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Twin and family studies of the human electroencephalogram: a review and a meta-analysis

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Abstract

Electrophysiological measures may be useful markers of the genetic underpinnings of complex behavior and psychopathology. Twin and family studies have been used to estimate the genetic contribution to the individual differences in a variety of electrophysiological measures. These studies are briefly reviewed here and published twin correlations from a number of studies with comparable methodology were selected for structural equation meta-analyses. For electroencephalographic (EEG) alpha power (11 twin groups) the heritability estimates in each of the single studies were high (averaged 79%), but it was not possible to equate the twin correlations across studies in the meta-analysis. In contrast, combining the data on alpha peak frequency (five twin groups) revealed a 'meta'-heritability of 81% (95% CI: 76–84%). Aggregating the twin correlations of five twin studies on the P300, the estimated meta-heritability is 60% (95% CI: 54–65%) for P300 amplitude and 51% (95% CI: 43–58%) for P300 latency. It is concluded that genomic variation contributes significantly to individual differences in all EEG and event related potential (ERP) measures studied to date.

Keywords: Review; Twin and family studies; Heritability meta-analysis; EEG; ERP

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1. Introduction

Individual differences in psychiatric disorders can for a large part be explained by genetic influences, usually expressed in heritabilities ($=h^2$: the percentage genetic variance of total, observed variance). For example, the heritability of schizophrenia is estimated to be approximately 80% (Cardno and Gottesman, 2000), and the heritability estimates of alcoholism liability ranges from 50 to 60% (Prescott and Kendler, 1999). Despite the large genetic contribution, it has proven difficult to find specific 'genes of psychopathology'. One promising strategy to identify such genes is to study the neurophysiological processes associated with psychopathology (Carlson et al., 1999; Kuperberg and Stephan, 2000; Polich and Bloom, 1999). It is believed that these neurophysiological processes, the so-called 'endophenotypes' of psychiatric disorders, have a more simple genetic architecture, and, therefore, provide more power in gene finding approaches (Boomsma et al., 1997; Kosslyn and Plomin, 2000; de Geus et al., 2001). Good endophenotypes of psychiatric disorders should be (1) meaningfully associated with the disorder; (2) stable over time, and; (3) under significant genetic control (Almasy et al., 2001; Cornblatt and Malhotra, 2001; de Geus et al., 2001).

Electroencephalographic (EEG) and event related potential (ERP) parameters are obvious endophenotypes in psychiatry. Much research supports the first criterion for these endophenotypes, i.e. a significant association between various EEG and ERP parameters and psychopathological behavior. One consistent finding, for example, is that reduced P300 amplitude is associated with an increased risk for alcoholism (Porjesz et al., 1998; Porjesz et al., this issue). A similar reduction is seen in unaffected family members of alcoholics, so it is assumed that the P300 reduction indexes the liability for this disorder instead of reflecting its effects. The second criterion of temporal stability of EEG power and ERPs has also held up in virtually all studies done so far. For example, test–retest correlation coefficients for EEG power are around 0.8 for both absolute and relative power (Pollock et al., 1991; Salinsky et al., 1991) and test–retest correlations for P300 latency in auditory tasks range from 0.32 to 0.84, and for amplitude from 0.67 to 0.93 (Segalowitz and Barnes, 1993). The third criterion will be the main topic of this paper: to what extent are individual differences in electrophysiological measures determined by genetic and environmental factors?

The relative influences 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. For instance, in the twin design, the resemblance between identical, monozygotic twin pairs (MZ) is compared with the resemblance between fraternal, dizygotic twin pairs (DZ). MZ twin pairs are genetically identical to each other, whereas, fraternal twins share, on average, 50% of their segregating genes. In contrast, sharing of environmental factors is assumed to be highly comparable for MZ and DZ twins. On this biometrical basis, a set of expectations can be generated for the MZ and DZ correlations under various models that differ in the presence and the size of the expected genetic and environmental contribution. With the help of structural

equation modeling, the observed resemblance in twins is compared with the expected values from all conceivable models. The best model is the model where the discrepancies between the observed and expected statistics are minimal. This best fitting model can be used to derive the estimates of variance attributable to additive effects of alleles at multiple loci (a^2), non-additive genetic effects due to interaction of alleles at a locus (d^2), common environmental effects (c^2) that are shared by all siblings in a family, and nonshared environmental effects (e^2), that are unique to each sibling (Neale and Cardon, 1992). Broad heritability is the proportion of observed, phenotypic variance that can be explained by all sources of genetic factors, and equals to $(a^2+d^2)/(a^2+c^2+e^2+d^2)$. Narrow heritability, or just heritability, is the proportion of observed variation accounted for by the additive genetic component.

This paper will begin by briefly reviewing the twin and family studies on the heritability of EEG and ERPs (listed in Tables 1 and 2). These were tracked in the standard way by using web-based resources (keywords: twin, genetics, heritability, ERP, EEG) supported by inspection of the reference section of the papers found. The main aim of our review was to identify papers with a comparable methodology that could be used in a structural equation modeling meta-analysis. This meta-analysis constitutes the second part of this paper. Why do a meta-analysis? Twin and family research on the causes of individual differences require large samples (hundreds of subjects) in order to obtain meaningful statistical power. This needs to be reconciled with the time-consuming nature and the relatively large expenses involved in electrophysiological measurements. Many of the existing studies had sufficient power to robustly detect familial contribution, but may have lacked the power to discriminate additive from non-additive genetic transmission or to separate genetic from common environmental influences. As a consequence, large discrepancies are visible in the results of the papers summarized in Tables 1 and 2. With a meta-analysis of all comparable studies reporting twin correlations on ERP and EEG measures, we hoped to resolve some of these discrepancies. Specifically, we hoped to obtain more accurate estimates of the genetic and environmental contribution to individual differences in the human EEG.

2. A review of twin and family studies on EEG spectral power and ERPs

2.1. EEG alpha power and alpha peak-frequency

The EEG power spectrum is traditionally divided into a number of broad bands, which are relatively more or less important in different mental states. Of these, power in the alpha band has been used most often in studies on the genetics of EEG. Therefore, the review and meta-analysis will be restricted to the EEG alpha rhythm. Although there is enough evidence to suggest that EEG power in the alpha frequency band is determined by genetic factors (Vogel, 2000; Boomsma et al., 1997; van Beijsterveldt and Boomsma, 1994), some disagreement exists about the mode of genetic transmission. Data from several studies (Lykken et al., 1982; Christian et al.,

Table 1
Overview of twin and family studies on EEG

Study	Subjects	Age	EEG parameter	Genetical analysis	Results
Davis and Davis, 1936	8 MZ	15–58	α-activity	Clinical eye	MZ concordant
Gottlober, 1938	15 families	>14	α-index; α-frequency	Clinical eye	No significant parent–offspring correlations
Raney, 1939	17 MZ; UR	7–16	α-index	Clinical eye spearman rank correlations	α-activity: rMZ = 0.61; α-frequency: rMZ = 0.91; α-amplitude: rMZ = 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 and Harvald, 1958	8 MZA	22–72	Index, frequency, and amplitude of dominant EEG	Clinical eye	MZ concordant
Vogel, 1958	110 MZ; 98 DZ	6–30	α-index; α-amplitude; α-persistence	t-test	MZ concordance > DZ concordance
Heuschert, 1963	26 MZ	50–79	α-index; α-amplitude; α-persistence	Variance analysis	MZ concordance
Vogel, 1966a	30 families	9–73	EEG–β variant	Segregation-ratio	Autosomal dominant inheritance
Vogel, 1966b	24 families	9–60	EEG–β variant	Segregation-ratio	Autosomal dominant inheritance
Zung and Wilson, 1966	4 MZ; 2 DZ	8–19	Sleep patterns	Visual inspection	MZ concordant, DZ discordant
Dieker, 1967	4 MZ; 2 DZ; 35 families	12–80	Low voltage EEG variant α-index, α-amplitude, α-persistance	Clinical eye segrega-tion-ratio	MZ concordance > DZ concordance; evidence for autosomal dominant inheritance
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 families	>10	EEG α-variants; EEG β-variants	Segregation-ratio multifactorial	Certain α- and β-variants autosomal dominant inheri-tance

Table 1 (*Continued*)

Study	Subjects	Age	EEG parameter	Genetical analysis	Results
Young et al., 1972	17 MZ; 15 DZ	19–40	α-index; α-amplitude; α-frequency	Intraclass correlations	α-index: rMZ = 0.5; rDZ = 0.2; rUR = 0.0; α-amplitude: rMZ = 0.5; rDZ = 0.3; rUR = 0.1; α-frequency: rMZ = 0.5; rDZ = 0.3; rUR = 0.0
Hume, 1983	39 MZ; 43 DZ		α-index; α-frequency	Intraclass correlations	α-index: rMZ = 0.64; rDZ = 0.33, α-frequency: rMZ = 0.75; rDZ = 0.4
Lykken et al., 1974	39 MZ; 27 DZ		EEG power spectra (relative): δ, θ, α, β	Intraclass correlations	δ: rMZ = 0.76; rDZ = −0.01; θ: rMZ = 0.86; rDZ = −0.03; α: rMZ = 0.82; rDZ = −0.02; β: rMZ = 0.82; rDZ = 0.15
Surwillo, 1977	7 MZ; 14 UR	8.5–11.2	Interval histogram of EEG halfwave durations	Intraclass correlations	Median: rMZ = 0.9; rUR = 0.15; mode: rMZ = 0.7; rUR = −0.02
Propping, 1977*	26 MZ; 26 DZ	$m = 23.3$; $m = 23.8$	α-amplitude; α-frequency; β-frequency	intrapair correlations	α-amplitude: rMZ = 0.63; rDZ = 0.39 2 h after alcohol intake: α-amplitude: rMZ = 0.75; rDZ = 0.12
Lykken et al., 1982*	25 MZ; 50 MZ; 26 MZ	19–55	EEG power spectra (relative): δ, θ, α, β	Intraclass correlations	δ: rMZ = 0.84; rMZA = 0.09; rDZ = 0.26; θ: rMZ = 0.80; rMZa = 0.76;rDZ = 0.04; α: rMZ = 0.86; rMZA = 0.93; rDZ = 0.13; β: rMZ = 0.72; rMZA = 0.61; rDZ = 0.37
Meshkova and Ravich-Shcherbo, 1982	20 MZ; 20 DZ; 20 UR	18–26	Index, frequency and amplitude of α and β	Intraclass correlations	For all leads and measures: rMZ from 0.58 to 0.96; rDZ from: 0.12 to 0.65; rUR: no positive correlations
Whitton et al., 1985	6 MZ; 6 DZ	4–10	EEG power spectra: bi spectra	t-test within pair difference	MZ concordance > DZ concordance
Anokhin, 1987	45 families		EEG power spectra	multivariate genetic analysis	Whole brain organization is mainly of genetic nature
Stassen et al., 1987	26 MZ; 26 DZ	$m = 23.3$; $m = 23.8$	EEG spectral pattern	Theoretical similarity function	MZ similarity > DZ similarity
Stassen et al., 1988	27 MZA; 21 DZA	$m = 40.9$; $m = 42.2$	EEG spectral pattern	Theoretical similarity function	MZ similarity > DZ similarity
Christian et al., 1988	26 MZ; 26 DZ	$m = 23.3$; $m = 23.8$	EEG power spectra: % β-waves	Intraclass correlations	Before alcohol: rMZ = 0.85; rDZ = 0.54; after alcohol intake: rMZ = 0.91; rDZ = 0.05

Table 1 (*Continued*)

Study	Subjects	Age	EEG parameter	Genetical analysis	Results
Linkowski et al., 1989	14 MZ; 2 DZ	16–35	Sleep patterns and delta sleep	Genetic variance analysis	Genetical influences on sleep stage 2, 4 and delta sleep
Linkowski et al., 1991	11 MZ; 15 DZ		EEG sleep patterns	Genetic model	Genetic influence on stage 2 and 4
Anokhin et al., 1992	17 families (191 persons)		Low voltage EEG variant	Segregation-ratio linkage	Autosomal dominant mode of inheritance
Steinlein et al., 1992	17 families (191 persons)		Low voltage EEG variant	Linkage	Localization at chromosome 20
Gavrish et al., 1984*	30 MZ; 26 DZ; 29 MZ; 19 DZ; 26 MZ; 22 DZ	10–11; 14–16; 18–25	EEG power spectra: α and β	Twin correlations	Age 10–11: α: rMZ = 0.81 rDZ = 0.53; β: rMZ = 0.89; rDZ = 0.18; Age 14–16: α: rMZ = 0.95; rDZ = 0.42; β: rMZ = 0.83; rDZ = 0.26; Age 18–25: α: rMZ = 0.90; rDZ = 0.66; β: rMZ = 0.76; rDZ = 0.49
Ibatoullina et al., 1994	20 MZ; 17 DZ	5–6	EEG coherence: θ, α	Genetic model	θ: h^2 from 0 to 66%; α: h^2 from 0 to 41%
Eischen et al., 1995	10 families		EEG power spectra: δ, θ, $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$	Correlations for related family members and unrelated persons	EEG spectral power are more similar in related family members than those from unrelated controls
Sviderskaya and Korol'kova, 1995	11 MZ; 20 UR	18–30	Topographical map	Topographical cross correlation analysis	High heritability of left anterior area and right parieto temporal lobe
* van Beijsterveldt et al., 1996	91 MZ; 122 DZ (M+F)	16	EEG power spectra: δ, θ, α, β	Genetic model	δ: $h^2 = 76$; θ: $h^2 = 89$; α: $h^2 = 89$; β: $h^2 = 86$
* van Baal et al., 1996	71 MZ; 96 DZ (M+F)	5	EEG power spectra (relative and absolute): θ; $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$	Genetic model	Absolute power: θ: $h^2 = 81$, $\alpha 1$: $h^2 = 81$; $\alpha 2 = 78$, $\beta 1$: $h^2 = 73$; $\beta 2$: $h^2 = 64\%$
* Christian et al., 1996	53 MZ; 38 DZ (M+F)	30	EEG power spectra (relative and absolute): θ, α, β	Genetic model	Absolute power: θ: $h^2 = 62$; α: $h^2 = 59$; β: $h^2 = 40\%$

Table 1 (*Continued*)

Study	Subjects	Age	EEG parameter	Genetical analysis	Results
Sorbel et al., 1996	53 MZ; 38 DZ (M+F)	30	EEG power spectra: δ, θ, α, β	Genetic model	After alcohol intake: increase of h^2 from an average of 47% to an average of 80%
Martinovic et al., 1997	26 MZ; 46 DZ	7–15	EEG power spectra: total power	Twin correlations	For several leads: rMZ from 0.74 to 0.94; rDZ from 0.54 to 0.82
van Baal et al., 1998a	70 MZ; 97 DZ (M+F)	5	EEG coherence: θ	Genetic model	For several connections: h^2 from 30 to 71%
van Beijsterveldt et al., 1998a	91 MZ; 126 DZ (M+F)	16	EEG coherence: δ, θ, α, β	Genetic model	δ: h^2 from 30 to 56%; θ: h^2 from 51 to 73%; α: h^2 from 47 to 81%; β: h^2 from 52 to 70%
* McGuire et al., 1998*	33 mz; 17 dz; 45 mz; 24 dz	15; 17	EEG power spectra (absolute and relative): δ, θ, α, β	Genetic model	age 15: (absolute power) θ: h^2 from 58 to 78%; α: h^2 from 62 to 78%; age 17: (absolute power) θ: h^2 from 76 to 86%; α: h^2 from 76 to 83%
Stassen et al., 1999*	13 MZ	18–71	EEG power spectra: θ, α, β	Twin correlations	θ: rMZ = 0.75; α: rMZ = 0.79; β: rMZ = 0.66
van Baal et al., 2001a	70 MZ; 97 DZ (M+F)	5 and 7	EEG coherence θ	Longitudinal genetic model	For several connections: age 5: h^2 from 53 to 75%; age 7: h^2 from 36 to 77%
Posthuma et al., 2001b*	47 MZ; 253 DZ/sibs; 44 MZ; 192 DZ/sibs	$m = 26.2$; $m = 50.4$	EEG power spectra: α peak frequency	Genetic model with regression of age and sex on mean	Adults: $h^2 = 71\%$; older adults: $h^2 = 83\%$

MZ, monozygotic twin pairs; DZ, dyzygotic twin pairs; MZA, monozygotic twin pairs reared apart; UR, unrelated pairs; M, males; F, females; h^2, heritability; m, mean; *, used in meta-analayis.

Table 2
Overview of twin and family studies on ERPs

Study	Subjects	Age	ERP parameter	Paradigm	Modality	Genetical analysis	Results
Dustman and 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; for C4: auditory: rMZ = 0.8; rDZ = 0.7; rUR = 0.5; for C4: somatosensory: 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 et al., 1973	33 MZ; 34 DZ	18–57	Augmenting/reducing response	Light flashes and tones	Visual auditory	Intraclass correlation	rMZ = 0.4–0.6; rDZ = 0.4
Rust, 1975	20 MZ; 20 DZ	17–44	P2, N2, P3, N3a: amplitude and latency	Tones	Auditory	Genetic model	Amplitude: h^2 from 86 to 89%; latency: h^2 from 35 to 81%
Gershon and Buchsbaum, 1977	51 patients, 139 relatives		Augmenting/reducing response	Light flashes	Visual	Intraclass correlation	rSibling–sibling = 0.29
Surwillo, 1980	6 MZ	9–13	P1, N1, P2, N2, P3: latency	Oddball	Auditory	Mann–Whitney U test	N1,P2: MZ concordance ~ UR concordance N2, P3: MZ concordance > UR concordance
Malykh and Ravich-Shcerbo, 1986	25 MZ; 25 DZ	18–30	Motor related brain potential (MRBP)	Reaction task		Intraclass correlation	Amplitude of MRBP components: MZ concordance > DZ concordance
Kotchoubei, 1987	22 MZ; 21 DZ	17–29	N1, P2, N2, P3, N4: amplitude and latency	Habituation task	Auditory	Genetic model	Habituation process: low h^2; N1,P2, N2 amplitude: high h^2 (70%); P3: low h^2

Table 2 (*Continued*)

Study	Subjects	Age	ERP parameter	Paradigm	Modality	Genetical analysis	Results
Polich and Burns, 1987	10 MZ 20 UR	18–30	P3 targets: amplitude	Oddball	Auditory	Product-moment correlation	P3 amplitude: rMZ = 0.64; rUR = 0.2; P3 latency: rMZ = 0.89; rUR = 0.44
Rogers and Deary, 1991*	10 MZ; 10 DZ	18–60	P3 targets: amplitude and latency	Oddball	Auditory	Intraclass correlation	P3 amplitude: rMZ = 0.50; rDZ = 0.35; P3 latency: rMZ = 0.63; rDZ = −0.21
Bulayeva et al., 1993	86 family members (M+F)	20–60	Early ERPs: amplitude and latency	Reversing checkerboard	Visual	Genetic modeling	Early ERPs: h^2 from 28 to 88%
Eischen and Polich, 1994	10 families (M+F)		P3 targets: amplitude and latency	Oddball	Auditory visual	Correlations	P3 amplitude and latency: correlation family members > correlations unrelated persons
O'Connor et al., 1994*	59 MZ; 39 DZ (M+F)	22–46	N1, P3 targets: amplitude and latency	Oddball	Auditory	Genetic model	P3 amplitude: h^2 from 41 to 60%; P3 latency: no h^2; N1: amplitude: h^2 from 11 to 62%; N1 latency: h^2 from 19 to 57%
Myles-Worsley et al., 1996	26 MZ; 13 DZ (M+F)	10–39	P50 ratio	Paired stimulus	Auditory	Intraclass correlations	rMZ = 0.50; rDZ = 0.13
Young et al., 1996	15 MZ; 12 DZ (M+F)	21–51	P50 ratio	Paired stimulus	Auditory	Intraclass correlations	rMZ = 0.57; rDZ = 0.00
Katsanis et al., 1997*	30 MZ; 34 DZ (M)	17–18	N1, P2, N2, P3 targets: amplitude and latency	Oddball with two conditions: -easy-difficult	Visual	Genetic model	Easy: P3 amplitude: h^2 = 78%; P3 latency: c^2 = 61%; difficult: P3 amplitude: h^2 = 79%; P3 latency: h^2 = 67%
van Baal et al., 1998b	66 MZ; 99 DZ (M+F)	5 and 7	P3 nontargets and targets: amplitude and latency	Oddball	Visual	Multivariate genetic model	For several leads at age 5: P3 amplitude: h^2 from 0 to 77%; P3 latency: h^2 from 19 to78%. For several leads at age 7: P3 amplitude: h^2 from 0 to 86%; P3 latency: h^2 from 36 to 94%
van Beijsterveldt et al., 1998b*	91 MZ; 122 DZ (M+F)	16	P3 nontargets and targets: amplitude	Oddball	Visual	Multivariate genetic model	Males: P3 target: h^2 from 29 to 57%; P3 nontarget: h^2 from 49 to 71%; females: P3 target: c^2 from 26 to 52%; P3 nontarget: c^2 from 22 to 53%

Table 2 (*Continued*)

Study	Subjects	Age	ERP parameter	Paradigm	Modality	Genetical analysis	Results
Begleiter et al., 1998	100 families 607 persons (M+F)	16–70	P3 targets: amplitude	Oddball	Visual	Multivariate genetic model	P3: h^2 from 28 to 51% no common genes for anterior and posterior areas
Almasy et al., 1999	100 families 604 persons (M+F)	16–70	P3, N1 nontargets and targets: amplitude and latency	Oddball	Visual and auditory	Genetic model	Visual: P3 amplitude: h^2 from 15 to 53%; P3 latency: h^2 from 2 to 49%; auditory: P3 amplitude: h^2 from 27 to 56%; P3 latency: h^2 from 6 to 31%
Almasy et al., 2001	100 fam 604 persons (M+F)	16–70	P3, N4: amplitude	Lexical decision task	Primed, unprimed and nonsense words	Genetic model	P3 amplitude: h^2 from 9 to 54%; N4 amplitude: h^2 from 9 to 44%
Wright et al., 2001*	140 MZ; 166 DZ; 48 sibs (M+F)	16–17	P3: amplitude and latency	Delayed response task	Visual	Genetic model	P3 amplitude: h^2 from 48 to 61%; P3 latency: h^2 from 44 to 55%
Hansell et al., 2001	140 MZ; 166 DZ; 48 sibs (M+F)	16–17	Slow wave	Delayed response task	Visual	Multivariate genetic model	Frontal: h^2 from 35 to 37%; Parietal: h^2 from 51 to 52%
van Beijsterveldt et al., 2001	90 MZ; 113 DZ (M+F)	16 and 18	P3: amplitude	Oddball	Visual	Longitudinal genetic model	P3 amplitude, males: h^2 from 30 to 81%; P3 amplitude, females: c^2 from 41 to 79%; no changes in h^2 with increasing age
Anokhin et al., 2001	91 MZ; 122 DZ (M+F)	16	P3 amplitude EEG delta power	Oddbal rest condition	Visual	Bivariate genetic model	Males: cross-correlation P3-EEG: rMZ = 0.50; rDZ = 0.27; females: cross-correlation P3-EEG: rMZ = 0.55; rDZ = 0.37

MZ, monozygotic twin pairs; DZ, dyzygotic twin pairs; MZA, monozygotic twin pairs reared apart; UR, unrelated persons; M, males; F, female; h^2, heritability; c^2, shared environment; *, used in meta-analysis.

1996; Posthuma et al., 2000) suggested that genetic dominance effects might explain individual differences in EEG alpha power. These studies obtained very high MZ twin correlations for relative EEG powers, but very low (or even zero) DZ correlations (see Fig. 1). If EEG power is influenced by additive genetic factors, then it is expected that the DZ correlation is half of the MZ correlation. A pattern of low DZ correlations with high MZ correlations suggests non-additive transmission and could be the result of the interaction of genes at different loci (epistasis) or interactions between genes at the same locus (dominance). The same pattern of twin correlations is observed in studies examining alpha frequency peak (Christian et al., 1996; Lykken et al., 1982; Posthuma et al., 2001b; Stassen et al., 1999). As shown in Fig. 2, EEG alpha frequency showed very high MZ twin correlations, but DZ correlations were lower then half the MZ correlations. Combining the results of EEG twin studies in the meta-analysis may clarify whether the mode of genetic transmission is purely additive, purely non-additive or a combination of both.

A notable feature of Table 1 is that the heritability estimates obtained in family studies of EEG (Anokhin, 1987; Eischen et al., 1995; Stassen et al., 1998; Trubnikov et al., 1993) are very consistent with the results obtained in twin studies. Two critical assumptions of the twin method are that MZ and DZ twin pairs experience equal environments (see Evans this issue for a detailed treatment of this equal environment assumption), and secondly that results obtained in twins can be generalized to singletons. The finding of comparable heritability estimates in family and twin studies strongly suggests that the manifestation of genetic factors in the EEG is similar in twin and non-twin populations. A more direct test of this assumption is possible using an extended twin family design. In an extended twin family design, differences in means and in variance components are tested between twins and their singleton siblings within the same family. Posthuma et al. (2001b; this issue) did so for alpha peak frequency and for the Lateralised Readiness Potential and found no significant differences. Other EEG parameters, however, have yet to be tested.

From the studies on EEG alpha power in Table 1, only 11 studies were selected for the meta-analysis. Main reasons for exclusion were a lack of quantitative methods to measure the EEG (Davis and Davis, 1936; Lennox et al., 1945; Raney, 1939; Surwillo, 1977; Vogel, 1958, 1970), no report of twin correlations (Christian et al., 1996; Dumermuth, 1969; Eischen et al., 1995; Stassen et al., 1987), no (separate) report of EEG power in the alpha frequency (Anokhin, 1987; Martinovic et al., 1997), report of twin correlations on the relative powers only (Lykken et al., 1982), or the use bipolar references to obtain EEG power (Young et al., 1972). The remaining studies often used (entirely) different electrode locations. In the meta-analyses, only the results for the central electrode were used, simply because this location was included in most studies reviewed. Two studies did not report results for the central electrode. For these studies we used the EEG power averaged over all leads (Christian et al., 1996) or the results for the occipital electrode (Propping, 1977). It should be mentioned that a number of other differences are present in the studies finally included in the meta-analysis. We did not put any restrictions on location of the monopolar reference electrode, we included twin correlations of power spectra as well as amplitude spectra, eye movement corrections were treated

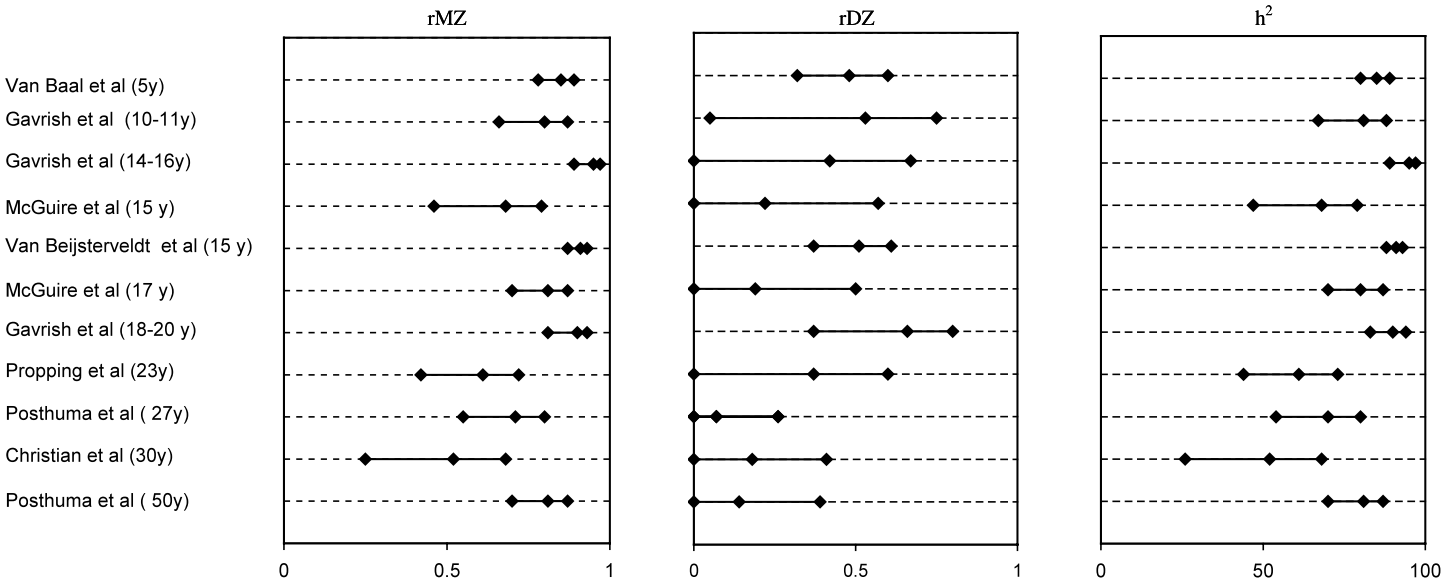

Fig. 1. An overview of studies used for the meta-analysis of EEG alpha power. The analysis includes only studies that reported both MZ and DZ twin correlations. In the left panel the MZ correlations (rMZ) and their 95% CI are given, in the middle panel the DZ correlations (rDZ) and their 95% CI, and in the right panel the estimates of the heritability (h^2).

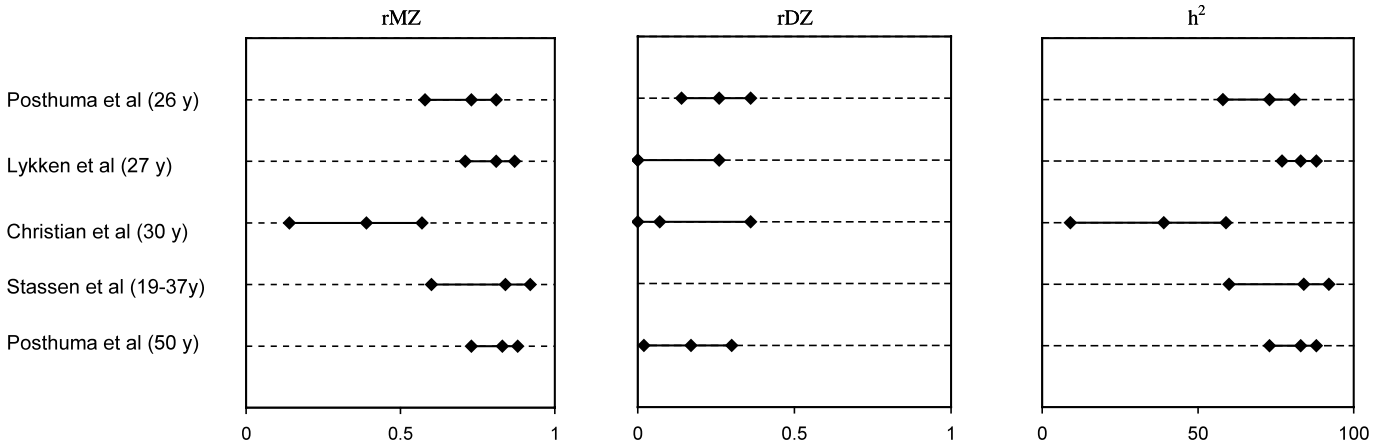

Fig. 2. An overview of studies used for the meta-analysis of alpha peak frequency. The analysis includes only studies that reported both MZ and DZ twin correlations. In the left panel the MZ correlations (rMZ) and their 95% CI are given, in the middle panel the DZ correlations (rDZ) and their 95% CI, and in the right panel the estimates of the heritability (h^2).

differently across studies (removal of epochs with eye blinks, regression of EOG/EEG), we assumed that genetic and environmental influences on EEG alpha power were the same for men and women, and age specific influences were largely ignored (except for gross differences between children, adolescents and adults).

2.2. P300 amplitude and latency

In Table 2, an overview is given of all twin and family ERP studies. Most twin studies points to the existence of moderate to high genetic influences on P300 amplitude (for earlier reviews see Vogel, 2000; Boomsma et al., 1997; van Beijsterveldt and Boomsma, 1994), although there is less consensus regarding the extent to which genetic factors contribute to the phenotypic variance in the P300 latency. The meta-analysis was limited to include twin samples from normal healthy populations only. Converging results, however, were obtained in the Collaborative Study on the Genetics of Alcoholism (COGA). This large study, initiated in 1989, collects ERP data in families selected on the basis of multiple alcoholic family members to investigate the genetic factors that influence susceptibility to alcohol dependence and abuse (Porjesz et al., 1998, this issue). Amongst other variables, the heritability of the P300 was examined across different tasks and modalities. ERPs were measured in visual and auditory P300 paradigms (Almasy et al., 1999, 2001; Begleiter et al., 1998; Williams et al., 1999). Across the scalp the heritability of the P300 amplitude varied between 30 and 53% in response to visual stimuli and 27–56% in response to auditory stimuli.

Although the current evidence for the importance of genes is overwhelming, estimates of the magnitude (heritability) and form (additive, non-additive) of the genetic contribution to the P300 differ sharply across studies. Again, in most of the studies in Table 2 only low power was obtained to discriminate between genetic additivity versus non-additivity or between common environmental and genetic sources of twin resemblances. A meta-analysis could potentially solve this power problem, and to that end we identified six studies that reported actual MZ and DZ twin correlations. In these studies, the P300 was assessed in the visual modality as well as the auditory modality. Four studies tested the P300 in a traditional oddball paradigm (O'Connor et al., 1994; Polich and Burns, 1987; Rogers and Deary, 1991; van Beijsterveldt et al., 1998b); in two studies the P300 was elicited in a task requiring more effort (Katsanis et al., 1997; Wright et al., 2001). These inconsistencies in methodology are not conducive to meta-analysis, but further reduction of the number of studies would have compromised the main objective of an increase in power. Since the P300 is best recorded at parietal electrode locations, the meta-analysis used the P300 amplitude and latency measured at Pz.

2.3. Other EEG and ERPs measures

Most studies assessing the heritability of electrophysiological measures have used either EEG power, EEG alpha frequency, or the P300. In more recent years, genetic analyses have been applied to other electrophysiological indices that could constitute

meaningful endophenotypes for psychiatric disorders. Mostly, only one or two papers have reported on these indices. Therefore, a meta-analysis cannot be performed. However, for completeness, the main findings will be briefly summarized below.

2.3.1. P50

Very early ERPs are influenced mainly by the physical characteristics of the stimulus. They are used to study the nervous pathways that transmit the incoming information to the sensory areas in the brain. ERPs in the 50–200 ms range are used to study the effects of arousal and attention on (automated) information processing. Of special interest is the P50 in response to paired auditory stimuli, because the P50 has repeatedly been indicated as a biological marker for schizophrenia (Freedman et al., 2000). In normal subjects the response to the second stimulus is suppressed (P50 gating), but schizophrenics and their relatives show less suppression of the second P50 wave (Freedman et al., 1991). Twin studies showed that there is evidence for substantial influence of genetic factors (Myles-Worsley et al., 1996; Young et al., 1996). Young et al. reported that 44% of the variance in P50 gating is due to heritable factors.

2.3.2. EEG coherence

EEG coherence is the normalized cross-correlation of the EEG signal at two different electrodes. Coherence has been suggested to index the degree of functional connectivity between the brain areas underlying the two electrodes, and should prove very useful in the study of higher order mental processes. Only a few studies examined the genetics of EEG-coherence. Ibatoullina et al. (1994) calculated heritabilities for interhemispheric coherences from 20 MZ and 17 DZ twin pairs, aged 5 and 6 years old. For most combinations of electrode pairs the contribution of genetic influences to the coherence was low. In twins of the same age, van Baal et al. (1998a) examined the coherence of the theta frequency of electrode pairs along the anterior–posterior axis in 209 5-year-old twin pairs. They found a substantial influence of genetic factors on EEG-coherences. Between 37 and 75% of the variance was explained by genetic factors depending on electrode location and interelectrode distances. Long distance coherences showed higher heritabilities compared with the heritabilities of short distance coherences. The same twin pairs were tested 1 year and 6 months later. In the intervening period changes in the genetic architecture of EEG coherence were found. For frontal connections, the influence of genetic factors decreased, while the estimates of heritability of posterior connections increased (van Baal et al., 2001a). van Beijsterveldt et al. (1998a) performed a study in an adolescent group of 213 twin pairs and found the heritability of the EEG coherence averaged over all electrode combinations to be 60, 65 and 60% in the θ, α and β frequency band, respectively.

2.3.3. N400

The N400, a negative ERP that occurs after approximately 400 ms is elicited by a semantically incongruent word in a sentence. The degree of incongruency is reflected

in the amplitude of the N400. Although in healthy subjects a N400 is only obtained in unprimed words, in alcohol-dependent subjects they also occur in response to primed words (Porjesz and Begleiter, 1996), which indicates semantic deficits in these subjects. Therefore, this specific deficit may serve as another electrophysiological endophenotype indexing underlying genetic susceptibility to alcohol dependence. There is only one study that measured the heritability of the N400 (Almasy et al., 2001). The participants of the COGA study performed a lexical decision task. Heritabilities of the N400 to primed words ranged from 9 to 30%, with highest heritabilities on occipital leads. To unprimed words 13–41% of the variance was explained by genetic factors.

2.3.4. Slow wave

A Slow Wave can be elicited in a delayed-response task that occurs 1–4 s after removal of a target stimulus that is to be kept in memory. The amplitude of the Slow Wave been shown to reflect working memory load (Ruchkin et al., 1995). There is one study that examined the genetic influence on the Slow Wave during a spatiovisual working memory task (Hansell et al., 2001). In a sample of 391 16-year-old twin pairs, it was found that at prefrontal site 35–37%, and at parietal site 51–52% of the variability of the Slow Wave was determined by genetic factors.

In summary, twin and family studies provide solid evidence for an influence of genetic factors on electrophysiological indices. Performing a meta-analysis on these studies may provide a more precise and less biased estimate of the relative contribution of genetic factors to the total interindividual variance (heritability). Moreover, a meta-analysis may resolve whether these genetic factors are of an additive or a non-additive nature.

3. Meta-analysis of twin studies on EEG spectral power and ERPs

3.1. Methods

The meta-analysis was done using structural equation modeling with the software package MX (Neale et al., 1999). With MX it is possible to combine the published MZ and DZ correlations from multiple studies into a single estimate for heritability and to compare the size of heritabilities across studies. For the reported twin correlations we first calculated their 95% confidence intervals (95% CI) and tested whether MZ twin correlations could be constrained to be equal across studies. Next, for each study the heritability and the 95% CI were estimated on the basis of the reported twin correlations. The genetic model used to obtain these estimates depended on the observed pattern of twin correlations in each study. When the DZ correlation was more than half of the MZ correlation, an ACE model was applied because this correlation pattern suggests that shared environment determines the trait. An ADE model was applied when the DZ correlation was less than the half of the MZ correlation, because this correlation pattern suggests that non-additive genetic

factors contribute to variability of the trait. In the next step, whether the heritability estimates could be constrained to be equal across studies was tested. Subsequently, a test was conducted to determine whether non-additive genetic effects (D) were significant by dropping D from the model or, where relevant, whether shared environmental effects (C) were significant by dropping C from the model. Note that estimating D and C at the same time is not possible in a design using only MZ and DZ twins reared together. To test the submodels, hierarchic χ^2-tests were used. A difference χ^2 statistic was computed by subtracting the χ^2 for the full model from that for a reduced model with degrees of freedom (df) for the test equal to the difference between df for the full and the reduced model.

3.2. Results

3.2.1. EEG alpha power and alpha peak-frequency

The studies included in the meta-analysis of EEG alpha power are depicted in Fig. 1. First, we estimated the 95% CI of the MZ and DZ correlations of EEG alpha power for all individual studies (see most two left panels in Fig. 1). In the next step, we tested whether the MZ twin correlations could be equated across studies. This test resulted in a significant deterioration of the fit of the model ($\Delta\chi^2 = 82.23$, $\Delta df = 10$). As shown in Fig. 1 two studies showed lower MZ twin correlations. However, the fit of the model is still deteriorated ($\Delta\chi^2 = 44.53$, $\Delta df = 8$) after exclusion of these two studies. One possible explanation for the differences in MZ correlations is that the size of measurement error differs across studies. MZ correlations can be regarded as an indication of the lower bound of the test–retest reliability, since the MZ correlation can not exceed the correlation of the same subject measured on two occasions. To test this explanation, one could incorporate information about the reliability of the trait in the model in order to make a distinction between real environmental influences and measurement error. The information provided by the studies did not allow us to test this kind of model.

To obtain heritability estimates (including genetic additive and genetic non-additive variance) and their 95% CI of the individual studies, an ADE model was applied to all studies. Results are depicted in the right panel of Fig. 1. They show that a substantial part of the variance in alpha power is determined by the genetic factors in all studies. We tested whether the estimates of h^2 could be constrained to be equal across the studies. Note that the (broad) heritability included both genetic additive and genetic non-additive variance. Due to the large age differences across studies, constraining h^2 to be equal across samples was done in various steps. In the first step, the heritability was compared in two very young samples (age 5 and 10) (Gavrish and Malykh, 1994; van Baal et al., 1996). The results showed no deterioration of the fit ($\Delta\chi^2 = 0.77$, $\Delta df = 2$), which indicated that the heritability estimates are similar in the two samples. In the next step, the h^2 was constrained to be equal in four samples included young adolescent twin pairs (Gavrish and Malykh, 1994; McGuire et al., 1998; van Beijsterveldt et al., 1996). The fit deteriorated when the estimates of h^2 were equated across the adolescent groups ($\Delta\chi^2 = 34.90$, $\Delta df = 6$), meaning that the h^2 estimates differ across the four samples. The same was done for

the five adult samples (Christian et al., 1996; Posthuma et al., 2000; Propping, 1977). The fit of this model deteriorated ($\Delta\chi^2 = 28.37$; $\Delta df = 8$) and, thus, it is not allowed to constrain the h^2 across the five samples. In the last model the estimates of h^2 were constrained to be equal across all the studies. The fit of the model dropped significantly ($\Delta\chi^2 = 106.13$, $\Delta df = 20$) and it yielded an h^2 estimate of 79% (95% CI:76–81%). As it was not possible to equate the heritability across studies, we could not apply a high power test for the significance of D. Thus, the only conclusion based on these studies can be that variability in EEG power is largely determined by genetic factors.

The meta-analysis of alpha frequency included five samples (see Fig. 2). The MZ and DZ correlations and their 95% CI are given for each individual study. With the exception of the study of Christian et al. (1996), the MZ twin correlations could be constrained to be equal across studies ($\Delta\chi^2 = 5.63$; $\Delta df = 4$). Subsequently, the broad heritability (a^2+d^2) of all the studies were constrained to be equal. The fit of the model deteriorated significantly ($\Delta\chi^2 = 32.12$; $\Delta df = 8$). The fit of the model did not deteriorate when the study of Christian et al. (1996) was excluded ($\Delta\chi^2 = 5.17$; $\Delta df = 6$). In the last model the significance of genetic dominance was tested by removing D from the model. This lead to a large drop in the fit ($\Delta\chi^2 = 24.47$; $\Delta df = 1$), which indicated that the genetic transmission is a combination of additive and non-additive genetic effects. The overall estimate of h^2 (a^2+d^2) for alpha peak frequency is 81% (95% CI:76–84%).

3.2.2. P300 amplitude and latency

Meta-analyses were performed separately for P300 amplitude and latency. First, for each individual study the MZ and DZ twin correlations with a 95% CI were estimated (see Fig. 3). Next, we tested whether the MZ correlations could be constrained to be equal across studies. As noted earlier, the MZ correlations could be regarded as an indicator of the lower bound of the reliability. The model with equal MZ correlations showed no reduction in the fit for either P300 amplitude ($\Delta\chi^2 = 9.55$, $\Delta df = 5$) or latency ($\Delta\chi^2 = 2.11$, $\Delta df = 4$), indicating that across studies the reliability of the P300 measurements was equal. To estimate the heritabilities of the individual studies, an ADE model was chosen as the starting model. The results are given in the upper part of Fig. 3. All studies report a substantial genetic influence on the P300 amplitude. Highest heritabilities (around 70%) for P300 amplitude were reported by Katsanis et al. (1997).

In the next step, we tested whether the heritability estimates could be equated across studies. The fit of this model was not significantly worse ($\Delta\chi^2 = 12.72$, $\Delta df = 10$) meaning that comparable heritability was found across studies. To test the significance of non-additive genetic effects, D was dropped from the model. Results showed no deterioration of the fit of the model ($\Delta\chi^2 = 0.0$, $\Delta df = 1$), indicating a purely additive genetic mode of transmission. The overall estimate for the heritability for P300 amplitude was 60% (95% CI:54–65%). Unique environmental factors contributed 40% (95% CI:35–46%) to variance in P300 amplitude. It should be noted that measurement error is included in the unique environmental factors.

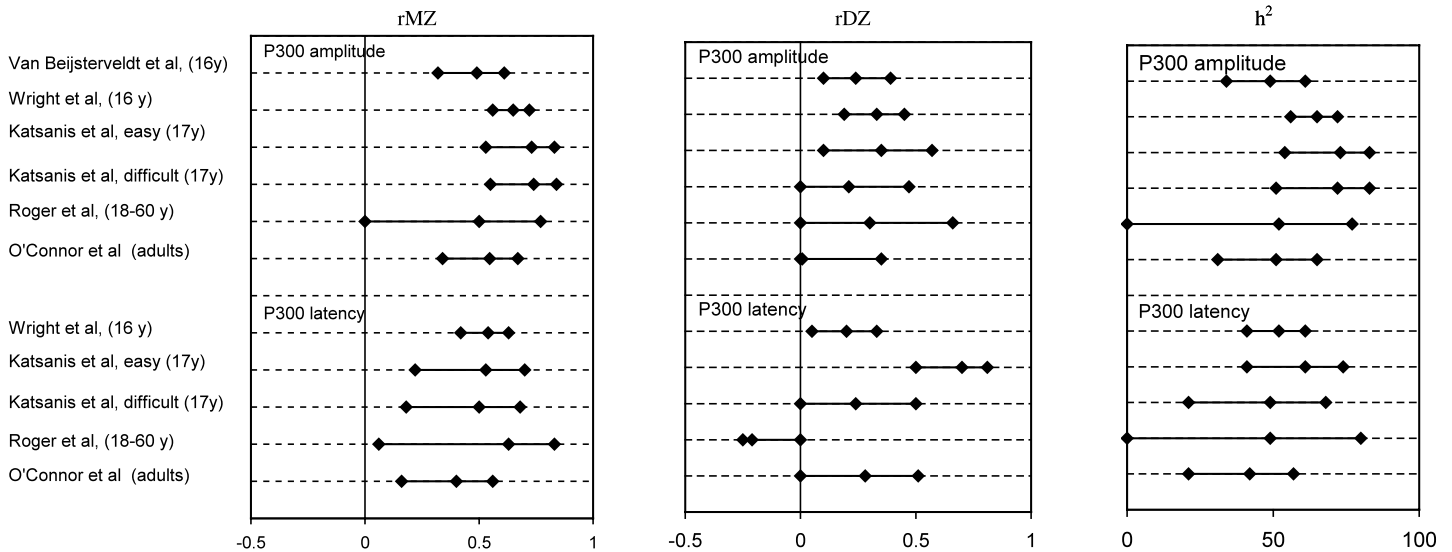

Fig. 3. An overview of studies used for the meta-analysis of P300 amplitude and latency. The analysis includes only studies that reported both MZ and DZ twin correlations. In the left panel the MZ correlations (rMZ) and their 95% CI are given, in the middle panel the DZ correlations (rDZ) and their 95% CI, and in the right panel the estimates of the heritability (h^2).

A slightly different analysis was performed for the P300 latency. One study reported very high DZ twin correlations, which may indicate the influence of shared environmental factors. Therefore, an ACE model was chosen as the starting model. In order to generate an overall estimate of the heritability for the P300 latency, the estimates of a^2, c^2, and e^2 were equated across studies. No deterioration of the fit of the model appeared ($\Delta\chi^2 = 11.85$, $\Delta df = 8$), which showed that the estimates derived from these studies were comparable. The results for the test of significance of C, by dropping C from the model, showed no deterioration of fit of the model ($\Delta\chi^2 = 0.01$, $\Delta df = 1$). Thus, an AE model was the best fitting model. In this model, genetic factors explained 51% (95% CI:43–58%) of the variance with unique environmental factors explaining the remaining variance.

4. Discussion

The meta-analysis of the alpha peak frequency of the EEG combined the results of 5 different twin groups. High heritability (81% (95% CI:76–84%)) was found for alpha peak frequency, and a dominant mode of genetic transmission could be demonstrated. The meta-analysis of the EEG alpha power combined the results of 11 different twin groups. In each study, the estimate of heritability was very high, but it was not possible to equate the estimates across studies. The variable estimates of heritability across studies could be due to differences in reliability of the different methods used in the studies, but we had no means to check this because most papers only reported twin correlations, and no information on variances or test–retest correlations. In addition, variable estimates for heritability across studies could be due to differences in study design and data processing. Not all studies used the same electrode location, used the same reference electrodes, or included persons within the same age range. If we nevertheless averaged the heritabilities across studies, 79% of the variance could be explained by genetic factors. A test for dominance was difficult, because the overall test of excluding dominance as a source of variance was a test with a large number of df, and a test for every study separately could not benefit from the gain in statistical power provided by the accumulation of subjects of different studies. However, the parameter estimates suggest that in adults non-additive genetic influences are important, whereas, for adolescents and children a purely additive model is sufficient.

Five P300 twin studies were available for the meta-analysis. Aggregating the results of these studies showed convincing evidence for the influence of genetic factors. Across studies, the estimated heritability of the P300 amplitude was 60% (95% CI: 54–65%) and for P300 latency it was 51% (95% CI: 43–58%). In the meta-analysis, the estimates of heritability could be constrained across studies, in spite of the use of different modalities and different levels of task difficulty. Heritability of P300 amplitude and latency found in the four studies that used a traditional oddball paradigm was comparable with that found in the two studies that used tasks requiring much more effort. This suggests that the genetic contribution to the P300 is the same for easy and difficult tasks. However, this issue should properly be

addressed in a design where the same subjects perform multiple tasks. Using such design, Katsanis et al. (1997) established a significant difference in heritability between easy and difficult tasks. Since our meta-analysis was conducted on correlation matrices it had lower power to detect task difficulty effects as the analysis of the original covariance matrices used in the study by Katsanis et al.

As for EEG power, a test for non-additivity of P300 measures was difficult. However, the parameter estimates suggest that for the P300 amplitude and the P300 latency dominant genetic influences are not important.

4.1. Limitations of the meta-analysis

The advantage of the meta-analysis is that it gave a robust estimate of heritability of the EEG and ERP measures. Due to the large heterogeneity of EEG/ERP measures across studies and the limited availability of relevant information, a number of important issues have been left unaddressed. First, it was not possible to test for sex-differences in genetic architecture. In the human brain structural and functional sex differences are suggested (Good et al., 2001). For example, using in vivo magnetic resonance morphology sex differences were found in size and morphology of the corpus callosum (Steinmetz et al., 1995). Recently, Gur et al. (2000) found that males and females activated different brain areas during verbal and spatial tasks. These differences raise the question of whether the extent of genetic influences is the same in males and females and whether the same genes are expressed in males and females. We have addressed the existence of sex differences in the genetic architecture of EEG power and the P300 in young twins (van Baal et al., 1998b) and in adolescent twins (van Beijsterveldt et al., 1998b). For EEG power and for P300 amplitude in response to non-targets, virtually no sex differences in heritability were found in both young and adolescent cohorts (van Baal et al., 1996; van Beijsterveldt et al., 1996). In the young cohort, no sex differences were found for the P300 amplitude in response to targets, but in contrast, significant sex differences were found in the adolescents. Additive genetic factors were found for males, while for females the P300 amplitude was influences by shared environmental factors. Although it is hard to explain what kind of shared environmental factors could influence the variability of the P300 amplitude, the sex-differences were stable across a 2 year period (van Beijsterveldt et al., 2001). Nonetheless, even in this study with a relatively large sample size of 213 twin pairs, statistical power was not sufficient to robustly discriminate genetic from common environmental effects when simultaneously allowing for sex differences.

A second limitation of our meta-analysis is that it could not meaningfully model a possible change in genetic architecture across the life span. Neural differentiation and growth of the developing nervous system may be influenced to a varying degree by genetic and environmental factors. That is, the relative contribution of genetic factors could increase as children grow older (as seems to be the case for IQ) or decrease (as seems to be the case for blood pressure). A change in heritability of a trait may indicate the switching off and switching on of different genes at different ages, but this need not be so. Heritability could increase, even if the same genes

remained involved, simply because the environmental influences decreased or because the effects of some genetic factors are amplified across development. Conversely, the total heritability of a trait can remain stable although different genes are switched on and off at various ages. A longitudinal design has the potential to study whether the same genes contribute to the observed trait on different time-points. Evidence for changes in the genetic architecture of EEG coherence over time was found by van Baal et al. (2001a,b). In their study the same children were tested twice: once at age 5 and one at age 7. Heritability increased with age for occipito–cortical connections in the right hemisphere, but heritability decreased with age for prefrontal-cortical connections in the left hemisphere. Besides, evidence was found that at age 7 new genetic factors emerged.

A third limitation of our meta-analysis is its limitation to a single electrode location. Do genes influence all brain areas to the same extent? This is unlikely since the various brain parts differ in cytoarchitecture. For example, in the prefrontal cortex, cortical connections are more extensive and appear to be organized in a way fundamentally different from those in the posterior cortex (Gevins and Illes, 1991). During ontogeny, the prefrontal cortex is the last to mature. Various studies revealed that the genetic influences were larger in posterior regions than in frontal regions (Meshkova and Ravich-Shcherbo, 1982; Trubnikov et al., 1993). Meshkova suggested that "in the more recent organs and functions the variability is higher than in the older regions, that depend on the effect of genetic factors and have become more refined by selection". In their twin study of EEG alpha activity they indeed found higher MZ correlations for parietal and occipital areas than for central, temporal and frontal areas. The results of this EEG study agree with a recent MRI study (Pfefferbaum et al., 2001). In a group of 33 MZ and DZ elderly twin pairs (mean age 75), it was found that the anterior part of the interhemispheric connecting pathway was more susceptible to environmental influences than the posterior pathway.

A related question is whether the same genes are expressed in all brain areas. Multivariate genetic analyses of the P300 amplitude suggest that distinct genetic factors influence the occipital versus the frontal areas (Begleiter et al., 1998; van Beijsterveldt et al., 1998b; Wright et al., 2001). These data support the idea of different neural sources for the P300, and additionally suggest that each neural source may recruit different genetic mechanisms. Differential genetic influence for frontal and posterior regions is also suggested for the slow wave amplitude recorded during a delayed-response task (Hansell et al., 2001). In contrast, for resting EEG power, it seems that the same genes are expressed in all brain areas (Anokhin, 1987; van Beijsterveldt et al., 1996).

4.2. Concluding remarks

Indices from a more elementary neurobiological level can be very useful in the search for genes for complex psychiatric disorders. An important requirement, however, is that a substantial part of the variance in these indices must be of genetic origin. Our meta-analysis clearly showed that the EEG alpha rhythm as well as the

P300 meet this requirement. A review of other electroencephalo-graphic measures (EEG coherence, P50, N400, SW) also supports substantial heritability for these EEG/ERP parameters, although much less work has been done on them.

EEG alpha power and peak alpha frequency had substantially higher heritability than the P300 amplitude and latency. This may suggest, at first sight, that the EEG measures may be the best endophenotypes to use in future linkage and association studies. However, heritability estimates should be judged in combination with the reliability of the trait and with the theoretical meaning of the trait. The reliability of a trait sets an upper limit to its heritability (Falconer, 1981). Heritability is calculated as the variance accounted for by genetic factors divided by the total variance. Since the total variance includes both the measurement error and nonshared environment, a high measurement error always reduces the heritability estimate. In general, the test–retest reliability of EEG parameters is higher than that of ERP measures, which suggest that the genetic contribution to the 'true' individual differences in ERP amplitudes and latencies is underestimated. To resolve this, genetic models could incorporate measures of the reliability of the EEG/ERP traits in order to distinguish 'real' non-shared environmental variance from measurement error (van Baal et al., 1998b).

As ERPs depend directly on cognitive task manipulations, whereas, resting EEG measures do not, the obvious choice would be to use ERPs rather than EEG. Again, however, appearances may deceive. A number of studies reported that individual variation in EEG power is significantly associated with variability in P300 amplitude (Başar et al., 1984; Intriligator and Polich, 1995). In the study of Intriligator and Polich (1995) positive correlations were reported between EEG power (obtained during rest) and the P300 amplitude (obtained in an oddball paradigm). The strongest correlations were observed for the delta, theta, and lower alpha band. Results from recent studies suggest that the ERP morphology is a compound that results from the superposition of oscillatory responses at different frequency ranges (Karakaş et al., 2000; Klimesh et al., 2000). Results of a recent twin study suggested that, at least in males, a part of the individual differences in P300 amplitude and EEG delta power is influenced by a common set of genes (Anokhin et al., 2001).

Whether an EEG or ERP endophenotype is meaningful ultimately depends on its association with the behavioral trait or disorder of interest. A rational strategy to select an optimal endophenotype, therefore, is to inspect the endophenotype and the trait of interest in the same genetic analysis. In such a bivariate analysis, the covariance, like the variance, is decomposed into a genetic and environmental component. This can reveal the extent to which the association between endophenotype and target trait is indeed due to a common genetic factor. Promising examples of bivariate genetic studies are done by Posthuma et al. (2001a). To find an index of intelligence at a more fundamental level, they examined the correlation between inspection time (measure for perceptual speed) and IQ. Results suggest that the correlation was entirely due to a common genetic factor. Recently, they did the same for intelligence and MRI (Posthuma et al., 2002). The association between cortical structures and intelligence was affected by the same genetic factors.

The most fruitful approach probably uses multiple electrophysiological measures, each closely related to a specific cognitive dysfunction in the disorder of interest. The selection of such endophenotypes can be accomplished only in an extensive collaboration between the fields of behavior genetics and neurosciences.

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