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

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

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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 and Rende 1991; Bouchard and 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 and McAnulty 1990), learning disabilities (John et al. 1980), autism (Courchesne 1987), psychopathology (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 and Pfefferbaum 1985), dementia (Sloan and 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 be-

C. E. M. van Beijsterveldt (✉) · D. I. Boomsma
Department of Psychophysiology, Vrije Universiteit,
De Boelelaan 1111, NL-1081 HV Amsterdam, The Netherlands

tween 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 and Stewart 1971; Vogel and 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 (β). 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 β-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 mean-amplitude, the average 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. The α-rhythm originates in a group of subcortical cells (especially those in the thalamic nuclei) that induce the rhythmic activity of the neurons in the cerebral cortex (Andersen and Andersson 1968). This rhythmic activity is modified by impulses from other parts of the brain, especially the ascending reticular activiting system in the brainstem, and the limbic system. The α-rhythm may act as a modulator that screens and selectively amplifies incoming information.

An EEG tends to be a stable individual characteristic that varies considerably 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 and Davis 1936). Raney (1939) reported high correlations in MZ twins for percentage α-activity (0.87), α-amplitude (0.76), and α-frequency (0.91) 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 genetically 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 0.52, and the DZ correlation was 0.29; the correlation for unrelated subjects (UR) was 0.02. The only significant differences between MZ (0.90) and DZ correlations (0.56) were found for β-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 0.64 and 0.32 respectively, and for the β-frequency 0.75 and 0.40, indicating heritabilities for both parameters of around 60%. The higher correla-

tions for β could have arisen because the EEG was recorded during auditory stimulation and because α-activity was replaced β-activity.

Meshkova and Ravich-Shcherbo (1982) also calculated α and β by means of bandpass filters. For 20 MZ twins, correlations in the range of 0.58 to 0.96 were obtained for all α-parameters over all regions of the brain, whereas the correlations in the DZ group (20 pairs) were considerably lower (0.11 to 0.65). 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 α-frequency, α-index, and mean α-amplitude show MZ correlations in the range of 0.4 to 0.9 and DZ correlations in the range of 0.3 to 0.6. 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 0.8 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 0.76 and 0.86, leading to heritability estimates of around 0.80. However, the correlations for the DZ group ranged from –0.20 to 0.15. 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, Whitton 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 and 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 and 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 individual 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.

Table 1 Review of twin and family studies and electroencephalography (EEG). *MZA* Monozygotic twins reared apart, *MZT* monozygotic twins raised together

Study	Year	Subjects	Age (*m* mean)	EEG parameter	Genetic 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: *r*MZ = 0.61 α-frequency: *r*MZ = 0.91 α-amplitude: *r*MZ = 0.66
Lennox et al.	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[a]	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-peristence
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-persistance	Clinical eye segregation ratio	MZ concordance > DZ concordance
Kuhlo et al.	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-variation EEG β-waves	Segregation ratio	Certain α- and β-variants: autosomal dominant most normal α- and β-variants: multifactorial
Young et al.	1972	17 MZ 15 DZ	19–40	α-index α-amplitude α-frequency	Intraclass correlations	α-index: *r*MZ = 0.5, *r*DZ = 0.2, *r*UR = 0.0 α-amp: *r*MZ = 0.5, *r*DZ =0.3, *r*UR = 0.1 α-fre: *r*MZ = 0.5, *r*DZ =0.3, *r*UR = 0.0
Lykken et al.	1974	39 MZ 27 DZ		Power spectra (0–19.9 HZ)	Intraclass correlations	Delta: *r*MZ = 0.76, *r*DZ = –0.01, theta: *r*MZ = 0.86, *r*DZ = –0.03 alpha: *r*MZ = 0.82, *r*DZ = –0.20, beta: *r*MZ = 0.82, *r*DZ = 0.15
Surwillo	1977	7 MZ 14 UR	8.5–11.2	Interval histogram	Intraclass correlations	Median: *r*MZ = 0.9, *r*UR = –0.30 mode: *r*MZ = 0.7, *r*UR = –0.24
Propping	1977	26 MZ 26 DZ	*m* = 23.3 *m* = 23.8	α-frequency α-amplitude β-frequency	Intrapair correlations	α-freq: *r*MZ = 0.69, *r*DZ = 0.33 α-ampl: *r*MZ = 0.63, *r*DZ = 0.39 β-freq: *r*MZ = 0.73, *r*DZ = 0.32

Table 1 (continued)

Study	Year	Subjects	Age (*m* mean)	EEG parameter	Genetic analysis	Results
Lykken et al.	1982	25 MZ 50 MZ 26 DZ	19–55	Power spectra (0–19.9 HZ)	Intraclass correlations	α-freq: *r*MZ = 0.8, *r*MZA = 0.9, *r*DZ =0.35 β-freq: *r*MZ = 0.7, *r*MZA = 0.6, *r*DZ =0.5
Meshkova & Ravich Shcherbo (USSR)	1982	20 MZ 20 DZ 20 UR	18–26	Power, frequency and amplitude of α & β	Intraclass correlations	For all sites: *r*MZ = 0.58–0.96 α: *r*MZ > *r*DZ, β: *r*MZ = *r*DZ
Hume	1973	39 MZ 43 DZ		α-frequency α-index	Intraclass correlations	α-freq: *r*MZ = 0.75, *r*DZ =0.4 α-index: *r*MZ = 0.64, *r*DZ =0.33
Whitton et al.	1985	6 MZ 6 DZ	4–10	Power spectra bispectra	*t*-test within pair differences	MZ concordance > DZ concordance
Zung & Wilson	1967	4 MZ 2 DZ	8–19	Sleep patterns	Visual inspection	MZ concordance, DZ discordant
Anokhin	1987	45 fam		Power spectra	Multivariate genetic analysis	Whole-brain EEG organization is mainly of a genetic nature
Stassen et al.	1987	26 MZ 26 DZ	*m* = 23.3 *m* = 23.8	Spectral analysis	Theoretical similarity function	MZ concordance > DZ concordance (> UR concordance)
Stassen et al.	1988a	27 MZA 21 DZA	*m* = 40.9 *m* = 42.2	Spectral analysis	Theoretical similarity function	MZ concordance > DZ concordance > UR concordance
Christian et al.	1988	26 MZ 26 DZ	*m* = 23.3 *m* = 23.8	Spectral analysis β-frequency	Intraclass correlations	Before alcohol: β: *r*MZ = 0.85, *r*DZ = 0.54 after alcohol: β: *r*MZ = 0.91, *r*DZ = 0.05
Linkowski et al.	1989	14 MZ 2 DZ	16–35	Sleep patterns	Genetic variance analysis	Genetic influences on stage 2, 4, and delta sleep
Bouchard et al.	1990	35 MZA 42 MZT		α-index α-midfrequency	Intraclass correlation	α-index: *r*MZ = 0.80, *r*MZT = 0.81 α-midfreq: *r*MZA = 0.80, *r*MZT = 0.82
Anokhin et al.	1992	17 fam		Low-voltage EEG variant	Segregation ratio	Autosomal dominant linkage-localization EEG variant
Steinlein et al.	1992	17 fam		Low-voltage EEG variant	Linkage	Localization EEG variant

[a] N.B. MZA Monozygotic twins reared apart, M2T monozygotic twin raised together

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 and 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 β-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 and 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) 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 β-variants showed a Mendelian pattern of autosomal dominance (Vogel 1966a, b), but most β-variants showed a model of multifactorial inheritance (Vogel and 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 and 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 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 and 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.

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 0.4 to 0.9 for latency and amplitude measures of the P300, and from 0.4 to 0.8 for the latency 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 = 0.7). The reliabilities of the amplitude of exogenous components (N100 and P200) were low; for N100, a test-retest correlation of 0.09 was found, whereas for P200, it was 0.23, and for the latency, the correlations were 0.48 for N100 and 0.51 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 (0.82) than for DZ (0.58) and UR pairs (0.61). 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 0.77, DZ correlations 0.53, and UR correlations 0.11. 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 wave shape 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 been 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 0.59 and 0.57, and DZ correlations were 0.36 and 0.10, respectively. For the latency measures of the P100, N140, and P200, the MZ correlations were 0.47, 0.50 and 0.31, whereas the DZ correlations were 0.03, 0.56, and 0.26. 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 0.32 to 0.84, and for amplitude from 0.67 to 0.93 (Segalowitz and 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

Table 2 Review of twin and family studies and event related potentials (ERPs)

Study	Year	Subjects	Age	ERP parameter	Paradigm	Modality	Genetic analysis	Results
Dustman & Beck	1965	12 MZ 11 DZ 12 UR	5–17	Waveform similarity	Light flashes	Visual	Product-moment correlation	For C3: rMZ = 0.8, rDZ = 0.6, rUR = 0.6
Osborne	1970	13 MZ 16 DZ 38 UR	11–22	Waveform similarity	Light flashes	Visual	Intraclass correlation	rMZ = 0.8, rDZ = 0.5, rUR = 0.1
Lewis et al.	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 = 0.7, rDZ = 0.4, rUR = 0.3 auditory: rMZ = 0.8, rDZ = 0.7, rUR = 0.5 somatosens: rMZ = 0.5, rDZ = 0.5, rUR = 0.4
Young et al.	1972	17 MZ 15 DZ	19–40	Waveform similarity	Clicks	Auditory	Product-moment correlation	rMZ = 0.7, rDZ = 0.4, rUR = 0.1
Buchsbaum	1974	33 MZ 34 DZ	18–57	Auditory, visual augmenting/reducing response	Light flashes & tones at different intensities	Auditory, visual	Intraclass correlation	rMZ = 0.4–0.6, rDZ = 0.0–0.4
Rust	1975	20 MZ 20 DZ	17–44	Amplitude, latency P2, N2, P3, N3[a]	Tones	Auditory	Genetic modeling	Amplitude heritability from 86% to 89% latency heritability from 35% to 81%
Geshon & Buchsbaum	1977	51 patients 140 relatives		Augmenting/reducing response	Light flashes at different intensities	Visual	Intraclass correlation	rSibling-Sibling = 0.29
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)	Peaction 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 heritability for P3
Polich & Burns	1987	10 MZ 20 UR	18–30	Amplitude/latency P3 of infrequent tones	Oddball	Auditory	Product-moment correlation	P3 amp: rMZ = 0.64, rUR = –0.20 P3 lat: rMZ = 0.89, rUR = –0.44
Rogers & Deary	1991	10 MZ 10 DZ	18–60	Amplitude/latency P3 of infrequent tones	Oddball	Auditory	Intraclass correlation	P3 amp: rMZ = 0.50, rDZ = 0.35 P3 lat: rMZ = 0.63, rDZ = –0.21
Bulayeva et al.	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% to 88%
O'Connor et al.	1994	59 MZ 39 DZ	22–46	Amplitude/latency of P3 of infrequent tones	Oddball	Auditory	Genetic modeling	P3 amp: heritability from 41% to 60% P3 lat: no heritabilities

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

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 0.64 and 0.95 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 0.5 and a DZ correlation of 0.35 for P300 amplitude. The correlations for the latency measures were 0.63 for MZ and –0.21 for DZ pairs. The correlations for the P300 were comparable with the results of Polich and Burns (1987). 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 and Ravich-Shcherbo 1986) and habituation (Kotchoubei 1987). In the first study (Malykh and 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 amplitude was indicated for the readiness potential: for the central parts of the cortex, MZ correlations were 0.84 and DZ correlations 0.61. 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 and 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 portion of genetically induced variability is suggested, as seen by the higher similarity in MZ twins compared with DZ twins and UR subjects (Table 2). When looking at waveform similarity, this result is observed repeatedly (Dustman and Beck 1965; Osborn 1970; Lewis et al. 1972; Young et al. 1972). MZ correlations between 0.71 and 0.88, DZ correlations between 0.33 and 0.58, both for auditory and visual waveform ERP, were found. The higher similarity in MZ twins could reflect similar nonspecific anatomical features, 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., the 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 assessment 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 and 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 and Gabrielli 1985; Neale and Cardon 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 × age or genotype × 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 and Eaves 1977), individual genetic profiles to be estimated (Boomsma et al. 1991) and interactions to be detected 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 and 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 and 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 and Milner 1984). Interest in the possibility of studying linkage between a quantitative trait and a genetic marker has been renewed (e.g., Haseman and 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.

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