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Neurobiological Approaches in Human Behavior Genetics[1]

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An attempt should be made to base analysis of problems in human behavior genetics on existing knowledge of human biochemical genetics and neurobiology. Examples for this approach are studies showing HY antigen patterns of the opposite sex in transsexuality, slight psychological deviations in heterozygotes of recessive metabolic diseases such as phenylketonuria and lipid storage diseases, and psychological studies in healthy individuals with various genetic variants of the normal human electroencephalogram (EEG). Results of such studies will help gradually to replace emotional controversy by rational assessment of facts.

The history of human genetics can be conceived as a contest between two leading paradigms: the work of Mendel which laid the foundations for the gene concept and the work of Galton which showed how information on the genetic component of human diversity can be gained by comparison of relatives and twins with biometrical methods. Mendel's gene concept has now been extended to comprise biochemical and molecular genetics; it developed into an empirically well-founded theory for the explanation of the basic mechanisms of heredity. The explanatory power of this theory has proved to be much greater than anticipated; phenomena such as aging and cancer are now being analyzed using genetic concepts, and so far, the limits of its application have not yet become

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apparent. Hence, Mendel's paradigm proved to be potentially much deeper than Galton's biometrical approach.

For many problems in human genetics, however, it is only *potentially* deeper; in practice, most behavior genetic problems have so far eluded analysis based on Mendel's principles. During the first decades after the rediscovery of Mendel's laws, many scientists tried to press family data on complex phenotypes such as mental diseases or intellectual or artistic abilities into the Procrustean berth of Mendelian segregation figures. Compared with these naive attempts, it marked a definite progress in critical attitude when the majority of research workers in this field turned to Galton's paradigm—comparison of phenotypes between relatives and twins by biometrical methods. So far, this approach has provided almost all the behavior genetic information that is so urgently needed for theoretical but also for practical reasons—genetic counseling and education. Many scientists have attempted to establish links between the biometric approach and Mendelian genetics, most notably Fischer in his famous 1918 paper and his successors in quantitative genetics. These attempts, however, did not lead to a deeper understanding of the interaction between genetic variability and external influence on the development of psychological phenotypes: Biometrical research is not founded on a sufficiently stringent theory. Therefore, results from empirical studies can often be interpreted equally well from a hereditarian or an environmentalist viewpoint. In my opinion, the well-known controversies between these groups of scientists which have led to so much uproar in the general public are caused not by stupidity or ill will on either side but by the theoretical weakness of the basic theory and the resulting ambiguity of empirical results. When results of possible emotional appeal are intrinsically ambiguous, an unusual level of critical self-control is required in order not to give preference to the interpretation in closest accord with one's own prejudices.

To remove the present-day ambiguities concerning genetic mechanisms of human behavior, application of the principles established by Mendel and his successors is necessary. Recent developments in basic genetics as well as the successful application of genetic approaches in other fields of human genetics are now suggesting new ways for a more thorough analysis of behavior genetic problems. These approaches are based on the general assumption that psychological variation between individuals is caused by interaction between genetically determined variation of brain function and the environment. Therefore, genetic analysis requires an assessment of the various levels at which genetic variability could influence behavior and, hence, a detailed knowledge of neurobiology. Two research strategies are possible.

(1) In the more traditional approach, one starts from a psychological phenotype and examines whether individuals showing this phenotype differ from other individuals in any genetically determined neurobiological parameter. Well-known examples of this approach are studies on neurotransmitter enzymes in affective disorders or schizophrenia. So far this approach has only rarely led to clear-cut results regarding genetic determination. Most investigators have been caught in the complex network of regulatory processes equilibrating biochemical processes inside as well as outside the nervous system. Very recently, however, a result has been published that, if confirmed, would shed new light on the genetic determination of an important aspect of sexual development: gender identity.

The formation of testicles during early embryonic development is determined by the HY antigen, a genetic marker under the influence of a regulatory gene on the Y chromosome. In all normal males, this HY antigen can be demonstrated in various tissues throughout their lifetimes. There exists a special group of individuals with disturbed gender identity—the transsexuals. Male transsexuals, for example, despite their unambiguously male phenotypes, the presence of testicles, and a normal XY karyotype, experience themselves as women. They dress as women, try to establish sexual relationships with men, and, in an increasing number of cases, undergo surgical correction of their secondary sex characters. Most observers believe psychodynamic factors to be responsible for this abnormal development, despite the observation that many transsexuals do not conform at all to our preconception of a "neurotic." Recently, Cleve's group in Munich has determined the HY antigens in his series of male and female adult transsexuals. Surprisingly enough, more than half the transsexuals failed to show the HY pattern typical for their phenotypic sex: The males were HY negative, and the females were HY positive (Eicher *et al.*, 1979; Spoljar *et al.*, 1981). The result was confirmed only partially in another series by a group of Göttingen (Engel *et al.*, 1980). These findings are very new and need confirmation as well as much further research. Taken at face value, they point to a specific influence of a biological factor, the HY antigen, on an aspect of brain development connected with an important behavioral character—the experience of gender identity. On the other hand, the fact that the abnormal HY status was not found in all transsexuals points to different causes of this anomaly in different individuals.

(2) Instead of examining the biological basis of a specific psychological phenotype, recent data on the ubiquitous occurrence of genetic polymorphisms and their physiological significance suggest an alternative strategy.

(a) Find a genetically determined polymorphism which fulfills the following conditions:

(i) It leads to an individually constant somatic phenotype which has a clear-cut genetic basis.

(ii) It can be examined without undue intrusion into the integrity of the proband's body.

(iii) Knowledge of the underlying physiological and/or biochemical mechanisms suggests an influence on behavior.

(b) Using psychological methods, compare groups of individuals differing in this polymorphism.

(c) On the basis of the outcome of this comparison together with your a priori knowledge of the ways in which the genetic polymorphism under examination may influence brain physiology and behavior, develop a hypothesis on the genetic–physiological mechanism for this aspect of behavior.

(d) Derive observable consequences from this hypothesis and test them using new observations.

This strategy has only one disadvantage: It is difficult to follow. Most genetic polymorphisms in humans have been discovered in the blood, because blood is easily accessible for examination. But associations between blood polymorphisms and brain function are in most cases not obvious intuitively, and might be present only occasionally. Moreover, most blood polymorphisms have been discovered accidentally, when an appropriate method happened to be available. The physiological function, for example, of most blood group antigens and even of many blood enzymes is not yet known. There are, in fact, reports in the literature of associations of ABO and HLA types with psychological phenotypes (Vogel and Helmbold, 1972; Dausset and Svejgaard, 1977). But the evidence is ambiguous. Even if some of these associations are confirmed by further studies, they are not very informative for behavior genetics as long as nothing is known about the physiological mechanisms by which these polymorphisms influence behavior.

More relevant information can be expected from studies of polymorphisms influencing—directly or indirectly—brain function itself. Such polymorphisms are difficult to find, but some promising results have been achieved during recent years. I shall give examples of three approaches: investigation of proteins from the brains of deceased human beings, psychological and biochemical examination of heterozygotes for recessively inherited metabolic diseases, and psychological and biochemical studies of carriers of hereditary variants of the human electroencephalogram (EEG).

Studies of brain proteins of deceased individuals have been per-

formed repeatedly. A recent study by Comings (1979) using a two-dimensional technique revealed a genetic polymorphism associated with behavioral anomalies: Among 103 controls who had died from various, nonpsychiatric disorders, 28 (27.2%) were heterozygous for type Pc1-DA and 4 (3.9%) were homozygous for Pc1-DD. The majority of the population was homozygous Pc1-AA. Among 42 patients who had committed suicide, or were known otherwise to have suffered from depressive disorders, 22 (52.4%) showed type Pc1-DA and 5 (11.9%) had type Pc1-DD. For schizophrenia, no increase in types DA and DD in comparison with the controls was discovered. Of course, family studies could not be performed, but Comings presented evidence strongly suggesting a genetic polymorphism. The presence of the gene $Pc1^D$ in single or double doses may contribute to a genetic liability for depressive disease.

Here, results are available at two widely separate levels: the levels of the genetically determined protein, on the one hand, and the psychological phenotype, on the other. So far, the biological mechanism linking these two levels has remained unknown: a promising topic for further research.

A slightly closer relationship between the levels of gene-determined proteins on the one hand and psychological phenotypes on the other exists in heterozygotes of hereditary metabolic diseases. Usually, the mode of inheritance of such diseases is autosomal recessive. In many of them, the homozygotes suffer, in addition to various other clinical signs, from severe mental retardation. As a rule of thumb, the heterozygotes tend to have about half the enzyme activity of the normal homozygotes. In some diseases, such as phenylketonuria (PKU), their average enzyme activity is lower. Under normal living conditions, this reduced enzyme activity is sufficient for maintaining function; the heterozygotes do not suffer from clear-cut clinical symptoms. Heterozygote tests, however, usually reveal a certain weakness when the metabolic pathways involved are put under specific stress. It is reasonable to suspect that such stress situations might occasionally occur not only in an experiment but in real life as well. And indeed, slight neuropsychological abnormalities in heterozygotes of metabolic diseases have occasionally been reported. Systematic studies, however, have been conspicuously lacking for a long time. Only very recently, statistically convincing evidence has been presented for heterozygotes of three diseases: phenylketonuria; lipid storage diseases, especially metachromatic leukodystrophy; and ornithine transaminase deficiency (Table I). One hundred parents of PKU patients (heterozygotes) were tested in Austria. They showed a slightly but significantly lower verbal I.Q. than the controls. Interesting enough, PKU homozygotes, when treated with a phenylalanine-restricted diet, showed the same slight deviation. In both

Table I. Slight Deviations of Intelligence Test Scores in Heterozygotes of Metabolic Diseases

Condition	Number of heterozygotes examined	Type of deviation in heterozygotes	Reference
Phenylketonuria	100	Slight decrease in verbal I.Q.	Thalhammer *et al.* (1977, 1979, 1980)
Lipid storage diseases, especially metachromatic leukodystrophy	38	Slight weakness in spatial cognition; increase in reaction time; increased neuroticism	Christomanou *et al.* (1980)
Ornithine transaminase deficiency (X linked)	7	Slight decrease in performance I.Q.	Batshaw *et al.* (1980)

groups, treated homozygotes as well as heterozygotes, increased intracellular levels of phenylalanine and some other metabolites were described (Thalhammer *et al.*, 1977, 1979, 1980).

A recent study of heterozygotes for various lipidoses, for example, metachromatic leukodystrophy and globoid cell leukodystrophy, gave similar results. The heterozygotes showed lower I.Q. values than the matched controls. Here, one item that tested spatial cognition was also affected. Moreover, significant differences between heterozygotes and controls were found in personality scores indicating psychosomatic disorder, depression, and emotional instability (Christomanou *et al.*, 1980). The third example is ornithine transaminase deficiency, an X-linked disorder of the urea cycle leading to ammonia intoxication of the brain. Heterozygotes have recently been shown to have a slightly but significantly lower performance I.Q. than controls (Batshaw *et al.*, 1980).

Considering the well-known biochemical peculiarities in heterozygotes of most, if not all, hereditary metabolic diseases, one can reasonably anticipate that slight deviations in average I.Q. and/or other behavioral characteristics in clinically healthy heterozygotes might be the rule rather than the exception. Heterozygotes of metabolic diseases, however, are common. Harris (1975) has calculated from a newborn screening study in Massachusetts that no less than 11% of the population of this area is heterozygous for at least one of the 14 conditions screened in that population. It is tempting to expand this consideration. Let us assume that there are genes for another 100 recessive diseases in the same population and that each of them has a homozygote frequency of 1 in 1,000,000 (heterozygote frequency, 1:500). Neglecting multiple heterozygotes, this would add another 20% to the number of heterozygotes, giving an overall frequency of 11% + 20% = 31% heterozygotes for 114 recessive an-

omalies in the population. Since many metabolic diseases are detrimental for brain function, a slight influence of heterozygosity on the brain in only a fraction of these genes could contribute significantly to the genetic variability in intellectual performance, feeling tone, and behavior (Matthyse, 1980). Well-controlled neuropsychological studies of heterozygotes can be performed easily; this straightforward approach promises important insights.

Having discussed protein studies of human brains and neuropsychological investigations of heterozygotes of metabolic diseases, I shall now turn to the field of our own investigations: psychological and biochemical studies of carriers of hereditary EEG variants.

The normal human resting EEG exhibits a strong interindividual variation which is almost entirely genetically determined, as shown by comparison between monozygotic and dizygotic twins. Moreover, family studies gave evidence of simple Mendelian modes of inheritance for some EEG variants (Vogel, 1970). On the other hand, research in neurophysiology helped to develop fairly well-founded theoretical concepts of the origin of the human EEG—especially the α rhythm—and, in part, of its function (Andersen and Andersson, 1968). According to these concepts, the "battery," where the EEG waves are produced, consists of groups of neurons in the cerebral cortex. A pacemaker, or, more precisely, a number of functionally connected pacemakers, in the thalamus induces the rhythmic activity of these neurons. This rhythmic activity is modified by other parts of the brain, especially the ascending reticular activating system (ARAS) and the limbic system. The α rhythm seems to act as a modulator which screens and selectively amplifies incoming information. If these concepts are basically correct, differences in information processing and, consequently, psychological differences in individuals showing the various EEG variants are to be expected. This consideration, together with some data from the literature on psychological associations of EEG patterns, encouraged us to compare probands with various inherited EEG variants by psychological methods.

The subjects of this study were 298 male adults between 19 and 60 years of age who were ascertained irrespective of health complaints (volunteers for service in the German air force). Two hundred nineteen showed different inherited EEG patterns; 79 were controls with inconspicuous EEG patterns. Figure 1 shows the EEG variants, their modes of inheritance, and the number of probands per variant. This number is limited by the fact that the variants are not very common: Their population prevalence has been determined previously to be of the order of one or, at most, a few percent.

All probands were examined using several tests for various aspects

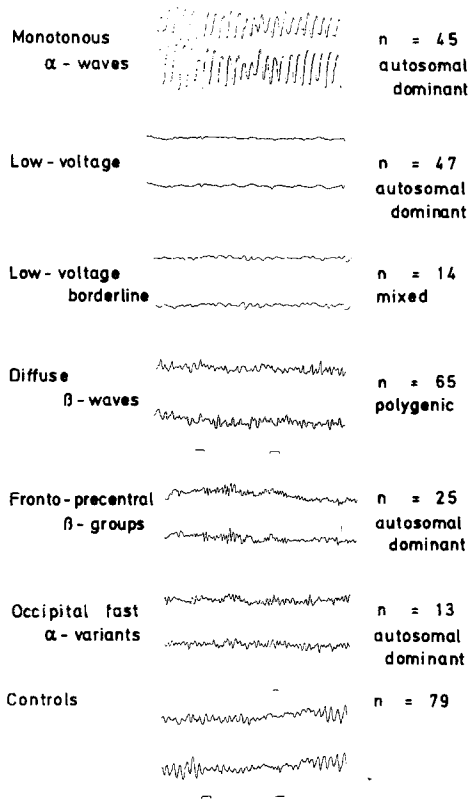

Fig. 1. The EEG variants examined, their modes of inheritance, and the number of probands per variant. Data from Vogel *et al.* (1979a,b) and Vogel and Schalt (1979).

of intelligence, ability to concentrate, stress resistance, sensory and motor skills, and personal propensities and attitudes. We applied exclusively test methods for which extensive diagnostic experience is available, and which can be evaluated objectively. In the personality field, standard questionnaires were used. Detailed results of this study have been published elsewhere (Vogel *et al.*, 1979a,b; Vogel and Schalt, 1979). In what follows I shall mention in a slightly oversimplified fashion only the main results together with their most likely neurophysiological interpretation.

The EEG with monotonous α waves is characterized by unusually regular α waves with a high amplitude which are seen not only in occipital leads, where α rhythm is often fairly regular, but also over the frontal part of the cortex. Population prevalence among male adults was found to be about 4–6%. Studies in 35 families suggested an autosomal-dominant

mode of inheritance (Dieker, 1967; Vogel, 1970); there are some difficulties with the classification of borderline cases which, we hope, will soon be overcome by computerized EEG analysis.

Psychologically, the average male proband with this EEG trait is distinguished by an active and sthenic attitude; he is emotionally stable and well controlled. He shows above-average precision in concentration tests and short-time memory, and is stress resistant. However, he is not very quick. Considering the neurophysiological hypothesis on the function of the α rhythm mentioned above, this personality pattern can be explained by strong modulation and selective amplification of afferent stimuli.

The "countertype" of the monotonous α rhythm is the low-voltage EEG. This EEG variant is characterized by a complete lack of α waves in the resting EEG. A certain, small amount of α waves may be seen in some cases shortly after closing of the eyes and during hyperventilation. Population prevalence runs between about 4 and 5% of the adult male population. Study of 60 families revealed an autosomal dominant mode of inheritance (Vogel and Götze, 1959; Vogel, 1962, 1970). In the population, there are some ambiguities in the classification of borderline cases; family studies have shown some of these to belong to the low-voltage variant genetically, whereas others are extreme variants of the common α EEG (Reinke, 1966).

Psychologically, the attitude of the average low-voltage proband is relaxed and carefree. He is extravert and group-oriented and shows little spontaneous activity. Intelligence and especially spatial perception appear to be above average, but performance on concentration tests is relatively poor. Neurophysiologically, this EEG pattern is compatible with weak modulation and selective amplification of afferent stimuli. Hence, this EEG variant is in a certain way the countertype of the monotonous-α EEG not only neurophysiolically but psychologically as well.

In a third EEG type, for which significant information is available, the α waves are in all leads diffusely mixed with faster activity, the β waves. This EEG variant is more common in females than in males, and its frequency among adults increases with age. In females, this increase is somewhat more accentuated than in males. Genetic studies suggest a multifactorial mode of inheritance.

Our male probands with this EEG variant showed, on the average, low scores on tests of spatial orientation; low speed together with high error proneness on concentration tests; long reaction times; and, in general, signs of low stress resistance.

It is a general experience of basic research in neurophysiology that a high tonic arousal in the reticular system (ARAS) and a high input of

the ARAS into thalamic nuclei, for example, by experimental stimulation, lead in most cases to EEG desynchronization. Therefore, the psychological results in individuals with diffuse β activity can most readily be explained by a relatively high level of tonic arousal in the reticular system (ARAS) which interferes with the modulating influence of the α rhythm. This may lead to disturbances in brain function. Under certain conditions an unusually high level of tonic arousal may even lead to psychiatric disease. In this context it is interesting that Itil (1978) described an association of this EEG type with schizophrenia. Most EEG studies in schizophrenics are impeded by ubiquitous usage of psychotropic drugs. Itil's patients, however, were untreated. Moreover, similar EEG patterns were also described in as yet unaffected relatives of the patients, i.e., persons at risk. Experienced research workers, such as Rosenthal and Kety (1968) and M. Bleuler (1972), envisage the multifactorial causation of schizophrenia as an interplay between a genetic disposition and—often external—stress. A reduced stress resistance of normal, unaffected probands with a diffuse β EEG would fit well into such a concept.

For two other distinct, but rarer, genetically defined EEG types, evidence from limited proband samples is available. There is one variant in which the occipital α waves are replaced by about 17- to 19-Hz waves with all the properties of α waves. This variant was found in about 0.4–0.6% of the male population. Studies in 24 families suggested an autosomal-dominant mode of inheritance (Vogel, 1966b). Our 13 probands were distinguished by good intelligence and capacity for abstract thinking and especially by high motoric dexterity. If this result is confirmed by further studies, it could also be interpreted neurophysiologically: Individuals having this EEG variant might possibly be able to process incoming information unusually quickly.

In another EEG type for which fairly good information is available, characteristic groups of β waves can be seen in frontal or precentral leads. This EEG variant occurs in about 2% of the male adult population; again, the mode of inheritance was found in 30 families to be autosomal dominant (Vogel, 1966a). Some drugs may cause a similar EEG pattern. Psychological examination of 24 probands with this EEG variant failed to show any special psychological features. In contrast to the probands with the diffuse β waves, probands with frontoprecentral β groups did not show any signs of increased tonic arousal. This points to a different biological mechanism for these two types of the β EEG.

Another group of EEG studies has been performed by P. Propping of our group. In a first step, he showed, by studies of adult male twins as well as by comparison of individuals with the above-described EEG variants, that the reaction of the resting EEG to a defined dose of alcohol

is genetically determined. The EEGs of monozygotic twins show identical reactions. Between individuals, however, strong differences do occur. The type of reaction depends on the individual's resting EEG: Individuals having a continuous and regular α rhythm in the resting state show relatively little EEG change after alcohol intake. On the other hand, probands with a poorly synchronized resting EEG and few α waves (borderline α) often show a dramatic increase in α activity after alcohol consumption. Probands with the typical low-voltage EEG show almost no reaction to alcohol, and the reaction in probands with diffuse β waves is also weak (Propping *et al.*, 1980a). Considering the above-mentioned cerebral mechanisms of EEG production, the result, especially in probands with a borderline-α EEG, suggests a certain inhibition of the tonic arousal activity in the reticular system which might result in a more undisturbed activity. This might lead subjectively to an improvement in feeling tone and, hence, to easier conditioning for alcohol intake and, given appropriate environmental conditions, to alcoholism. Recently, EEG family studies by Propping and co-workers have shown a lower α activity and a higher degree of EEG desynchronization in alcoholics and their (nonalcoholic) family members than in adequately matched nonalcoholic controls (Propping *et al.*, 1981). The fact that the difference was found also for the nonalcoholic family members proves that the EEG difference in probands is genetically determined and not a secondary effect of alcohol. On the other hand, more detailed analysis showed the difference to be confined to female alcoholics. Subdivision of the alcoholic sample into clinical subtypes according to Jellinek pointed in the same direction: Many of the male alcoholics belonged to types α and γ, for which the environment appears to be mainly responsible, whereas the majority of female alcoholics was classified as types β and δ, for which mainly internal factors such as internal tensions and conflict situations are thought to be more important. Hence, these studies suggest a biological mechanism for an increased genetic liability to an environmentally caused psychological condition, alcohol addiction. Moreover, they suggest an additional clue for distinguishing different kinds of alcoholism.

It is tempting to speculate on the genetic and biochemical causes for the psychological and neurophysiological differences between EEG variants and to develop experimental designs for examining these causes more closely. Here, Propping of our group has recently added another piece of evidence.

Functional connection between neurons is mediated by a group of chemical compounds called neurotransmitters. An important portion of functional specificity within the brain can be explained by neurotransmitter specificity. Current biological theories of mental disease postulate

as causative factors abnormalities of synthesis, release, reception at the effector cell, or degradation of neurotransmitter molecules such as dopamine or serotonin. On the other hand, some of the enzymes responsible for neurotransmitter metabolism can be found in the blood, and twin as well as family studies have shown variation in their activity to be under strong genetic control in man. The enzyme dopamine-β-hydroxylase (DBH) catalyzes the last step in the synthesis of norepinephrine, the main transmitter in the sympathetic portion of the autonomic nervous system. But functional differences in the autonomic system appear to be partly responsible for differences between EEG variants. Therefore, Propping compared DBH activities in individuals with various EEG variants and found conspicuous differences (Propping *et al.*, 1979, 1980b). In blood serum the mean activity of this enzyme was almost twice as high in male probands with a monotonous-α variant as in those with a low-voltage EEG. This result, which was first described among male students volunteering in Propping's studies, has more recently been confirmed in family studies. But in female probands DBH differences between carriers of various EEG variants have not been found. On the other hand, some probands of all variants had low enzyme activities. This shows that the enzyme activity cannot be the direct or even the only cause of EEG variation. It indicates, however, the pervasive difference between EEG variants encompassing also other functional states of the nervous system. One could hypothesize that the same mechanism which leads, through some connecting steps, to different types of electrical cortical discharges also influences peripheral release of the enzyme DBH. It will be one of the goals of further research to identify these mechanisms and to come closer to the structural and molecular basis of EEG variation (Fig. 2).

Our second goal will be to test our hypothesis that psychological differences between EEG variants can be traced back to corresponding differences in information processing. Here, we plan to proceed in two directions: First, we shall complement our psychological test program by including tests permitting, in addition to performance as such, also cognitive strategies of the individual proband. At the same time, we plan to extend our EEG studies, including analysis of visually or acoustically evoked potentials in our program. Twin studies, especially by Buchsbaum (1974), have shown that these average evoked potentials are under genetic control. In the past, they have been correlated, for example, with I.Q. results, and in a recent hypothesis, the reaction time as measured by evoked potentials has been asserted to be the main psychological equivalent of Spearman's main factor of intelligence, *g*. Moreover, a simple mode of inheritance has been postulated (Weiss, 1979). While this is certainly an oversimplification, the concept that speed of information

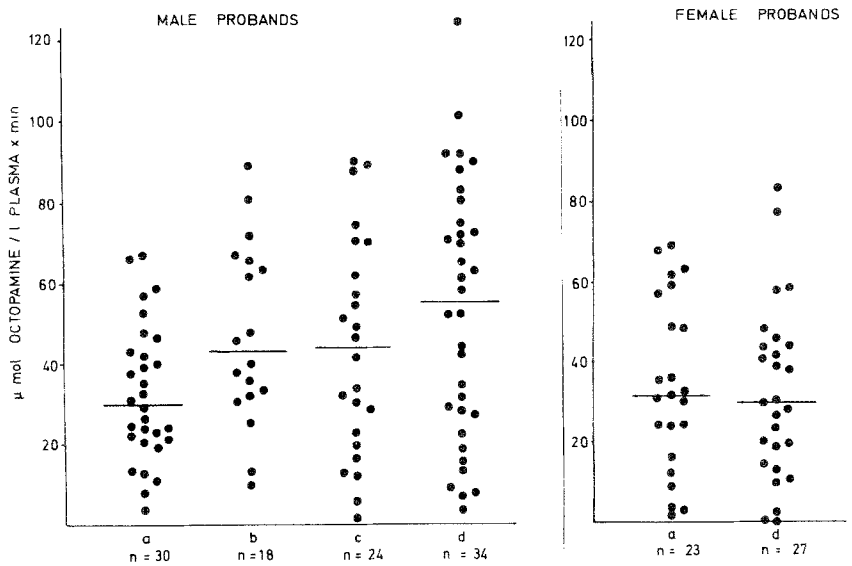

Fig. 2. DBH plasma activity in carriers of EEG variants. (a) Low-voltage EEG; (b) badly synchronized α EEG; (c) diffuse-β EEG; (d) monotonous-α EEG.

processing in the brain might have something to do with intellectual performance has much a priori appeal.

Another aspect of evoked potentials that has been investigated in recent years is their relationship to personality, temperament, and liability to mental and affective disorders. Here, the difference between "augmentors" and "reducers" is especially interesting: In augmentors, the size of the evoked potential increases with increasing intensity of stimulation, whereas in reducers, the size of the evoked potential decreases with increasing stimulus frequency (Buchsbaum, 1974). More recent studies in Sweden by Perris and his group (1980) have shown that both mechanisms are available in most individuals; only the level at which augmentation switches over to reduction appears to be different (v. Knorring *et al.*, 1978). According to Buchsbaum's work, this difference is related to the psychological health of the individual: Patients with bipolar affective disorders, high neuroticism scores, or socially deviant behavior tend to be augmentors. Test results suggest that augmentors are in general more disinhibited and sensation seeking than reducers. Schizophrenics, on the other hand, appear more often to be reducers.

None of the genetic and psychological studies of evoked potentials has considered the type of the resting EEG. We hope to close this gap by further studies, at the same time collecting more precise data on differences in information processing between inherited EEG variants.

At the beginning of this lecture, I compared the two paradigms on which human genetics is founded, Galton's biometric approach and Mendel's gene analysis. I concluded that genetic analysis by Mendelian principles has potentially a higher explanatory power. It was also mentioned, however, that this is only potentially true. In the actual analysis of behavior genetic problems, many practical difficulties arise that can be overcome only gradually, thus inhibiting fast progress in this field. On the other hand, I hope to have shown by a number of recent examples that our task, though difficult, is not hopeless. We cannot expect to get global, overall answers to questions such as: What are the mechanisms underlying genetic differences in intelligence? What is the genetic basis of differences in feeling tone and behavior, including mental disorder and addiction to alcohol and other drugs? What is the genetic basis of outstanding performance in the arts and sciences? On the other hand, a detailed analysis of brain function at various levels with emphasis on its consequences for behavior promises many more fascinating insights. Stepwise accumulation of particulate but unambiguous knowledge by the interaction between theory and experiment might help us to replace prejudiced controversies with a more rational appraisal of problems.

NOTE ADDED IN PROOF

Additional evidence on slight reduction of (especially verbal) I.Q. in PKU heterozygotes [Bessman *et al.* (1978). *Proc. Natl. Acad. Sci. USA* **75**:1562–1566] and heterozygotes of globoid cell leukodystrophy (Krabbe's disease) [Christomanou *et al.* (1981). *Hum. Genet.*, in press] is available. The problem of a relationship between I.Q. and evoked potentials is discussed by E. Callaway [(1975). *Brain Electrical Potentials and Individual Psychological Differences*, Grune & Stratton, New York]. A. R. Jensen [(1980). *J. Soc. Biol. Struct.* **3**:103–122] discusses the possible relationship between some reaction-time parameters and I.Q.

REFERENCES

Andersen, P., and Andersson, S. A. (1968). *Physiological Basis of the Alpha-Rhythm*, Appleton-Century-Crofts, New York.

Batshaw, M. L., Roan, Y., Jung, A. L., Rosenberg, L. A., and Brusilov, S. W. (1980). Cerebral dysfunction in asymptomatic carriers or ornithine transcarbamylase deficiency. *N. Engl. J. Med.* **302**:482–485.

Bleuler, M. (1972). *Die schizophrenen Geistesstörungen*, Thieme Verlag, Stuttgart.

Buchsbaum, M. A. (1974). Average evoked response and stimulus intensity in identical and fraternal twins. *Physiol. Psychol.* **2**(3A):365–370.

Buchsbaum, M. S., Murphy, D. L., Coursey, R. D., Lake, C. R., and Zeigler, M. G. (1977). Platelet monoamine oxidase, plasma dopamine-beta-hydroxylase and attention in a "biochemical high-risk" sample. The nature of schizophrenia. *Eur. J. Clin. Pharmacol.* **11**:337–344.

Christomanou, H., Martinius, J., Jaffé, S., Betke, K., and Förster, C. (1980). Biochemical, psychometric, and neuropsychological studies in heterozygotes for various lipidoses. *Hum. Genet.* **55**:103–110.

Comings, D. E. (1979). Pc Duarte. A common polymorphism of a human brain protein, and its relationship to depressive disease and multiple sclerosis. *Nature* **277**:28–32.

Dausset, J., and Svejgaard, A. (eds.) (1977). *HLA and Disease*, Munksgaard, Kopenhagen.

Dieker, H. (1967). Untersuchungen zur Genetik besonders regelmäßiger hoher Alpha-Wellen im EEG des Menschen. *Humangenetik* **4**:189–216.

Eicher, W., Spoljar, M., Cleve, H., Murken, J. -D., Richter, K., and Stengel-Rutkowski, S. (1979). HY antigen in transsexuality. *Lancet* **2**:1137–1138.

Engel, W., Pfäfflin, F., Wiedeking, C., and Epplen, J. T. (1980). HY antigen and transsexuality, and how to explain testis differentiation in HY antigen-negative males and ovary differentiation in HY antigen-positive females. *Hum. Genet.* **55**:315–319.

Fischer, R. A. (1918). The correlation between relatives on the supposition of Mendelian inheritance. *Trans. R. Soc. Edinburgh* **52**:399–433.

Harris, H. (1975). *The Principles of Human Biochemical Genetics*, 3rd ed., North-Holland, Amsterdam–Oxford.

Itil, T. M., (1978). Quantitative and qualitative EEG-Befunde Eis Schizophrenen. *Z. EEG–EMG* **9**:1–13.

Matthyse, S. (1980). Genetic detection of cerebral dysfunction. *N. Engl. J. Med.* **302**:516–517.

Perris, C., Gottfries, C. G., and v. Knorring, L. (1980). Visual averaged evoked responses in psychiatric patients. Relationship to levels of 5-hydroxyindoleacetic acid, homovanilic acid and tryptophan in cerebrospinal fluid. *J. Psychiat. Res.* **15**:155–181.

Propping, P. (1977). Genetic control of ethanol action on the central nervous system. An EEG study in twins. *Hum. Genet.* **35**:309.

Propping, P., Friedl, W., Nebel, B., and Feige, A. (1979). Plasma DBH, platelet MAO and proteins of red blood cell membranes in individuals with variants of the normal EEG. *Neuropsychobiology* **5**:309–316.

Propping, P., Krüger, J., and Janah, A. (1980a). Effect of alcohol on genetically determined variants of the normal electroencephalogram. *Psychiat. Res.* **2**:85–98.

Propping, P., Friedl, W., and Pluto, R. (1980b). Further evidence for correlation between EEG synchronization and plasma DBH activity in normal subjects. *J. Neur. Transmiss.* **49**:167–178.

Propping, P., Krüger, J., and Mark, N. (1981). Genetic disposition to alcoholism. An EEG study in alcoholics and their relatives. *Hum. Genet.* (in press).

Reinke, G. (1966). *Zur genetischen Grundlage der sogenannten Grenzfälle des Niederspannungs-EEGs und der diffusen β-Wellen bei jungen Männern*, Dissertation, Heidelberg.

Rosenthal, D., and Kety, S. S. (eds.) (1968). *The Transmission of Schizophrenia*, Pergamon Press, Oxford–London.

Spoljar, M., Eicher, W., Eiermann, W., and Cleve, H. (1981). H-Y antigen expression in different tissues from transsexuals. *Hum. Genet.* (in press).

Thalhammer, O., Havelec, L., Knoll, E., and Wehle, E. (1977). Intellectual level (IQ) in heterozygotes for phenylketonuria (PKU). *Hum. Genet.* **38**:285–288.

Thalhammer, O., Lubec, G., and Königshofer, H. (1979). Intracellular phenylalanine and tyrosine concentrations in 19 heterozygotes for phenylketonuria (PKU) and 26 normals. *Hum. Genet.* **49**:333–336.

Thalhammer, O., Pollak, A., Lubec, G., and Königshofer, H. (1980). Intracellular concentrations of phenylalanine, tyrosine and alpha-aminobutyric acid in 13 homozygotes and 19 heterozygotes for phenylketonuria (PKU) compared with 26 normals. *Hum. Genet.* **54**:213–216.

v. Knorring, L., Monakhov, K., and Perris, C. (1978). Augmenting/reducing: An adaptive switch mechanism to cope with incoming signals in healthy subjects and psychiatric patients. *Neuropsychobiology* **4**:150–179.

Vogel, F. (1962). Ergänzende Untersuchungen zur Genetik des menschlichen Niederspannungs-EEGs. *Dtsch. Z. Nervenheilk.* **184**:105–111.

Vogel, F. (1966a). Zur genetischen Grundlage fronto-päzentraler β-Wellen-Gruppen im EEG des Menschen. *Humangenetik* **2**:227–237.

Vogel, F. (1966b). Zur genetischen Grundlage occipitaler langsamer β-Wellen im EEG des Menschen. *Humangenetik* **2**:238–245.
Vogel, F. (1970). The genetic basis of the normal human electroencephalogram (EEG). *Humangenetik* **10**:91–114.
Vogel, F., and Götze, W. (1959). Familienuntersuchungen zur Genetik des normalen Elektroencephalogramms. *Dtsch. Z. Nervenheilk.* **178**:668–700.
Vogel, F., and Helmbold, W. (1972). Blutgruppen—Populationsgenetik und Statistik. In Becker, P. E. (ed.), *Humangenetik—ein kurzes Handbuch* Bd. 1, 4, Thieme Verlag, Stuttgart.
Vogel, F., and Motulsky, A. G. (1979). *Human Genetics—Problems and Approaches,* Springer Verlag, Berlin–Heidelberg–New York.
Vogel, F., and Schalt, E. (1979). The electroencephalogram (EEG) as a research tool in human behavior genetics: Psychological examinations in healthy males with various inherited EEG variants. III. Interpretation of the results. *Hum. Genet.* **47**:81–11.
Vogel, F., Schalt, E., and Krüger, J. (1979a). The electroencephalogram (EEG) as a research tool in human behavior genetics: Psychological examinations in healthy males with various inherited EEG variants. I. Rationale of the study; materials; methods; heritability of test parameters. *Hum. Genet.* **47**:1–46.
Vogel, F., Schalt, E., and Krüger, J. (1979b). The electroencephalogram (EEG) as a research tool in human behavior genetics: Psychological examinations in healthy males with various inherited EEG variants. II. Results. *Hum. Genet.* **47**:47–80.
Weiss, V. (1979). The heritability of difference scores when environments are correlated. *Biometric. J.* **21**:171–177.