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The Genetic Basis of the Normal Human Electroencephalogram (EEG)*

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Summary. The genetic basis of the normal human electroencephalogram (EEG) was analyzed. Twin investigations showed complete concordance for most EEG characteristics in monozygotic twins of all age groups. Differences in high age include focal abnormalities and dysrhythmic groups. These differences failed to show a relation to mental performance. For a number of special EEG variants, population frequencies were determined, and the mode of inheritance was established. The following variants were analyzed:

1. Variants of the alpha rhythm:

a) The low voltage EEG (simple autosomal dominance),

b) Borderline cases of the low voltage EEG (mixed genetic basis),

c) Quick (16—19/sec) alpha variants (simple autosomal dominance),

d) Slow (4—5/sec) alpha variants (mode of inheritance still unknown; behavioral abnormalities),

e) Monotonous α-waves (probably simple autosomal dominance).

2. The EEG with β-waves:

a) Differences in relation to age and sex were analyzed. β-waves are especially frequent in elderly women.

b) Certain types of β-groups in frontal and precentral leads show a simple autosomal dominant mode of inheritance.

c) For the diffuse β-waves, the general model of multifactorial inheritance in combination with a threshold effect seems to be appropriate.

Difficulties of the analysis are mentioned, and some theoretical and practical aspects of the results are discussed.

Zusammenfassung. Es wurde die genetische Grundlage des normalen menschlichen Elektrencephalogramms (EEG) analysiert. Zwillingsuntersuchungen zeigten vollständige Konkordanz für die meisten EEG-Merkmale bei eineiigen Zwillingen aller Altersgruppen. Unterschiede in hohem Alter betreffen Herdveränderungen und dysrhythmische Gruppen. Diese Unterschiede zeigten keine Beziehung zu der geistigen Leistungsfähigkeit. Für eine Anzahl spezieller EEG-Varianten wurde die Häufigkeit in der Bevölkerung bestimmt, und der Erbgang wurde ermittelt. Die folgenden Varianten wurden analysiert:

1. Varianten des α-Rhythmus:

a) Niederspannungs-EEG (einfach autosomal dominant);

b) Grenzfälle des Niederspannungs-EEG (sie stellen eine Mischung von Fällen mit verschiedener genetischer Grundlage dar);

c) Rasche (16—19/sec) β-Wellen mit den Eigenschaften von α-Wellen (einfach autosomal dominant);

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d) Die 4—5/sec Grundrhythmusvariante (Erbgang noch ungeklärt; auffällige Abnormitäten des Verhaltens);

e) Monotone α-Wellen (wahrscheinlich autosomal dominant).

2. Das EEG mit β-Wellen:

a) Es wurden die alters- und geschlechtsbedingten Unterschiede in der Häufigkeit von β-Wellen diskutiert. Bei älteren Frauen sind β-EEG besonders häufig.

b) Zwei bestimmte Typen von β-Gruppen in frontalen und präzentralen Ableitungen zeigten einen einfach autosomal-dominanten Erbgang.

c) Für die genetische Grundlage der diffusen β-Wellen eignet sich eine Beschreibung durch das allgemeine Modell der multifaktoriellen Vererbung mit Schwellenwerteffekt.

Schwierigkeiten der Analyse werden erwähnt, und einige theoretische und praktische Aspekte der Ergebnisse werden diskutiert.

I. Introduction

The Problem

The normal human electroencephalogram (EEG) presents very good conditions for a genetic analysis, as there is a conspicuous interindividual variability, together with a remarkable stability in the same person over many years. Moreover, genetic analysis seems to be worthwhile for theoretical as well as for practical reasons:

Whereas in the field of biochemical genetics, for example in enzyme or serum-protein variants, the mode of inheritance is often simple, and our main interest is directed towards a thorough biochemical analysis, the situation with the EEG is quite different: Here, the biochemical bases of the phenomena are completely unknown und will very probably remain so for a good time to come. Formal genetics can play a leading role in causal analysis.

Besides, there is a practical reason: When the EEG is used in medical diagnostics, evaluation is frequently hampered by the fact that the same EEG might be a normal variant in one case, but a symptom of brain damage in another.

When the genetic basis of normal variability is known, family examinations might help to clarify some of these ambiguous cases.

In view of these advantages, it is surprising to see how rarely the normal EEG has been analyzed from a genetic point of view. This, however, becomes understandable when the difficulties are considered which can again be divided into theoretical and practical ones.

First, there are definite changes of the EEG during childhood and youth, and the mature pattern is only reached at about 19—20 years. Besides, a definite sex difference is observable in higher age groups. Finally, the EEG shows certain signs of involution in very old persons. Different physiological conditions might also lead to transitory changes of the resting EEG, and in order to get reliable results, certain standard conditions are required.

The main practical difficulty is that not only the propositi but also their relatives have to be examined for at least 30—60 min and required apparati are relatively big, heavy, expensive and sensitive. In earlier years, we had to induce the relatives to come into an outpatient clinic in Berlin, whereas since 1963, a specially devised ambulant EEG laboratory with an 8-channel Schwarzer apparatus in a "Volkswagen-Großraum-Bus", has become available (for description see Vogel, 1964). In any case, family and twin examinations are unusually time-consuming compared, for example, with those for which only blood samples are needed.

An additional difficulty is the selection of propositi, especially for the less frequent variants, as series of normal adults are only rarely available.

During the first years of our investigations, we selected probands from the outpatients of an EEG laboratory in Berlin. Many of them showed an apparently normal EEG. However, as they had been sent to the laboratory for one or the other complaint, the material was obviously biased. Since 1963, in cooperation with the Institute for Air Medicine of the German Air Force, we recorded all applicants for service in the flying units who have successfully passed a psychological test program. Hence, material of normal young men, selected for a high standard of mental and bodily health, is available. The examinations were carried out using a standard program proposed by Jung (unipolar, bipolar and transversal leads; 3 min hyperventilation; amplification: 50 μV = 7 mm; frequency screen at 70 Hz).

II. Twin Investigations

Our analysis started with the general problem: *To what degree is the variability of the normal EEG due to genetic differences?* The most general method for solving this problem is the twin method. Besides, some twin data from the literature (Davies and Davies, 1936; Raney, 1937, 1939; Höchel, 1942; Lennox, Gibbs and Gibbs, 1945, and others) seemed to hint towards an important genetic component in the EEG variability.

We (Vogel, 1958) examined 208 twin sets of the same sex between 6 and 30 years of age, among them 110 monozygotic (MT), in the resting stage, with hyperventilation, oxygen lack, and during sleep.

In evaluating the results, we tried to use exact measurements and statistical comparisons as much as possible. The result of a comprehensive program of measurements was that there are no constant differences between MT in measurable EEG traits. In all qualitative traits compared, in the reaction to hyperventilation, and in the stages of natural sleep, EEG curves of healthy MT turned out to be alike. This similarity also includes occurrence of the 14 and 6/sec positive spikes during light sleep (Vogel, 1965). The individuality of the EEG as well as the similarity in MT was shown by a successful blind classification experiment.

From our investigations we concluded that the variability of the EEG under normal conditions is exclusively determined by heredity.

Now, the EEG changes very much with the development of the brain up to the age of 20, and the speed of these changes shows conspicuous interindividual differences. Our results prove the genetic basis of this aspect of brain development.

Dizygotic twins, on the other hand, may show a very different stage of EEG maturation.

Within the last years, these investigations were complemented in the following directions:

Heuschert (1963) tried to find out whether the known EEG changes in higher age groups have a hereditary basis, too. This problem was examined in 26 MT between 50 and 79 (mean age 64).

From all twin pairs, two EEG were taken within ¼—½ year. Besides, they were examined with the Hamburg-Wechsler and the Raven matrix intelligence tests. The result is that the EEG is very similar in old MT as well. This holds true not only for normal traits, but for abnormalities like slowing of alpha-waves,

lability of frequency, and diffuse theta-waves as well. In some pairs, differences were seen in active dysrhythmic groups and in focal abnormalities. It was concluded that even in higher age groups the EEG is predominantly genetically determined. Differences between the co-twins in the level of general intelligence as revealed by the tests did not show any relationship to the EEG differences mentioned (focal and dysrhythmic). Instead, they were correlated with differences in biography and intellectual exercise which seem to be more important for intellectual performance in high age groups than organic brain damage (provided that it is not too severe).

Complements to our twin examinations, published by other groups, include the results of Juel-Nielsen and Harvald (1958) in 8 MT reared apart which also showed complete concordance in the normal EEG. Zung and Wilson (1967) reported concordance of all-night sleeping patterns together with REM-(rapid eye movement) patterns in 4 MT. Dencker (1958) used the twin method for follow-up studies of cases with head injuries.

III. Family Investigations

The results of the twin investigations mentioned encouraged us to use the family method. However, in view of the well-known complexity of the EEG pattern, family investigations only promised to be rewarding, if we did not look for general similarities and differences between the members of families, but started with well-defined special EEG-types.

1. Variants of the Alpha-Rhythm (Fig. 1)

a) The Low Voltage EEG

There are certain variants of the alpha-rhythm which normally has a frequency of 10—11/sec with a maximum over occipital (and temporal) parts of the brain (Fig. 1).

The most conspicuous variant is the low voltage EEG which is characterized by a complete lack of alpha-waves in the resting EEG, whereas a certain amount of alpha-waves may be seen in some cases shortly after a closing of the eyes and during hyperventilation (Fig. 1 a).

Population Frequency. Gibbs *et al.* (1943) give a frequency of 11.6% among 1000 controls. Pine and Pine (1953) reported 7.25% among 2000 patients of their laboratory. We (Vogel and Götze, 1959) found 121 among 1707 cases from the Berlin laboratory (7.09%), and additionally 48 (2.81%) cases classified as "borderline".

Vogel and Fujiya (1969) found 4.20% typical and 2.25% borderline cases among 4622 young German males (Air force applicants) and 4.57% typical and 2.14% borderline cases among 3372 Japanese males with similar age distribution. These frequencies are lower than those mentioned in the literature, but the propositi were selected quite differently compared with earlier series.

Family Investigations. The over-all number of families analyzed is 60 with 117 children above 10 years. For a genetic analysis the question has to be answered whether there is a clear-cut alternative between persons with a low voltage EEG and persons with a normal alpha-EEG. In most cases the decision is quite obvious,

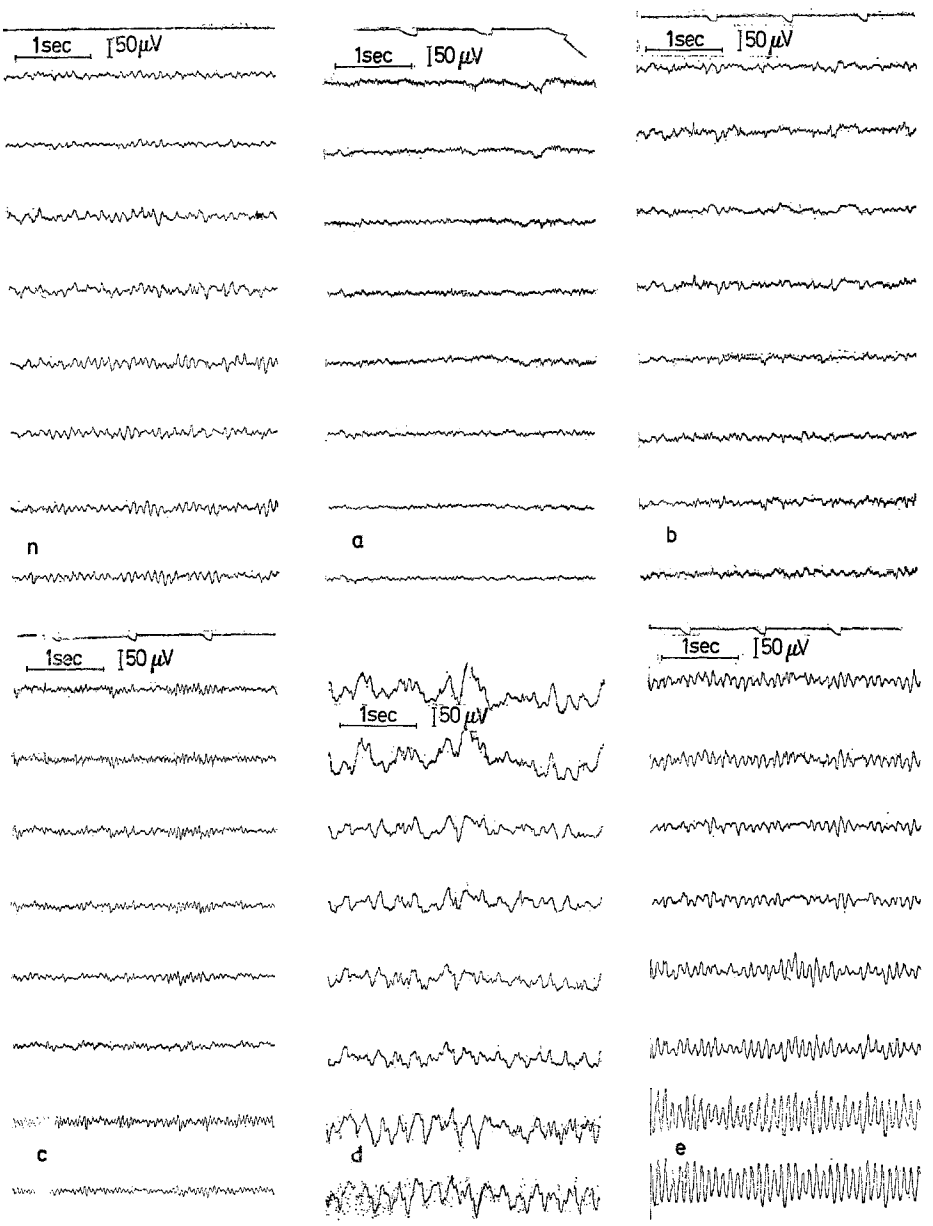

Fig. 1. Variants of the normal α-rhythm. n Normal, "average" alpha EEG; a low voltage EEG; b Borderline low voltage EEG; c Quick (16—19/sec) α-variants; d slow (4—5/sec) α-variants; e Monotonous α-waves. Unipolar leads (against one ear) from frontal, precentral, central, and occipital regions; resting stage; eyes closed

but there is a small number of borderline cases. One measure of the occipital alpha-rhythm called „percent tim alpha" is defined as follows:

$$\frac{\text{number of alpha-waves within 10 sec}}{\text{alpha-frequency} \times 10}.$$

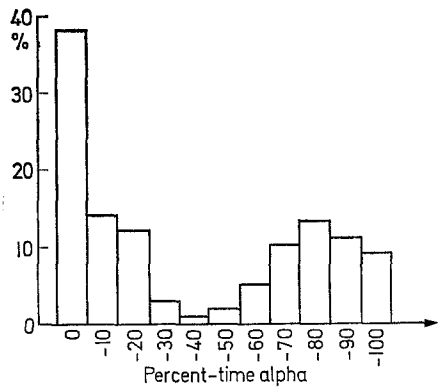

Fig. 2. Distribution of percent-time alpha among parents and siblings of 30 probands with low voltage EEG

It runs between 0 and 100.

This index was determined in occipital unipolar leads in 118 parents and siblings of 30 probands (Vogel and Götze, 1959).

The combined distribution for parents and siblings is seen in Fig. 2. There is a clear-cut bimodality. The graph shows, on the other hand, that not all persons with the low voltage type have the value 0. But wherever alpha-waves can be seen, their amplitude is very low. For a discussion of the borderline cases see below. The distribution of the right-hand part of the diagram corresponds of the distribution in the general population.

A condensed survey of the results for the different mating types is contained in Table 1.

In families, in which the parents and siblings of the propositus were examined, a statistical analysis of the segregation ratio was carried out according to the principles derived by A. Kaelin (1955; see also Vogel, 1961) for single selection ($K = 0$), which conforms to the maximum likelihood criterium. In families ascertained via one of the parents, the segregation ratio could be determined without correction. For all details about the families, see Vogel and Götze (1959), Vogel (1962a).

Table 1. *Segregation ratios for 60 families with 117 children; low voltage EEG*

	Mating type $+\times+$	Mating type $+\times-$	Mating type $+\times-$ only children 19 years and older classified
Expected (Simple autosomal dominance)	$P = 0.759$	$P = 0.509$	$P = 509$
Observed ($\hat{P}$ = estimate of the segregation ratio P)	$\hat{P} = 0.75 \pm 0.153$	$\hat{P} = 0.3647 \pm 0.0519$	$\hat{P} = 0.477 \pm 0.075$
Comparison	No difference	$c = \frac{(0.5090 - 0.364)}{0.0519} = 2.78$ $w = 0.005$ significant difference	$c = \frac{(0.509 - 0.477)}{0.075} = 0.43$ $w = 0.7$ no significant difference

Whereas the distribution among the parents points strongly to a simple autosomal dominant mode of inheritance, the estimated segregation figure for the mating type $+ \times -$ is significantly lower than expected. However, this difference disappears as soon as the analysis is confined to persons of at least 19 years of age. The obvious interpretation is that some of the persons examined during the second decade of life and showing an α-EEG belong to the low voltage group genetically and will develop their final EEG type later. This interpretation conforms to general experience about the age distribution of the trait. The data give conclusive evidence in favour of a simple autosomal dominant mode of inheritance.

b) Borderline Cases of the Low Voltage EEG (Fig. 1 b)

This clear-cut picture is somewhat impaired by the fact that there are some persons in the population who cannot be classified into either the low voltage or the non-low voltage group and have to be labelled provisionally as "borderline". In order to define this group somewhat more clearly a special study was carried out (Reinke, 1966). Starting with air force applicants, preliminarily classified as borderline, 23 families were examined. In 15 of them examination of the propositus could also be repeated. In 5 of them the propositus had a clear-cut low voltage EEG at the second examination, and the family showed the dominant mode of inheritance. There was no doubt that these cases had to be classified as "low voltage". In three other families the proband as well as his relatives showed a normal alpha-EEG at the re-examination. Here, the alpha-reduction during the first examination was very probably due to external disturbances, for example psychical tension or fatigue. In five other cases, the propositus again had a borderline EEG at the time of the control examination, but the relatives exclusively showed an alpha-EEG; the borderline EEG has to be considered as an extreme variant of the alpha-type.

On the other hand, there were two families in which the EEG of the propositus was borderline, but other family members had typical low voltage curves. In these cases, the borderline EEG had to be considered an extreme variant of the low voltage type. Families, in which the examination of the proband could not be repeated, very probably belong to the same groups.

The following statement about persons which had to be classified as "borderline" after routine examinations seems to be justified: Some of them can easily be attributed to the low voltage or to the normal alpha-group when the examination is repeated under optimal conditions. They might account for a good part of the cases called "borderline" in population surveys (see above). However, as is to be expected from the distribution of percent-time alpha, there remain some cases which cannot be classified on the basis of the EEG phenotype, but on the basis of the family examinations only. Until additional criteria are found, they will be considered as "true borderline".

c) Occipital Slow β-waves

(Quick Alpha-Variants 16—19/sec; Fig. 1 c)

There is another variant of the normal EEG in which the normal occipital waves do not show a frequency of 8—13/sec (alpha-waves per definitionem), but 16—19/sec.

According to the usual definitions, these would have to be called β-waves, and are described as "occipital slow β-waves". The general behaviour, however, shows that they are modified alpha-waves: The distribution over the surface of the skull as well as the occipital maximum are characteristic for alpha waves, and so is the complete blocking when the eyes are opened. The trait was briefly mentioned by Vogel (1962b), and a genetical analysis was presented by Vogel (1966b).

Population Frequency. Among 1984 EEG examinations of air force applicants 12 cases were found (0.6%). The confidence belts for $P = 0.95$ (Stevens, 1942) are 6.2 and 20.96.

The corresponding figure for 3372 Japanese is: 14 (0.42%); Confidence belts: 7.65—23.49 (Vogel and Fujiya, 1969). See also: Vogel (1966b).

Families. 24 sibships in 22 families, complete and incomplete, were examined. In four cases, both parents of the propositus could be examined, and in each of them one parent showed the trait. In three additional families, only the mother could be examined, as the father had died. In two of them, the mother showed the trait. The trait was transmitted five times by the mother, once by the father, and in one case probably by the father. Analysis of siblings was confined to persons of at least 19 years of age, as the pattern cannot be diagnosed in younger persons.

An over-all estimate of the segregation ratio for all three groups gives:

$$\hat{P} = 0.499 \pm 0.097.$$

As the trait is rare, practically all sibships might be assumed to have a heterozygous and one "normal" homozygous parent, and the expectation for a simple autosomal dominant mode of inheritance is very near to 0.5. Expected and observed values correspond very well. It can be concluded that this trait shows a simple autosomal dominant mode of inheritance.

Differences between Families and Difficulties in the Diagnosis. As has already been mentioned, there are some common characteristics in all families examined: The frequency (about 16—19/sec), the alpha-like distribution over the surface of the skull, and the blocking when the eyes are opened.

On the other hand the following differences can be seen: Some but not all persons have some isolated 10/sec alpha-waves after eye closing and/or after hyperventilation. There are also differences of the amplitude, and here the intrafamiliar variability is smaller than the interfamiliar one.

Besides, not all continuous β-waves belong to the type described here. Very quick β-waves (>20/sec) which do not disappear when the eyes are opened do not present diagnostic difficulties. The diffuse β-waves, however, sometimes react to eye opening, and their frequency might be <20/sec. Furthermore, expecially but not exclusively in elderly women, they might be so abundant that no or almost no alpha waves are left. On the other hand, some single alpha or theta waves might be mixed with the quick alpha variants. This creates serious diagnostic difficulties in some cases.

Relationship to Other Inherited EEG Variants. Two family observations with two of the inherited variants each give some hints as to their interaction: One of these families was ascertained via the 58 years old father, who showed a typical low-voltage EEG (see also Vogel, 1962b). His wife had 16—17/sec quick alpha

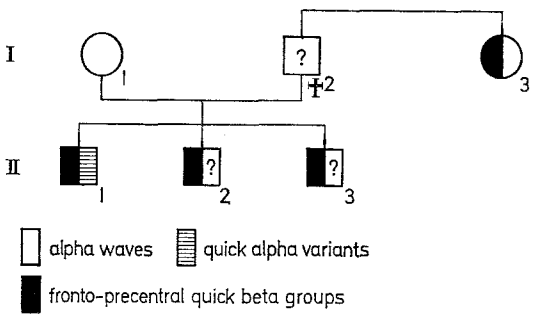

Fig. 3. Pedigree with quick α-variants and fronto-precentral β-groups

variants. The two sons, 22 and 24 years old, showed a clear-cut low voltage resting EEG. When the eyes were closed, however, 16—17/sec occipital waves were seen in both of them. They disappeared completely after 1—2 sec. As was mentioned above, the same frequently happened with alpha waves in the low voltage EEG. The conclusion seems to be justified that the gene for the low voltage EEG in this family is epistatic to the gene for quick alpha variants. Besides, as most β-waves are not suppressed in the low voltage EEG, this observation gives an additional argument in favor of the conclusion that the 16—19/sec occipital waves are variants of alpha and not of beta waves.

The last conclusion is strengthened by a second family observation (Fig. 3): One proband ♂, 20 years old, shows occipital 16—17/sec alpha variants, and, additionally, numerous fronto-prencental groups of quick (>20/sec) β-waves (II, 1). This trait seems to be a simple dominant, too, as will be described below. The two brothers, 11 and 9 years old (II, 2 and 3), have not yet reached the age of manifestation for the quick alpha variants, and show juvenile alpha EEG. Numerous quick fronto-precental β-groups, however, are present on both of them. The mother (I, 1) has a normal alpha EEG, which is free from both of the rare traits. Hence, both traits must have come from the father (I, 2). Unfortunately, he died early, but his sister (I, 3) was available. She showed a 10—12/sec alpha EEG of somewhat low amplitude, but completely without quick alpha variants. However, abundant groups of quick, fronto-precental β-waves were present.

The EEG of this person shows that both traits are inherited independently.

d) The 4—5/sec Rhythm (Fig. 1 d)

This variant was first described by Vogel and Götze (1959). Results of psychological examinations were reported together with an additional family by Müller-Küppers and Vogel (1965). Kuhlo (1967) described additional aspects of the EEG, and Kuhlo *et al.* (1969) gave a survey of 40 cases.

According to the last-mentioned paper, the frequency in patient populations is estimated as being about 0.1%. Among the Japanese males examined by Vogel and Fujiya (1969), 4/3372 (0.12%) were found.

The resting EEG shows regular occipital or occipito-temporal 4—5/sec waves instead of the alpha waves. These waves are blocked, like alpha waves, when the eyes are opened. They differ from superficially similar waves in children in their behaviour after the closing of the eyes: They do nor reappear immediately. First alpha waves can be seen which are replaced by 4—5/sec waves after some

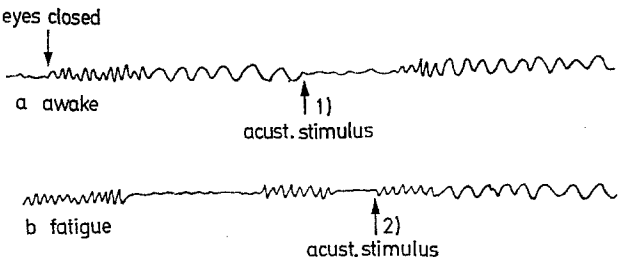

Fig. 4a and b. The 4—5 c/sec rhythm: a Closing of the eyes and acustic stimulation when the proband is awake. b Acustic stimulation when proband is drowsy (After Kuhlo, 1967)

seconds. Besides, the specific pattern can be disturbed by small stimuli (as clasping of hands, crackling of EEG paper, a.s.o.): The 4—5/sec waves are immediately replaced by normal alpha waves.

Shortly before the starting of natural sleep, on the other hand, when alpha waves normally increase in amplitude, the 4—5/sec waves disappear, and alpha waves are seen.

Afterwards, the alpha waves will also disappear, and sleep begins (Fig. 4, from Kuhlo, 1967).

Kuhlo (1967) showed by follow-up study of a case with contusio cerebri that the 4—5/sec waves do not take part in the slowing down of α frequency observed after the brain trauma.

There is no doubt that this trait has a genetic basis as two monozygotic twin pairs as well as three sibships with more than one trait carrier have been observed so far. However, the mode of inheritance is still obscure: Simple dominance can be excluded, and a simple autosomal recessive mode of inheritance which was provisionally assumed by Vogel and Götze (1959) cannot be supported without additional assumptions since there are too many sibships without any further cases.

Among 40 siblings examined so far, there were (excluding the two monozygotic twins) only four who showed the trait. 9 fathers, 13 mothers, and 8 other near relatives were free of it.

Many explanations are possible, some of which may be mentioned: 1. The genetic basis could be more complicated, leading to lower expectations for siblings; 2. The trait might not be present during the whole life, disappearing some time in adult life. Up to now we have not been able to observe any person who showed the trait but had lost it when he was examined some years later. However, there is some indirect evidence that the trait might disappear in middle age: The average age of the probands at their first examination was much lower than in the populations examined (23,19 years in Berlin; 23,18 years in Freiburg; 26,15 years in Stuttgart). Reliable data for comparison are available from the Berlin Laboratory for the year 1962. Here the average age of 4371 examined individuals (excluding the age group 0—10 years, for which the trait cannot be diagnosed) was $42{,}94 \pm 0{,}25$ years.

The mean age of siblings in families in which secondary cases were observed was definitely lower than in families without secondary cases.

3. Besides the hereditary cases, exogenous ones (phenocopies) might also exist. (Kuhlo *et al.*, 1969).

Most striking among many of the cases, especially the males, but also some of the females, is an accumulation of psychological pecularities. They include different types of grossly abnormal behaviour up to severe psychopathy or even psychosis. This was first stated by Vogel and Götze (1959), examined with psychodiagnostic methods by Müller-Küppers and Vogel (1965), and fully confirmed and amplified in different material by Heintel *et al.* (1967). Other reports in the EEG literature, which seem to relate to the same EEG trait, even when this trait is described ambiguously, point in the same direction (among others Petersén and Sörbye, 1962; Dongier *et al.*, 1965). To our knowledge, this is the first physiologically characterized hereditary variant in man which shows a qualitative influence on personality without necessarily impairing intelligence.

e) Monotonous High Alpha Waves (Fig. 1e)

This is the last variant of the alpha rhythm which has been studied up to now. A comprehensive analysis was published by Dieker (1967). This EEG trait is characterized by unusually regular α-waves which show a high amplitude and are to be seen not only in occipital leads but also over the frontal parts of the cortex. Otherwise, they behave like normal α-waves.

Admittedly, this characterization is somewhat diffuse, and Dieker tried to find an exact quantitative measure. Motokawa (1943) proposed a measure, which was called "Kontinuität" and defined as follows:

$$K = \frac{\text{number of } \alpha\text{-waves with an amplitude above the mean}}{\text{number of continuous groups of these } \alpha\text{-waves}}.$$

This measure indicates how frequently α-waves of simple amplitude follow each other continuously. For reason, which cannot be discussed here, K was multiplied by the "percent-time alpha", giving a new measure which was called "Persistenz" (persistence; p). This value p was shown to give a fairly good measure of the regularity of α-waves.

Population Frequency and Twins. The population frequency was determined in four series:

1. Among 4622 German air force applicants, the trait was found in 178 (3.85%).

2. Among 3372 Japanese, we saw it in 144 (4.27%). In both series, the diagnostic criterion was the optical impression.

3. Among 306 twins, the trait was seen in 19 (6.21%) (Criterion: Optical impression).

4. In 280 air force applicants, 19 (6.75%) were found. Here, p (persistence) was used as the criterion. Monozygotic twins are also concordant for this trait. Of the 19 twin pairs which showed it in the material published in 1958, 6 (4 MT and 2 DT) could be reexamined 12 years later. The trait proved to be constant over this time which included the maturation time of the EEG (Dieker, 1967).

Family Investigations. 35 families with 146 persons were examined. The distribution of p among parents and siblings of the propositi is seen in Fig. 5. This distribution is clearly biomodal, showing a maximum of $p = 175$, a minimum between 275 and 325, and a second maximum of $p = 325$—375 which corresponds to the variant under investigation.

The left part of the curve with the first maximum is very similar to the distribution in an unselected population sample of 280 air force applicants, whereas

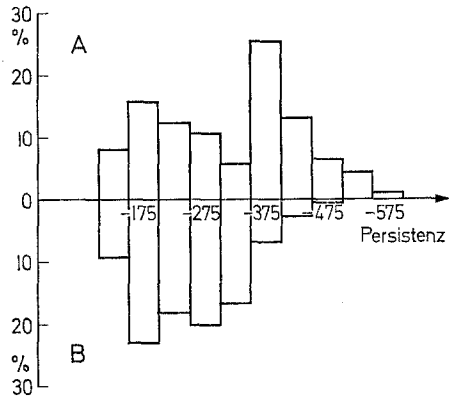

Fig. 5. Distribution of p (persistence). A: among parents and siblings of 35 probands with monotonous α-waves, and B: among 280 air force applicants

the right maximum cannot be found in the sample: apparently the trait is too rare.

For this trait, all families were ascertained by one of the children. 28 of the 35 families were complete: both parents could be examined. In 6 families, both parents showed a value of $p \geq 300$, which was considered evidence for the trait. This conclusion was confirmed by the optical impression. In 18 families one parent showed the trait. There remain 4 families in which both parents showed < 300. These families illustrate some difficulties and limitations of the method of evaluation, and a more extensive discussion seems to be appropriate:

In one of these families the father has a very regular EEG with high „Kontinuität" but a very low amplitude and a $p = 280$ due to a percent-time alpha of 80 only. But he is completely bald-headed. However, it is well known to all EEG experts, that bald heads have an unusually high electric resistance and hence a low brain wave amplitude. It seemed to be justified to classify this man as carrier of the variant.

In a second family, the father had an unusually regular alpha-EEG, which, however, was frequently disturbed by traffic noises. Obviously, this man, too, had the variant which could not manifest itself at the time of the examination due to external reasons.

In the third family the 55 years old mother is the trait carrier. The „Kontinuität" is depressed by diffuse β-waves which frequently interrupt the α-waves. As will be shown below, these β-waves are especially frequent in elderly women. Here it might be stressed that our frequency estimates for the regular α-waves are based on young people and especially on men.

In the fourth family, both parents as well as a sister have an EEG which clearly deviates: The EEG is irregular and has relatively low amplitude. However, the general conditions are very uncertain; the parents' marriage had ended with divorce many years ago, and illegitimacy is an obvious explanation. Blood examinations were not permitted.

The segregation ratios were again calculated for $k = 0$ (see Table 2). The results are fully compatible with the genetic hypothesis of a simple autosomal dominant mode of inheritance. For a full tabulation of the families as well as for details of the calculations see Dieker (1967).

Possible Assortative Mating. One unexpected result has to be mentioned: In view of the population frequency, the number of families in which both parents have the trait is very high. Taking into account the population frequency as well as the higher expectation for carriers in the mating type $+ \times +$, as compared

Table 2. *Segregation ratios for 35 families; monotonous alpha waves*

	Complete families		Incomplete families
	Mating type $+\times+$	Mating type $+\times-$	Mating types $+\times+$ and $+\times-$
Expected (Single autosomal dominance)	0.7574	0.5074	Between 0.7574 and 0.5074
Observed ($\hat{P}$ = estimate of the real value P)	$\hat{P} = 0.60 \pm 0.2191$	$\hat{P} = 0.5294 \pm 0.0856$	$\hat{P} = 0.66 \pm 0.158$
Comparison	No significant difference	No significant difference	No significant difference

with the type $+\times-$, 1,17 of 27 families would be expected, and 6 were found. The difference is significant with $\chi^2_{(DF=1)} = 20.75$; $P \approx 10^{-5}$. Positive assortative mating has to be considered. For the β-EEG, a similar result was found. The problem will be mentioned in the discussion.

2. *The EEG with β-Waves*

a) β-Waves, Age and Sex

Whereas, with few exceptions, every human EEG contains α-waves, only a certain fraction shows a significant admixture of higher frequencies (>13/sec), which are called β-waves. In some cases, they dominate the whole resting EEG, whereas in other persons they are to be seen together with other frequencies, especially α-waves. The β-EEG shows a wide range of variability. It has been known for a long time that this variability is influenced by age and sex (see Gibbs, Atlas; Jung, 1952; Smith, 1954). Vogel and Götze (1962) studied frequency and type of the β-EEG in relation to age, sex and other variables among 4970 patients of an EEG laboratory. Among them there were 413 persons whose EEG in the resting stage with closed eyes showed a clear-cut β-activity at least in some parts of the cortex. (For exact criteria of classification see Vogel and Götze, 1962.)

The clinical and EEG records of these patients were evaluated for a great number of different criteria. In the following, only age and sex will be mentioned. The frequency of the β-EEG (only normal and borderline cases) in the two sexes and in different age groups is seen in Fig. 6. Most striking is the difference between the sexes especially in higher age groups. β-waves are most frequent in elderly women. A certain raise with age, however, is seen in men as well. Even more instructive was a preliminary classification of the β-EEG into three types:

1. Groups of fronto-precentral β-waves. Occipital α-waves are present.

2. Continuous β-waves in occipital and frequently also in precentral leads. No or almost no alpha-waves are present.

3. Diffuse β-waves mixed with α-waves. Sometimes they are more frequent in anterior leads.

The genetic analysis has shown that this differentiation is only a preliminary one. In spite of it, it reveals interesting facts. Type 1 (fronto-precentral groups)

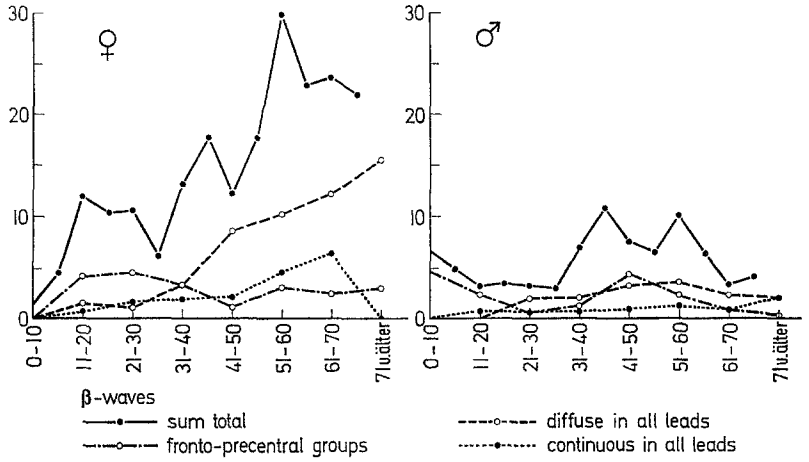

Fig. 6. Frequency of the β-EEG in a population sample. (For details see the text)

shows about the same frequency in both sexes and in all age groups. Type 2 (continuous β-waves) shows a small sex difference and a small increase with age. The major part of the age and sex difference turns out to be due to type 3 (diffuse β-waves).

b) Family Investigations

The results of our family investigations have to be seen against this background. In a first survey, we examined 224 families with 814 persons (Propositi, with and without β-waves, their parents, siblings, children and husbands; see Vogel, 1962b). Later on, additional families were examined for special problems (Vogel, 1966a, b; Reinke, 1966). The frequency of β-EEG among parents, siblings and children of the first series mentioned (224 families) is seen in Fig. 7.

The absolute numbers in each category and age group are very small. But it seems that the type of relationship is much less important for the frequency of the β-EEG than age and sex. There is a gradient mothers > sisters > daughters > fathers > brothers > sons. In all age groups and both sexes the frequency among near relatives is about twice or three times as high as in the general population. This result cannot be explained by a simple Mendelian mode of inheritance. A formal description of the following type seems to be adequate: We are concerned with multifactorial inheritance. Many different genes work together, constituting a "disposition" which might show a normal distribution.

Table 3. *Near relatives of probands with and without beta EEG (condensed from Vogel 1962b)*

Probands	*n*	Fathers		Mothers		Brothers		Sisters		Sons		Daughters	
		n	beta	*n*	beta	*n*	beta	*n*	beta	*n*	beta	*n*	beta
Beta EEG	109	23	7 (30.4%)	20	15 (75%)	24	5 (21.7%)	23	8 (34.8%)	73	9 (12.3%)	58	19 (32.8%)
No Beta EEG	115	36	4 (11.1%)	45	10 (22.2%)	36	4 (11.1%)	32	6 (18.8%)	54	3 (5.6%)	55	3 (5.5%)

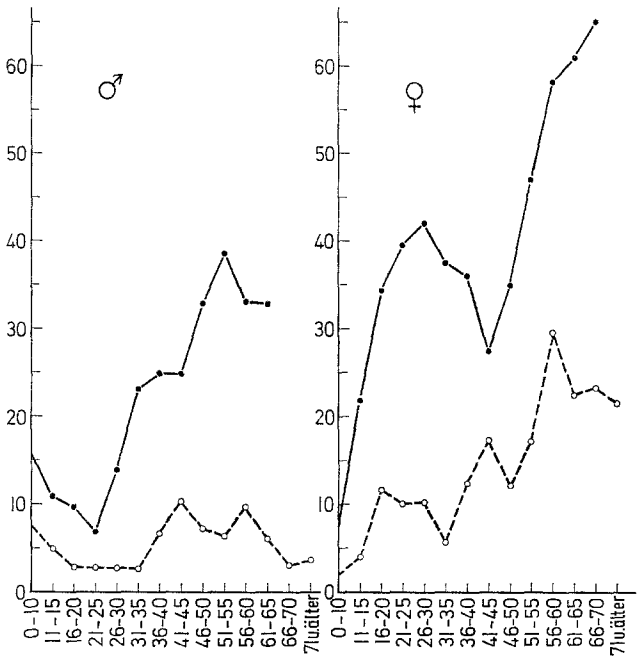

Fig. 7. Frequency of EEG with β-waves among near relatives (parents and siblings) of β-probands, according to age and sex. (The small number of observations in each group required the calculation of gliding means.) ●——● relatives, O - - - O population average

Additionally there exists a threshold above which β-waves are to be seen whereas below the threshold, there are no β-waves. The threshold changes its position with age, moving from the upper tail of the distribution towards the mean. For unknown reasons, the threshold in higher age is nearer to the mean in females than in males. For a more thorough analysis of this multifactorial system, it seemed to be appropriate to look for the type of β-waves again. Consideration of the three above-mentioned types—fronto-precentral groups; continuous β-waves; diffuse β-waves — showed that there was some degree of specificity inside the same family, which, however, was not complete: Among relatives of propositi with frontal groups, the other two types were also more frequent than in the population average. In only some of these families do special genes seem to act; in other families the genetic basis seems to be more unspecific. With this result, we returned to the original material of EEG curves. The problem was: Are there specific EEG types which can be isolated from the whole group of the β-EEG on the basis of combined phenomenological and genetic analysis? If so, are there hints for simple modes of inheritance? And when simple modes of inheritance cannot be found, are there additional criteria for the multifactorial hypothesis?

c) β-Groups in Frontal and Precentral Leads with a Simple Autosomal Dominant Mode of Inheritance

One variant which could be isolated relatively easily was described above as "The quick alpha variant". It contains a small part of the β-EEG termed "continuous".

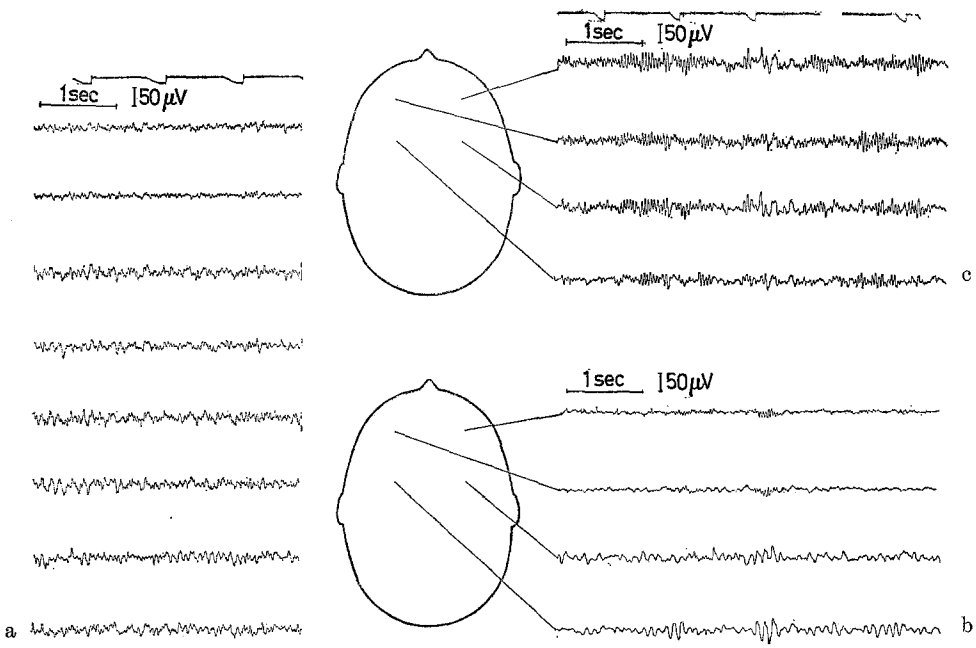

Fig. 8a—c. EEG types with β-waves. a Diffuse β-waves; unipolar leads. b Rare frontal groups (type number 1); unipolar, frontal and precentral leads. c More frequent fronto-precentral groups (type number 2); unipolar, frontal and precentral leads

Two other variants will now be described (for details see Vogel, 1962b, 1966a). Both are characterized by groups of fast (> 20/sec) β-waves in anterior leads.

Type No. 1. This type shows frontal groups of about 5—10 β-waves with especially high frequency (25—30/sec) and relatively low voltage. These groups are rare in the single EEG, and are relatively clearly demarcated. Sometimes, only very few groups can be seen during a 15 or 20 minutes recording (Fig. 8).

Population Frequency. Among 1984 German air force applicants, this trait was found in 9 (0.45%). Among 3372 Japanese males, it was seen in 4 (0.12%) (Vogel and Fujiya, 1969).

Family Investigations. 14 families, complete and incomplete, with 24 children were observed. In four families, both parents of the propositi were examined, and one of them showed the trait. Persons with the trait had 14 children, 6 of which showed it as well. Besides, there were 3 siblings of propositi, which also showed the trait; an additional sibling with a Langdon-Down-syndrome could not be classified. The segregation ratio might be estimated as follows:

$$\hat{P} = 0.559 \pm 0.121.$$

Obviously, it is fully compatible with the hypothesis of a simple autosomal dominant mode of inheritance. However, one propositus was observed whose parents did not show the trait. Hence, manifestation might be incomplete in some cases. In others, the groups are only to be seen after hyperventilation.

Type No. 2. In other persons, the β-groups are much more frequent, the amplitude is much higher, and frequency is not so extremely high (about 20—25/sec).

Furthermore, the groups are seen not only in frontal, but also in precentral and sometimes even in central leads. These groups are well demarcated, but more variable in length: In some cases, β-activity might even be almost continuous in precentral leads (Fig. 8), whereas in others, the groups are fairly short. Groups of different length are frequently found in members of the same families. In the same person, on the other hand, the length of groups also seems to be fairly constant.

Population Frequency. Among 1984 German air force applicants, this trait was found in 23 (1.47%); among 3372 Japanese males, we found it in 23 (0.68%).

Family Investigations. 16 families (14 complete, 2 incomplete) were examined[1]. In 13 of the complete families, both parents of the propositus could be examined. In two of them, both parents showed fronto-precentral β-groups. Besides, the propositi, only one brother was available who did not show any β-waves. In 11 families, one parent showed the trait. In 2 families, only one parent could be examined; in one of them the trait was present.

The segregation ratio was estimated among 41 siblings:

$$\hat{P} = 0.556 \pm 0.0956.$$

Obviously this figure is fully compatible with the genetic hypothesis of a simple autosomal dominant mode of inheritance.

Other EEG Types with Fronto-Precentral β-Groups. It is obvious, when the population frequencies given above are compared with those contained in Fig. 6. that the two EEG types mentioned above do not account for all fronto-precentral β-groups in the population. Among the young men of the air force material mentioned, there were 14 who showed a certain tendency to fronto-precentral groups together with diffuse β-waves in other parts of their EEG. In other age groups too, many EEG with diffuse β-waves show a certain tendency towards formation of groups in the anterior leads. However, these groups are not as well demarcated and β-frequency is not as stable. The experienced investigator is able to see the difference. In some cases, expecially in elderly women, errors of classification are possible. Here, the family examination might help to solve the problem.

Fronto-precentral β-groups and Brain Damage. Whereas in healthy persons, this EEG variant is clearly dominantly inherited, patients with severe brain damage sometimes display it for apparently external reasons. 5 cases were described by Vogel (1962b); all of them suffered from epilepsy, which was clearly exogenous in two. 2 of the 5 patients, the oldest, showed severe brain atrophy.

Fronto-precentral β-groups as Inconstant Findings. In the persons mentioned so far, the β-groups were constant over a longer time. Some observations indicate however that beta-groups might also be inconstant, for example in normal children, or in persons with brain damage. For details see Vogel (1962b).

d) Additional Examinations of Diffuse Beta Waves

Whereas in a minority of cases the introduction of additional criteria into the analysis led to the characterization of special types with simple modes of inheritance, most of the cases with β-EEG belong to a continuously distributed,

1 Two families described earlier (Vogel, 1962b) were not included in the calculations.

Table 4. *Persons with beta waves among near relatives of 29 propositi (air force applicants) with diffuse beta waves*

Degree of relationship	*n*	Beta waves	No beta waves
Fathers	22	13 (59.9%)	9
Mothers	25	20 (80%)	5
Sisters	28	18 (64.2%)	10
Brothers	25	6 (24.0%)	19
Sons	2	1	1
Daughters	1		1
Sum	103	58 (57.4%)	45

Table 5. *Persons with beta waves among near relatives of male and female propositi above and below the age of 30, 1962 and 1966 series*

Propositi	*n* (relatives)	Beta waves	%	No beta waves	%
4 ♀ (1962) age < 30	14	5	35.7	9	64.3
18 ♀ (1962) age ≥ 30	26	12	46.2	14	53.8
5 ♂ (1962) age < 30	16	11	68.3	9	31.7
24 ♂ (1962) age ≥ 30	37	19	51.3	18	48.7
22 ♂ (1966) age < 30	67	45	67.2	22	32.8
7 ♂ (1966) age ≥ 30	26	13	50.0	13	50.0

variable group without clear-cut subdivision. This group contains all cases labelled as "diffuse" together with many of the cases classified as "continuous" or "fronto-precentral". Within this group, we have to content ourselves with the very general formal model of multifactorial inheritance. However, some additional problems were examined by Reinke (1966).

First, the population frequency was established among 3554 air force applicants. There were 118 (3.32%); the confidence interval for $P = 95\%$ is between 96.63 and 142.51. This figure from Germany can again be compaired with the corresponding figure from Japan: 136/3372 = (4.03%).

29 families in which the propositus was a man, and in most cases a young one, were examined. Frequencies of β-waves in relatives are seen in Table 4. There is again the gradient mothers > sisters > fathers > brothers, as in the material analyzed earlier.

In Table 5, the frequencies of the β-EEG among the near relatives of the propositi with diffuse β-waves are compared in the 1962 series (male and female propositi < 30 and ≥ 30 years old) as well as in the new series. It turns out that in the 1962 series, the proportion of persons with β-waves is much higher among relatives of males than among relatives of females. The difference is significant ($\chi^2_{(DF=1)} = 4.88$; $P = 0.025$).

Frequency among the relatives of males is about the same in the 1962 and 1966 series. When younger and older males are compared, a β-EEG is more frequent in relatives of younger males ($\chi^2_{(DF=1)} = 4.06$; $P = 0.045$).

Among the relatives of female probands of the 1962 series, there is only a small difference ($\chi^2_{(DF=1)} = 0.95$; $P = 0.34$) in the opposite direction, but numbers are very small. The results with exception of the last one might be generalized as follows: *The lower the population frequency of diffuse β-waves in the group to which the propositus belongs, the more frequent is the same EEG type among his near relatives.*

Obviously, this result has to be expected when the genetic model of multifactorial inheritance in combination with the threshold is accepted: When population frequency is low, the disposition of a person who manifests the trait must be high, and vice versa (cf. C. O. Carter, 1964; Vogel and Krüger, 1967).

We also tried to look for intrafamiliar similarities of this EEG type. In some cases, similarities can be seen, but no clear-cut overall picture emerges (for details see Reinke, 1966).

Possible Assortative Mating. In connection with the monotonous alpha-waves, the unexpectedly high number of matings between persons of the same EEG type was mentioned. A similar result was also found for the beta-EEG in general (no specific type, Vogel 1962b). 17 of 56 propositi were married with a person with a beta EEG, whereas of 54 persons without beta EEG, only 5 were married with a beta bearer. The difference is significant ($\chi^2_{(DF=1)} = 7.65$; $P = 0.006$).

Possible Race Differences. There are only few literature reports on EEG comparison between different racial groups. Gallais *et al.* (1950/51) described a much higher frequency of δ and ϑ waves in 100 healthy negro soldiers as compared with whites. Mundy-Castle *et al.* (1953) compared 66 normal negro adults and 72 Europeans. They did not find any conspicuous difference, but the negros seemed to show somewhat fewer β-waves, the fronto-precentral α activity was increased, and the normal reaction to photic stimulation seemed to be less pronounced than in Europeans. Merrill and Cook (1957) examined the EEGs of 279 whites and 117 American negroes as to α-frequency, incidence of the low voltage EEG and other special types, β-waves, slow potentials and seizure discharges. They did not find any difference. Verhaegen (1956), who examined 74 negroes of the Kongo area, claims to have seen no deviation from whites. However, no control series was examined. Engel and Butler (1966) described a significantly lower time delay between visual stimuli and EEG response in negro as compared to white newborns.

In none of these investigations were genetically defined EEG variants examined, and the number of persons included in these series was much to small for any reliable conclusions. The first report in which both requirements were met was that of Vogel and Fujiya (1969) in which 3372 male Japanese were compared with 4622 German males of simular age distribution. The results were mentioned together with the EEG traits; the overall impression is that of a remarkable similarity of frequencies in the two populations. The only difference found was the lower frequency of EEGs with fronto-precentral β-groups in Japanese. In future the possibility has to be excluded that this difference is an artifact due to differences in technical conditions.

A vast field for studies in population genetics is opening here, but the technical difficulties for examing sufficiently great numbers of healthy persons are considerable.

Discussion

Genetic analysis of the normal human EEG has given the following results:

1. The twin data demonstrates complete genetic determination of the EEG including the maturation during childhood, the mature EEG during adult life, and also the "normal" continuous involution in high age. On the other hand, EEG anomalies in the aged which are obviously due to a pathological event, for example focal symptoms or dysrhythmias, are discordant in monozygotic twins. Apart from its obvious theoretical aspects, this result could have practical significance for all approaches to the testing of the influence of the EEG of changes in physiological conditions and drugs. (Method of co-twin control.) In spite of its obvious advantages, this approach has only rarely been used so far.

2. The twin examinations did not only show a high concordance in MT, but also conspicuous differences between different twin pairs, confirming the experience that the normal EEG shows a high and multi-dimensional interindividual variability. It was always highly unlikely that this variability could be completely analyzed in terms of simple modes of inheritance. Prima facie evidence was very much in favour of a multifactorial genetic system. This assumption was confirmed in most of the recordings with β-waves. A corresponding analysis for "normal" α-waves was started with very limited material only. Vogel and Götze (1959) found correlation coefficients between one parent and children for α-frequency: $r = 0.70$, for percent-time α: 0.46, and for average alpha amplitude: $r = 0.70$. However, there can be no doubt that the normal α pattern also has a multifactorial genetic basis.

3. Surprisingly enough, for some EEG types which can be delimited from the "average" population continuum, the formal criteria for simple modes of inheritance were demonstrated fairly convincingly.

The most comprehensive material and the most convincing evidence is available for the low voltage EEG. Here, only some borderline cases constitute a certain problem. However, in order to get optimal separation between the low voltage EEG and the average α-EEG, optimal conditions are required. Unipolar leads with 7 mm/50 μV amplification give the best results. Most laboratories use smaller amplification. Besides, the patient should be fresh (not tired), but completely relaxed. In many persons, a low voltage EEG can be faked by incomplete relaxation. Furthermore, the electrodes should be fitted in a way that a small electrical resistance is secured. Generally, for exact evaluation of normal variants, a high technical standard is required.

As to the genetic hypothesis of simple dominance, the question is justified whether the result could be faked by some sort of multifactorial inheritance in combination with a threshold. However, in the families, segregation between the two types is clear-cut in most cases, and the distribution of percent time α in the α part of relatives corresponds to the distribution in the general population. Besides, in all cases examined, at least one parent was affected, and the observed segregation ratio fitted the expectation excellently. Considering all these criteria any genetic hypothesis other than simple dominance would be farfetched indeed.

For the other variants, the available material is not as comprehensive. The occipital quick alpha variants can be distinguished fairly well from other β-waves

in most cases, and evidence for simple dominance is also fairly convincing; due to a possible overlapping with continuous β-waves which genetically belong to the diffuse type, a false classification cannot be excluded, especially for elderly women.

The 4—5/sec rhythm has to be deliminated against theta waves in some types of mild brain intoxication, against slow occipital waves in epilepsy of a young age, especially some centrencephalic states, and against some transient states in childhood.

This, however, is possible when the additional characteristics are taken into account (Blocking, when the eyes are opened; α-waves for a shorter or larger period after closing of the eyes, when the proband is disturbed, and drowsy). None of the other conditions mentioned shows all these characteristics. In spite of this, diagnosis of the 4—5/sec rhythm is problematic before the age of 13—15. Besides, very quiet and relaxed conditions are required during EEG examinations: In EEG curves written in a noisy room, the trait can hardly be ascertained, and will almost invariably be misclassified as "slow dysrhythmic" or simply as normal α-EEG.

Discrimination between the monotonous α-waves and the normal α-EEG is not as clear-cut as for the low voltage type. The newly introduced measure p (persistance) is very helpful, but in spite of it discrimination is not fully satisfying to date. The evidence in favour of simple dominance is fairly convincing, but misclassifications are still possible. The distribution of p among the "normal alpha" part of the relatives corresponds closely to the general population. This is a good argument in favour of a simple mode of inheritance.

As to the two variants of fronto-precentral β-waves which also seem to show simple dominance, one restrictive statement has to be repeated: The genetic conclusion was based on families of healthy probands. In patients with organic brain damage, very similar groups of β-waves might be observed without any evidence of a genetic basis.

Similar groups can also be seen in certain states of intoxication with different drugs, especially barbiturates. Chronic use of barbiturates induces diffuse β-waves in some persons, but not in all (see for example Essig and Fraser, 1958). It is tempting to speculate that a genetic disposition could have been important as well and that the drug only shifts the threshold. In principle, this question could be answered by comprehensive family investigations in combination with drug administration, and a new field of pharmacogenetics could be opened. However, experiments of this type, in human beings, meet with obvious practical difficulties which proved to be insurmountable, at least for us.

The genetic results are of possible theoretical interest for several reasons: First, a simple mode of inheritance points to a simple biochemical difference. When there is dominance, a structurally aberrant protein can be suspected. The genetic results might provide hints for future research on the physiological basis of the EEG phenomena and the biochemical basis of brain functions.

Secondly, when genetically determined electrical differences in different persons can be demonstrated, the question obviously presents itself whether other aspects of the brain function show a corresponding difference. Various aspects of this problem were discussed in earlier publications (Vogel, 1958, 1962a, b; Vogel and Götze, 1959, 1962; Reinke, 1966; Dieker, 1967). As to the status of health, some

loose correlations could exist, but there is no evidence for any relationship of an EEG variant and organic or functional disease. One variant, on the other hand, the 4—5/sec rhythm, seems to have a demonstrable impact on personality (Vogel and Götze, 1959; Müller-Küppers and Vogel, 1965; Kuhlo *et al.*, 1969). Statistical evidence of positive assortative mating for the monotonous α-EEG as well as for the β-EEG could possibly point into the same direction. Further research is needed.

The genetic results might also be used in practical diagnosis: A certain voltage depression, for example, is frequent after traumatization of the brain, and in some cases, a low voltage EEG might be present (see Vogel *et al.*, 1961).

Here, family investigations can help to decide, whether the brain is seriously damaged, or a trivial inherited variant is present. As to the fronto-precentral β-groups, it was already mentioned that they can be observed in healthy persons as normal variants, in persons with severe brain damage, and after intoxication. Here, the usefulness of family examinations is obvious.

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