; Van Beijsterveldt, 1996): EEG power, ERP-P300, and EEG coherence were assessed twice within a 1½-year interval. In addition, the subjects were administered an intelligence test (Boomsma & Van Baal, 1998; Rietveld, Van Baal, Dolan, & Boomsma, 2000; Rijsdijk, Vernon, & Boomsma, submitted) and a number of reaction time tasks (Rijsdijk, Veron, & Boomsma, 1998). In the adolescent group, peripheral nerve conduction velocity was assessed (Rijsdijk & Boomsma, 1997). The children were tested when they were 5 and 7 years old, the adolescents at 16 and 18 years. This paper reports on the results on EEG phenotypes obtained thus far. Specifically, the percentage of observed variance explained by genetic factors, as expressed in heritability (h^2), was estimated for EEG power (ages 5, 7, 16, and 18 years), EEG coherence (5, 7, 16 and 18 years), P300 latency (5 and 7 years), and P300 amplitude (5, 7, 16 and 18 years). Changes in the heritabilities and emergence of new genetic and environmental influences over the 1½-year interval within the same subsample were available for EEG coherence (children only) and for P300 amplitudes and latencies (both age cohorts). Differences in the heritabilities between the two age cohorts are reported.

Heritability of EEG Parameters in Children and Adolescents

EEG Power

In developmental electroencephalography studies, EEG power spectra have been used as the major index for brain maturation. EEG power spectra indicate the amount of variability that can be explained by cyclic fluctuations in the EEG in a certain frequency range. Around 1970, a Swedish group of researchers reported on EEG data of 561 children aged 1 to 21 years (Matoušek & Petersén, 1973). This study provided important data on the development of EEG. During development EEG changed from a signal containing mainly slow waves to a signal with substantially less delta (very slow, 1 to 4 cycles per second or Hertz — Hz) and theta activity (slow, 4–7 Hz), but more alpha (moderate, 8–12 Hz) and beta activity (fast, 13–30 Hz). 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) is often used to reflect these shifts in the dominant EEG frequency components. Our data showed that absolute and relative EEG power in all broad bands (delta, theta, alpha1, alpha2, beta1, and beta2) were highly heritable at ages 5, 7, 16, and 18 years, with h^2 = 70% on average at ages 5 and 7, and 85% at ages 16 and 18 (Van Baal, De Geus, & Boomsma, 1996; Van Beijsterveldt, Molenaar, De Geus, & Boomsma, 1996). In fact, these traits are among the most heritable polygenic traits found during development. This suggests that the individual differences in rhythmic activity of cortical pyramidal cells are under strong genetic control. At first sight, this finding shows great promise to bridge the gap between genes and behavior. If EEG power tells us something about brain maturation, then finding specific genes influencing these parameters 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. Relying on this principle, John and colleagues (e. g., John, Prichep, Fridman, & Easton, 1988) were able to discriminate between dementia, alcoholism, unipolar and bipolar depression, based on quantitative EEG data only ("neurometrics" approach). However, the direct association of EEG power with behavior has not been unequivocal. The relationship between EEG power and cognitive abilities is even less clear. In fact, it has been argued that there is no merit in investigating EEG when a person is committed to idle contemplation bearing little or no relationship to cognition. Thus, notwithstanding the fact that EEG power seems to track individual differences in the stage of maturation of the brain and that it is highly heritable, it is uncertain that individual differences in normal behavior or cognition may be well indexed by background EEG.

ERP-P300

To index brain processes underlying cognition, psychophysiological researchers have increasingly turned to the event related potentials (ERP's). One of its components, the P300 (also known as P3 or P3b) showed particular promise for this purpose. The P300 is a positive deflection in the ERP that occurs 300 ms or more after stimulus presentation. It can be reliably evoked, even in young children, in a simple oddball paradigm. In an oddball paradigm a series of stimuli are presented. The subject has to respond to target stimuli (e. g., drawings of cats), which have to be distinguished from (mostly more frequently presented) nontarget stimuli (e. g., drawings of dogs). The latency of the evoked P300 (i. e., the timing of its peak) provides a measure of mental processing speed that is independent of behavioral responding (Donchin, Karis, Bashore, Coles, & Gratton, 1986). Latency gradually decreases with age until young adulthood (Polich, Ladish, & Burns, 1990). Individual differences in P300 latency have been suggested to be related to faster processing speed in various tests of cognitive function (Emmerson, Dustman, Shearer, & Turner, 1990). P300 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 P300 amplitude has been associated with superior memory performance (Noldy, Stelmack, & Campbell, 1990). P300 latency has been used to index individual differences in cognition, whereas P300 amplitude has been used as an indicator of clinical disorders, for example, attention deficit hyperactivity disorder, autism, smoking, and alcoholism. This may indicate that P300 amplitude has a predictive value as an index of susceptibility for deviant behavior.

Latency of P300 appeared to be a heritable trait in 5-year-olds ($h^2 = 34\%$) and 7-year-olds ($h^2 = 70\%$), but did not show genetic influences in the adolescent twins. This probably results from the fact that the same task was used for both children and adolescents, which was a challenge to the young children, but was very easy for adolescents. Katsanis, Iacono, McGue, and Carlson (1997) tested for genetic influences on P300 latencies in 18-year-old subjects using an easy and a difficult condition. They showed substantial genetic influences in the difficult condition, but none in the easy condition. Taken together, given sufficient challenge, adolescent and child twin data suggest that a genetic contribution to individual differences in speed of information processing is present from an early age onward. This does not, however, preclude the possibility that different genes influence P300 latency at different ages.

For P300 amplitude we expected to find genetic influences, because it was recently shown that the dopamine D2 receptor gene polymorphism is associated with P300 amplitude (Anokhin, Todorov, Madden, Grant, & Heath, 1999b). However, a complex pattern emerged from the analyses: For children's P300 amplitude, there was a clear discrepancy between the heritability of target amplitude (which was low) and nontarget amplitude (which was moderate to high). The largest part of the individual differences in target P300 amplitude appeared to be explained solely by unique environmental factors. Yet, according to model, fitting nontarget P300 amplitude appeared to be influenced by the same genetic factor as target P300 amplitude, which suggests 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 (non)relevance of stimuli. This genetic factor did not affect individual differences in the part of the stimulus processing specific to targets. A far more complex pattern was found for adolescent's P300 amplitude, because distinct differences were found between males and females. Individual differences in P300 target amplitudes showed a familial pattern. But whereas for males genetic influences explained the differences in P300 amplitudes, for females these differences seemed to be explained by shared environmental influences (Van Beijsterveldt, Molenaar, De Geus & Boomsma, 1998b).

EEG Coherence

The P300 has a well-documented relationship to cognition, but its sources in terms of neural generators are largely unknown (Polich, 1996). EEG coherence provides another phenotype that is possibly associated with cognition (Anokhin, Lutzenberger, & Birbaumer, 1999a) and can be directly linked to processes like axonal sprouting, synaptogenesis, myelination, and pruning of synaptic connections (Kaiser & Gruzelier, 1996). Thatcher and coworkers (Thatcher, Krause, & Hrybyk, 1986) 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-compartment" 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,

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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 EEG coherence at the relatively short distances (i.e., several centimeters), whereas coherence at the longer distances is influenced by the long fiber system only.

Heritability estimates of EEG coherences provide support for a two-compartment model at age 5 because they are different for short- and long-distance coherences, ranging from 37% to 75% (Van Baal, De Geus, & Boomsma, 1998a). In children, the heritabilities of long-distance coherences were higher compared to the heritabilities of short-distance coherences. However, this was not observed in the adolescent data: Heritability estimates for all EEG coherences were about the same (60%) at age 16 (Van Beijsterveldt, Molenaar, De Geus, & Boomsma, 1998a). EEG coherence has a complex relationship with cognition, which depends on developmental stage. Based on studies of dementia and colossal disconnection patients (Dunkin, Osato, & Leuchter, 1995), in adults a decrease in coherence is thought to reflect a loss of functional connectivity, but in children the reverse picture is seen. Gasser, Jennen-Steinmetz, and Verleger (1987) showed that mildly retarded 10- to 13-year-old children had higher coherences than controls. Higher short-distance coherences were also found in dyslexics and in Down syndrome patients (Schmid, Tirsch, Rappelsberger, Weinmann, & Pöppl, 1992). In a population of normal children, Thatcher, McAlaster, Lester, Horst, and Cantor (1983) showed that a negative correlation exists between full-scale IQ and short-distance coherences. Kaiser and Gruzelier (1996) provided a possible explanation for these paradoxical interpretations of EEG coherence in adults and children: They proposed that coherence in childhood may increase during the formation of new connections and decrease through pruning of the nonfunctional 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, all further decreases in EEG coherence reflect pruning of essential functional connections, and thus will affect normal brain function. However, caution is needed in assuming that changes in EEG coherence solely reflect changes in synaptic density. Apart from synaptic growth, increases in EEG 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 until young adulthood, especially in the frontal cortex and peaks in young childhood. Increases in EEG coherence during 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.

Stability of Genetic Influences on the EEG

On average 1 year and 7 months after the first assessment, 192 of the initial 209 young twin pairs and 196 of the initial 213 adolescent twin pairs returned to the laboratory for a second measurement session. This allowed a longitudinal approach to the study of changes and stability of the influences on the EEG phenotypes during development. Developmental behavioral genetics recognizes the importance of shifts in genetic and environmental influences on interindividual differences during development. Therefore, in addition to the questions concerning the relative influences of genetic and environmental factors on individual differences in electrophysiological indices of brain functioning, changes in these influences over time were investigated. Two questions were addressed: First, does the relative importance of genetic over environmental influences, as expressed by heritability (h^2) change over time? Second, do new genetic influences emerge, that is, are partly different genes expressed at ages 5 and 7?

P300 was chosen as a first target for longitudinal genetic analyses. In adolescents, the heritabilities for nontarget and target P300 amplitudes remained predominantly similar for twins at 16 and 18 years. The phenotypic stability of the P300 amplitude from age 16 to 18 was high, and this stability could be attributed largely to the same familial factors (Van Beijsterveldt, Van Baal, Molenaar, Boomsma, & De Geus, in press). Results on children's P300 also showed that no new genetic influences emerged when the children were tested the second time. This is surprising because P300 appears to closely mirror the time-course of development of gray and white matter in young children (Courchesne, Elmasian, Young, & Courchesne, 1987). Changes in P300 amplitude are tentatively interpreted as a result of differences in synaptic density, whereas changes in P300 latency are probably related to changes in myelination. Previously, a relationship between P300 latency and IQ had been reported (Chalke & Ertl, 1965). Because it was reported

in the literature that new genetic factors emerge for IQ in the 5 to 7 age range (Cherny & Cardon, 1994), new factors were expected to emerge for P300 latency. Instead, the genetic factor found at age 5 still had large effects on P300 latency at age 7 on all leads. A significant additional genetic factor emerged only for P300 latency at midcentral and left parietal scalp locations; but this 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 P300 latency. However, in the same twins as used in this study, Boomsma and Van Baal (1998) 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 P300 latency in these twins is less surprising.

A priori, there were good reasons to expect a change in the genetic contribution to the amplitude of the P300 component. A discontinuity in P300 topography as a function of cognitive developmental stage was found by Stauder, Molenaar, and Van der Molen (1993). Using dipole analyses, different P300 sources were found for children in the Piagetian preoperational phase and for children in the operational phase. The corresponding phase transition occurs somewhere between ages 5 and 7. Therefore, 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 P300 would only be influenced by new environmental effects. It must be noted, however, that the current study did not allow for a detailed topographical analysis. In the oddball task of Stauder et al. (1993), P300 amplitude of children with the ability of volume conservation differed from children without volume conservation only at midfrontal electrode position. It is possible that with the emergence of operational thinking new genetic factors emerge only in the frontal P300 generators.

EEG coherences showed a more complex picture of age-related changes in genetic influences. In the young, developing brain, the heritabilities of EEG coherences changed with age. However, the direction of change was different for varying coherences. Heritabilities of right long distance and posterior EEG coherences increased in 7-year-olds, whereas the heritabilities of left frontal coherences decreased (Van Baal, De Geus, & Boomsma, in press). For adolescents, the heritabilities of most EEG coherences did not seem to change much from age 16 to age 18 years. For frontal EEG coherences, however, we observed a drop in heritability from age 16 to age 18 years. These results suggest important maturational changes throughout the young brain and more focal maturational processes in the adolescent brain. Figure 2 shows age-related changes in the heritabilities of left frontal short-distance EEG coherence and left long-distance coherence.

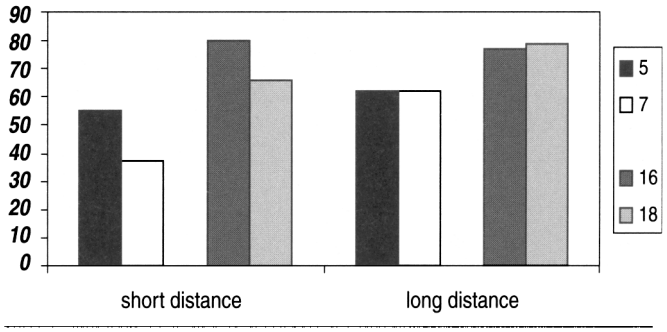

Figure 2
Age-related changes of heritabilities of EEG coherences. Heritabilities of left hemisphere short distance coherence (Fp1–F3) and of left hemisphere long distance coherence (Fp1–O1) at ages 5, 7, 16, and 18 years are shown.

In addition to testing age-related changes in the heritabilities, a multivariate variant of the twin design used in this study allowed the investigation of whether new genetic influences emerged during development. For children, additional new genetic factors were shown to emerge for posterior EEG coherences (Van Baal et al., in press). These genetic factors accounted for a relatively small part of genetic variance at age 7, which indicates that no massive changes in genetic sources were found. Although small, these new genetic influences were significant and were hypothesized to be caused by changes in the relative importance of synaptic growth and synaptic pruning between age 5 and age 7. Changeux and Danchin (1976) proposed that during development a genetically mediated overabundance of synaptic contacts is followed by the pruning of the nonfunctional part of these synaptic contacts. The consolidation of some and elimination of other contacts is supposed to respond to the demands of the environment. Genetic influences affect interindividual differences in a number of anatomical and neurophysiological parameters underlying EEG coherence, like axonal sprouting, synaptogenesis and myelination, whereas environmental influences are believed to account for the final process of pruning. The changes observed in the current study from age 5 to age 7 years in total genetic and environmental influences

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thus are interpreted as a change in the relative importance of the mechanisms of outgrowth of synaptic contacts and pruning.

Conclusion

The study described here provides information on the determinants of individual differences in brain function in a large, normative sample from childhood to adolescence. For most EEG indices (P300 amplitude to targets in children and P300 amplitude in adolescent women being the major exceptions) the main causes of variation were genetic differences between individuals. Such high the heritabilities are not always found for more complex, higher level behavioral traits like intelligence. For example, in this same group of children, variance in IQ at age 5 could be explained predominantly by common environmental influences shared by children growing up in the same family (Boomsma & Van Baal, 1998). 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, small genetically based differences at a young age may be amplified across the lifespan. For instance, a small advantage in processing speed or fronto-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 such a region, called a quantitative trait locus (QTL), high heritability is an advantage, because it enhances the possibility of finding a QTL that explains a substantial amount of the observed variance. The traits studied in this project 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 statistical power to detect QTLs (Boomsma, 1996). This multivariate advantage also applies to P300 latencies and nontarget P300 amplitudes. Although these are slightly less heritable, they have the additional advantage of being more directly linked to cognition than EEG power. A disadvantage of using P300 amplitudes and P300 latencies to locate QTLs is that we do not have a firm idea of which neurophysiological structures are responsible for the generation of the P300 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 EEG 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.

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