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# SUMMARY AND DISCUSSION

The core mission of this dissertation was to examine the genetic architecture of selected EEG and ERP measures that may index important individual differences in brain structure and function. To do so, data were used from an extensive 2.5-hour EEG recording session in a sample of 263 MZ, 303 DZ twins and 195 of their singleton siblings from two age cohorts, one with an average age of about 25 yrs, one of about 50 yrs.

## HERITABILITY OF EEG/ERP TRAITS

Table 1 gives a summary of the heritability of all EEG/ERP measures tested in this dissertation separately for age cohorts and sex where appropriate. If a measure was assessed at multiple leads, the two leads are provided that showed highest or lowest magnitude on the respective EEG/ERP measure. For example, for alpha power heritability is shown for the leads with the highest and lowest alpha power (O2 and T8, respectively). Additionally, the mean heritabilities across all leads are given. Frontal asymmetry, graph theoretical measures, and the anterior and posterior N1 do not provide topographic information and only the overall heritability is reported for these measures. All heritabilities provided in table 1 are uncorrected for measurement error.

The table is ranked by the magnitude of average/overall heritability, i.e. the most heritable traits are listed first. Only for the last five rows - frontal asymmetry in the middle-aged adults and working memory induced changes in SCP, alpha synchronization and theta desynchronization - no evidence of significant genetic contribution was found. For all other measures a significant heritability was found ranging from moderate to very high. This includes the new EEG measures based on graph theoretical analysis and detrended fluctuation analysis which this dissertation has, for the first time, established as heritable traits.

Age did not have a large impact on the heritability estimates. For the majority of the parameters, no systematic differences in MZ and DZ correlations across age cohorts were found, with the clear exception of frontal asymmetry, where heritability was only found in the young adult cohort. Likewise, no systematic sex differences in twin correlations were encountered in the bulk of our tests, even when significantly different means were found for males and females. Although power to detect subtle effects was low given the sample size, these results suggest that the heritability of many EEG/ERP variables are not subject to much change over the adult years, and that they do not differ between the sexes.

The main conclusion from Table 1 must be that brain activity recorded from the scalp can be reliably used to index stable genetic variation in adult brain function. Below, I will summarize the main findings of this dissertation in the order of the chapters.

### *Resting EEG Power*

As mentioned in the introduction of chapter 2, overall power from background EEG recordings has been related to psychopathology. Beta power has consistently been shown to be decreased in children with ADHD (e.g., Barry et al., 2003a, b; Lazzaro et al., 1998; Chabot & Serfontein, 1996; Satterfield et al., 1972). This beta power decrease is generally found with concurrent theta power increase, although different subtypes may exist (Clarke et al., 2001). Studies of alcoholism have shown deviant resting EEG for several frequencies. For example, increased beta power has been reported in alcoholics compared to controls (e.g., Gabrielli et al., 1982; Rangaswamy et al., 2002, 2004). The successful use of beta power as an endophenotype for alcoholism has been demonstrated in a linkage/association study (Porjesz et al., 2002; Edenberg et al., 2004; Dick et al., 2006), implying the dependence of both beta power and alcoholism on gaba-ergic ‘neural excitability’ (Rangaswamy et al., 2004; Porjesz et al., 2005). Alterations in other frequency bands have been reported in alcoholism too (Porjesz et al., 2005).

In adult subjects we find very high heritability of EEG power. Power in the alpha band is almost about as heritable as what could well be the most heritable quantitative trait in humans: body height (Silventoinen et al., 2006). Heritabilities of theta and beta power were also high and only delta power showed moderate heritability. Our findings in adults are highly consistent with many previous findings in childhood and adolescence (see van Beijsterveldt & van Baal, 2002). Heritability was significantly lower in middle-aged adulthood, but the difference was very modest (for example, 90% and 85% respectively for alpha power averaged over leads). Although these were not formally tested, topographic differences were also very minor, with comparable heritability of EEG power across the scalp.

To verify whether the classical frequency bands were recapitulated in ‘heritability bands’, we plotted heritability across the power spectrum in narrow 1 Hz frequency bins. This yielded a fairly continuous heritability spectrum, with gradually lower heritability for frequencies under 6 Hz (mainly frontal leads) and above 13 Hz (leads T7 and T8). Based on the proposed differences between different frequency bands with respect to their cognitive function or relation to psychopathology (theta, lower alpha 1 and 2, upper alpha: Klimesch, 1999; beta band in alcoholism: Rangaswamy et al., 2002; beta band in ADHD: Clarke et al., 2001) we tested the hypothesis that the heritability of EEG in different bands reflected different genetic factors. The data presented did not support this since at least 55%, and typically 60% - 75% of the genetic variation overlaps between the bands. This converges with findings by Anokhin et al. (2004) who also reported a substantial genetic covariation between the frequency bands delta, theta, alpha, and beta. We concluded, therefore, that a single genetic factor accounts for most

Table 1. Summary of heritabilities rank ordered by magnitude

Analysis	variable/frequency	subjects	@ max effect		@ min effect		mean/overall effect
			lead	h <sup>2</sup>	lead	h <sup>2</sup>	
Power	$\alpha$	Young Adult		0.85		0.9	0.88
		Middle-aged	O1	0.83	T8	0.79	
	$\theta$	Young Adult		0.87		0.84	0.80
		Middle-aged	Cz	0.77	T8	0.75	
	$\beta$	Young Adult		0.80		0.73	0.77
		Middle-aged	Pz	0.82	F7	0.66	
	$\delta$	Young Adult		0.56		0.63	0.57
		Middle-aged	Fz	0.46	T8	0.5	
Graph theoretical analysis	Path length, $\theta$	All		<i>n/a</i>		<i>n/a</i>	0.63
	Path length, $\beta_2$	All		<i>n/a</i>		<i>n/a</i>	0.60
	Path length, $\alpha_2$	All		<i>n/a</i>		<i>n/a</i>	0.59
	Path length, $\beta_1$	All		<i>n/a</i>		<i>n/a</i>	0.46
	Path length, $\alpha_1$	All		<i>n/a</i>		<i>n/a</i>	0.35
Visual oddball amplitude and latency	P300 amplitude	All	Pz	0.5	Fz	0.56	0.52
	Posterior N1 amplitude	All		<i>n/a</i>		<i>n/a</i>	0.50
	Anterior N1 latency	All		<i>n/a</i>		<i>n/a</i>	0.45
	P300 latency	All	Pz	0.45	Fz	0.42	0.44
	Posterior N1 latency	All		<i>n/a</i>		<i>n/a</i>	0.43
	Anterior N1 amplitude	All		<i>n/a</i>		<i>n/a</i>	0.22
Long range temporal correlations	DFA $\alpha$	All	P7	0.46	Fp2	0.58	0.47
	DFA $\beta$	All	C3	0.5	F8	0.37	0.42
Delayed response task (response anticipation)	DRT upper $\alpha$	All	P8	0.55	F8	0.45	0.48
	DRT $\theta$	All	O2	0.32	Cz	0.48	0.40
	DRT SCP	All	Pz	0.35	T8	0.08	0.23
Graph theoretical parameters	Clustering Coeff, $\beta_2$	All		<i>n/a</i>		<i>n/a</i>	0.33
	Clustering Coeff, $\beta_1$	All		<i>n/a</i>		<i>n/a</i>	0.32
	Clustering Coeff, $\theta$	All		<i>n/a</i>		<i>n/a</i>	0.24
	Clustering Coeff, $\alpha_1$	All		<i>n/a</i>		<i>n/a</i>	0.20
	Clustering Coeff, $\alpha_2$	All		<i>n/a</i>		<i>n/a</i>	0.20

Frontal EEG asymmetry	FA	Young females	<i>n/a</i>	<i>n/a</i>	0.37
	FA	Young males	<i>n/a</i>	<i>n/a</i>	0.32
	FA	Middle-aged females	<i>n/a</i>	<i>n/a</i>	0.11
	FA	Middle-aged males	<i>n/a</i>	<i>n/a</i>	0.01
Delayed response task (working memory effect)	DRT $\alpha$ memory effect	All	C4 0	O1 0.06	0.07
	DRT SCP memory effect	All	C3 0.04	P8 0	0.03
	DRT $\theta$ memory effect	All	O2 0.23	T8 0.08	0.03

*n/a*=not applicable; *h*<sup>2</sup>=heritability

of the genetic variation of EEG power across the entire 1 to 25 Hz frequency range.

### P300

The P300 is the positive deflection that begins 300 ms after the presentation of an infrequent target stimulus. In the field of cognition, it is thought to represent working memory processes called context closure (Verleger, 1988), context updating (Donchin & Coles, 1988), or event categorization (Kok, 2001). In the field of psychopathology, P300 amplitude has been systematically related to Alcoholism (Almasy et al., 1999; Polich et al., 1994) in alcoholics and family members of alcoholics. Also, reduced temporal P300 amplitude has been shown in Schizophrenia (Levit et al., 1973; Verleger & Cohen, 1978).

Adult P300 amplitude (50%) and latency (45%) in a visual oddball task showed substantial heritability. These results, too, seemed consistent with previous findings of twin and family studies in childhood and adolescence (e.g., Wright et al., 2001; Begleiter et al., 1998; see also van Beijsterveldt & van Baal, 2002).

The P300 is now widely believed to reflect multiple constituent components (Falkenstein et al., 1994; Dien et al., 2004) that may reflect stimulus evaluation, novel stimulus processing, and response selection processes respectively. This suggests that different genetic factors might influence the early, middle and late part of the P300. We therefore tested whether the P300 development over time (from 100 ms before the peak to 100 ms after) reflected the expression of different genes. Within 120 ms around the P300 peak at least 90% of the variation attributed to genetic influence on the signal amplitude were found to be overlapping. Within a 200 ms range (the full 100 before and after) at least 75% of the genetic variation was shared. We concluded that the subcomponents that constitute the full P300 wave, are influenced by the same genetic factor. From an individual differences perspective there is little evidence to suggest that differ-

ent parts of the P300 reflect stimulus evaluation, novel stimulus processing, and response selection processes, unless all these processes are influenced by the same genetic factor.

Recently, a central triggering mechanism for the P300 waves across the scalp was proposed by Nieuwenhuis et al. (2005) which is localized in the Locus Coeruleus. Individual differences in P300 latency at frontal, central and occipital leads could be explained by a single genetic factor, which, as argued in chapter four, may be consistent with a central trigger. In contrast, different genetic factors seem to influence the P300 amplitude at different scalp locations, suggesting local modulation of the P3 once triggered.

### *N1*

The visual oddball task showed a clear occipito-temporal N1, and an earlier anterior N1 (Vogel and Luck, 2000). The N1 reflects early attentional resource allocation (Luck, 1995; Altenmüller & Gerlof, 1999). We showed that for the visual N1 a refined peak picking strategy is needed that uses separate windows for the anterior and posterior N1. The two previous twin studies on the visual N1 had not assessed the anterior and posterior components separately resulting in low twin correlations for anterior N1 amplitude and all latency scores (Almasy et al., 1999; Katsanis et al., 1997). In contrast, our study showed that posterior amplitude (50%) and latency (43%) both have substantial heritability, with estimates of comparable magnitude as the P300. Only anterior N1 amplitude showed a low heritability, but heritability of latency was again of comparable magnitude as that of the posterior N1 and P300 latency. From these results we concluded that the N1 deserves the same level of attention by geneticists that has now been reserved exclusively for the P300.

### *Frontal EEG Asymmetry*

Frontal EEG asymmetry has been related, amongst others, to depression, anxiety, and affective style (approach vs. avoidance behavior) (e.g., Coan & Allen, 2004; Coan et al., 2006). Genetic analysis showed that in our sample, heritability was significant only in the young adult group (30% for males, 37% for young females). This is consistent with earlier studies by Coan (2003) in young adult males and females, and by Anokhin et al. (2006) in young adult females. No significant heritability was found in the middle-aged adults.

It is noteworthy that even in the young adults, heritability of frontal asymmetry is a far cry from the heritabilities of its constituent variables, F3 and F4 alpha power (89% and 90%).

*Graph theoretical parameters*

Graph theoretical ('Small-world') parameters clustering coefficient  $C$  and average path length  $L$  (Watts & Strogatz, 1998) define spatial patterning in connectivity between brain areas. Patterns with high clustering and low average path length are called 'small-world', and characterize an efficient functional brain network (Achard & Bullmore, 2007). Micheloyannis et al. (2005) reported the loss small world efficiency in a group of schizophrenics who had had a single psychotic episode. The same loss of 'small-worldness' was reported for a group of Alzheimer's patients by Stam et al. (2007). Ponten et al. (2007) reported that the small world parameters  $C$  and  $L$  show an increased ordered state (higher  $C$  but also higher  $L$ ) in functional connectivity from intracranial recordings in epileptic patients.

Chapter 6 showed that in adults  $L$  has substantial heritability in the different frequency bands (35% to 63%).  $C$  was less heritable (20% to 35%) which may reflect larger measurement error as evident in the low epoch-to-epoch reliability coefficients. Taken together we concluded that the constituents of 'small-worldness' of the brain are heritable traits.

*Long range temporal correlations*

Detrended Fluctuation Analysis (DFA) provides a measure of temporal patterning as opposed to the spatial patterning described in the graph theoretical approach. Generally, oscillatory activity in the EEG signal, such as alpha, shows clear time-based structure in the amplitude of these oscillations. Previous amplitude levels in the system tend to determine the level at later time-points, and the strength of this auto-correlation decays following a power law. A power law decrease over time in the auto-correlation is a property of self-organized critical systems (Linkenkaer-Hansen, 2001).

Recently, Linkenkaer-Hansen et al. (2005) showed that long-range temporal correlations in EEG theta activity show a breakdown in the depressed patients compared to healthy controls. Monto et al. (2006) reported that DFA exponent of beta activity in subdurally recorded EEG is increased near the ictal focus in epileptic patients. Non-epileptic brain areas showed normal DFA exponents. In addition, they reported a deviation of the power law scaling of amplitude in the lower beta band (around ca. 13 Hz) which was larger near to the ictal focus.

As the first study to investigate family resemblance in long range temporal correlations, chapter 7 revealed a clear genetic basis to individual differences in the DFA exponent (heritability around 50%).

*Delayed Response Task*

Chapter 8 investigated the relationships between the Slow Cortical Potential (SCP) and upper alpha synchronization, and theta desynchronization that are

all seen to emerge in the response anticipation period of the DRT task, and are similarly responsive to an increase in working memory load during this interval. Theta desynchronization and upper alpha synchronization showed significant heritability across the scalp in both low (alpha: 18% - 49%; theta: 35% - 60%) and high (alpha: 31% to 46%; theta: 35% to 65%) memory load conditions, the latter yielding the highest estimates. SCP showed low to moderate heritability at the midline, occipital, and left parietal electrodes, with estimates again being larger in magnitude in the high (25% to 43%) than in the low (21% to 37%) load condition. The slow cortical potential showed a specific heritability distribution which was mostly posterior, whereas upper alpha synchronization and theta desynchronization showed scalp-wide heritability. Trivariate analysis of SCP, upper alpha synchronization, and theta desynchronization showed that these parameters were largely influenced by *different* genetic factors, although some of the variation in upper alpha synchronization and ThD could be attributed to shared genes (ca. 20-25%). We concluded that these measures, although they share antecedent conditions—namely, the response anticipation in a delayed response task—do not reflect the same neural substrate.

Interestingly, the effect of memory load effect on these three parameters, although highly significant, were not heritable at all, which disqualifies them as endophenotypes of spatial working memory capacity.

#### *Ranking of EEG/ERP measures*

Why do the heritabilities of EEG/ERP parameters have the ranking they have? An obvious explanation is that they differ in the amount of measurement error. Since measurement error is attributed to the unique environmental component of the parameter, the relative contribution of the genetic component is reduced. It is reasonable to suggest that measurement issues are larger for Event Related Potentials (ERP), Event Related Spectral Perturbations (ERSP), and spatial or temporal patterning measures based on 4 to 6 relatively short (16 - 20 sec) epochs than for traits extracted from continuous recordings over a few minutes (Power, Frontal Asymmetry). N1 peaks, for example, are based on many trials that are averaged, but only on short periods within in those trials are used to determine the anterior N1 (88 - 168 ms) or posterior N1 (132 - 220 ms). Continuous recordings may have the advantage of all (or most) of the data providing information for the parameter in question.

To estimate measurement error—and its counterpart reliability—one can take the approach as taken in chapters four and six. In chapter four measurement error was estimated by taking the split half of trials, where odd and even trials were used to create two estimates for N1 amplitude and latency. The proportion overlap in variance between the two measures represents the amount of reli-



able variation, the rest was assumed to represent unstable variance. Posterior N1 amplitude and latency could be measured reliably (ca. 0.90). Here, adjusting the heritability estimates resulted in a negligible increase. Reliability was estimated to be much lower for Anterior N1 amplitude and latency (ca. 0.60). Adjusting for the unreliable variance increased these estimates from 22% to 35% for amplitude and from 45% to 56% for latency. These increases are not trivial.

In chapter six, a similar approach was used to incorporate measurement error into the genetic models, based on four repetitions of 16 sec epochs. This led to a large increase in the heritability of C and L. Heritability of uncorrected C ranged from 20% to 33% and increased to 37% to 62% after correction for measurement error. Heritability of uncorrected L ranged from 35% to 68% and increased to 46% to 89% after correction. Again, these increases are not trivial.

In conclusion, differential amounts of measurement error account for part of the low heritability found in some of the EEG/ERP measures. Clearly higher heritability estimates are obtained if reliability of the EEG/ERP measures is statistically taken into account. In addition, signal-to-noise ratio may be improved experimentally by increasing the number of trials and the length and/or the number of epochs.

## ENDOPHENOTYPES

An overarching idea driving our genetic dissection of ERP/EEG measures is the idea that they may be useful as endophenotypes. The obvious pathway to link genetic variation to variation in complex behavior is through the brain, i.e. allelic variation causes variation at the cellular level in the brain that in turn influences its network properties and complex output. To 'fill the gap' between genotype and complex behavior, the concept of endophenotype has been introduced (Gottesman & Shields, 1972; Gottesman & Gould, 2003; de Geus, 2002) to represent this intermediate brain level in the pathway from gene to its expression. Due to their simpler genetic structure, endophenotypes can (1) help localize parts of the genome that harbor genes for complex traits or diseases and, once candidate genes have been identified, (2) help explain how these genes exert their effects on brain and behavior.

As an example of the first, Williams (1999) could pinpoint the genomic region that codes for alcohol dehydrogenase on chromosome 4q through the use of the P300. Previous research had indicated that the amplitude of the P300 wave is reduced in alcoholics and family members of alcoholics. By using this endophenotype in a bivariate linkage analysis of alcohol problems and P300 amplitude, Williams et al. were able to detect a linkage peak on chromosome 4q, and a smaller peak near the GABA receptor gene area. Fine mapping of these areas resulted in

the identification of GABRA2 and ADH4, amongst others (Dick et al., 2005; Edenberg et al., 2004; Edenberg & Faroud, 2006).

Imaging genetics provides an example of how endophenotypes can be used to unravel the effects of an established candidate gene on brain activation (Hariri and Weinberger, 2003; Hariri et al., 2002; Hariri, et al., 2006; Meyer-Lindenberg et al., 2006). A functional variant in the serotonin transporter gene 5-HTT had been associated with neuroticism, particularly in combination with major life stress (Lesch et al., 1996; Caspi & Moffitt, 2006). Using fMRI, carriers of the risk allele were shown to have heightened activation of the amygdala in response to emotional stimuli. These results imply that amygdala activation assessed by fMRI is an endophenotype for effects of the 5-HTT gene on emotional processing, and perhaps anxiety differences in humans.

The results summarized in Table 1 bode well for EEG/ERP measures as potential endophenotypes. With a few exceptions, the ERP/EEG measures are heritable indices of brain function, fulfilling the second requirement listed on page 6 in the introductory chapter. Because they directly reflect brain activity they also seem to fulfill the fifth requirement of being meaningfully intermediate between genes and behavior. In keeping with the third requirement, these measures have shown significant association with disease states like depression, alcoholism, ADHD, schizophrenia, epilepsy, and Alzheimer in clinical populations (e.g., Allen et al., 1993; Almasy et al., 1999; Barry et al., 2003a, b; Begleiter et al., 1984; Blackwood, 2000; Bruder et al., 2001; Chabot & Serfontein, 1996; Clarke et al., 2001; Davidson et al., 1992; Debener et al., 2000; Ehlers & Schuckit, 1990, 1991; Elmasian et al., 1982; Field et al., 2000; Gabrielli et al., 1982; Gotlib et al., 1998; Henriques & Davidson, 1991; Lazzaro et al., 1998; Levit et al., 1973; Nitschke et al., 1999; Polich et al., 1994; Porjesz & Begleiter, 1990; Propping, 1977; Rangaswamy et al., 2002, 2004; Reid et al., 1993; Satterfield et al., 1972; Schaffer et al., 1983; Silva et al., 2002; Turetsky et al., 2000; Van Sweden & Niedermeyer, 1999; Verleger & Cohen, 1978; Vogel, 2000; Wiedemann et al., 1999).

We tried to replicate some of these associations in our non-clinical population-based sample. This met with little success. Frontal asymmetry did not show the expected relation to the risk for anxiety and depression. The small-world parameters C and L were not found to be related to cognitive performance (WAIS IQ). Similarly, individual differences in the DFA exponent did not predict Raven's IQ score. One potential explanation for the lack of these correlations is that frontal asymmetry, C, L, and DFA were all based on resting EEG. The unchallenged brain may not reveal those aspects of brain function that are functionally interesting. For example, resting state during which we collected EEG may not be as standardized as may appear from a methods section (Linkenkaer-Hansen,

personal communication, June 2007). Studies investigating ‘resting-state’ activity with fMRI have found that specific brain areas become activated. These areas are then deactivated during task execution (Raichle et al., 2001; Greicius et al., 2003; Raichle, 2006). However, we do not know what thought processes the subjects are engaged in during a resting state, which could consist of reminiscing, working memory activation, or consist of a real deactivated state. Measuring EEG under relevant (i.e., evoking and challenging) circumstances could provide a better match with behavioral traits. For frontal EEG asymmetry, for example, anxiety provoking situations could be used such as watching positively and negatively valenced scenes (Reeves et al., 1989) or emotional facial expressions (Jones & Fox, 1992). Likewise, endophenotypes of IQ should preferably be measured while performing actual IQ tasks such as the Raven’s.

By way of exploration we computed correlations between all of our EEG/ERP measures and four complex behavioral traits, namely anxious depression, attention problems, weekly alcohol use and full scale IQ (see appendix 1). Clearly, there is no simple one-to-one mapping between our measures and these specific traits. Future research must establish the true nature of the relation between the level of brain function and the level of complex behavior, and under which experimental conditions these measures start to capture variation in these types of behavioral traits.

## FUTURE DIRECTIONS

The EEG/ERP measures in this dissertation represent complex aspects of brain activity. Measures like C, L, and DFA have a strong theoretical basis and are directly linked to spatial and temporal organization of neural activity. Finding genes for these measures could constitute a major step forward in understanding individual differences in brain function and, potentially, how these phenomena are generated in brain tissue. Likewise, the “simpler” measures like P3, N1, and EEG power would be well served by increased genetic understanding. Finding even a single gene for a longstanding, but still quite elusive phenomenon like alpha oscillations—now nearing 90 years in age—could provide a bottom-up approach to its explanation in neural terms.

An important next step is to perform whole genome searches (through both linkage and whole genome association approaches) on these measures to find the genes underlying the heritabilities presented in Table 1. To do so, large samples with EEG data and genetic markers are needed. Fortunately, such samples are increasingly becoming available through biobanking of genetic material in several psychophysiological labs. The first successful gene finding studies have already been performed by Steinlein et al. (1992), who showed significant link-

age for the low-voltage EEG phenotype (Vogel, 1959, 2000) on chromosome 20q. Also, significant linkage of the biomarkers for alcoholism—P300 and beta power—were reported by the COGA group (Begleiter et al., 1998; Porjesz et al., 2002). Finally, Hansell et al. (2005) provided suggestive linkage for the SCP during response anticipation.

Taken together, I conclude that future identification of the actual genes underlying the heritability of my electrophysiological measures is both valuable and feasible.

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