Electro-encephalography in Drug Research

Edited by W. M. Herrmann

Gustav Fischer
Stuttgart · New York

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Editor:

W. M. HERRMANN, AFB · Arzneimittelforschung Berlin,
Kurfürstendamm 217, 1000 Berlin 19

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Introductory remarks

B. SCHNIEDERS

The scientific symposium on electroencephalography in drug research was one of a series of symposia staged by the Institute for Drugs of the Federal Health Office to allow experts to discuss and define the «present-day state of knowledge» in various fields of medicine as demanded by the law governing the use of drugs. The theme of this symposium, the titles of the workshops, and the individual papers suggest that, in addition to exchanging information, we shall indeed document present-day state of our knowledge of the role played by electroencephalography in drug research.

Electroencephalography has been used in clinical pharmacology since 1929 and the years following when H. BERGER furnished proof that cerebral potentials accompany human brain activity. As early as 1933 BERGER described EEG changes brought about under the effect of barbiturates, morphine, cocaine and scopolamine. In the 1950's and 1960's a series of papers appeared describing the effects of various drugs on human EEG (BENTE, 1956, 1961; BENTE and ITIL, 1954, 1955, 1957; FINK, 1959, 1961, 1963; ITIL, 1960, 1961, 1968; GOLDSTEIN et al., 1963; BORNSTEIN et al., 1965). Some of the pioneers of electroencephalography in drug research participated actively in the symposium and contributed to this volume.

As this demonstrates, EEG in clinical pharmacology is still a relatively young field. Although quantitative methods of evaluating the EEG were described as early as the 1930's, many years were, in fact, required before such methods became so practicable that this technique did not remain the domain of only a few laboratories in the world. Many more laboratories now have the necessary facilities at their disposal. If electroencephalography is to assume a more important role in clinical pharmacology, much more equipment and trained scientists must be made available. However, it is of even greater importance that universally valid criteria be established for quantitative analysis of the EEG and a convention be established defining the methods by which the EEG ist to be interpreted. Now, less than two years after the Symposium, Guidelines for Research in Pharmacoelectroencephalography in Humans have been established by an expert group and are published in this book in both the original German version as well as an authorized English translation.

Since computers for quantitative analysis of EEG data are no longer prohibitively expensive – no more expensive in fact than the EEG unit itself – and more and more scientists have come to realise that EEG constitutes an extremely useful tool without which pharmacological research would be inconceivable, future developments should proceed at an even faster pace than before. Taking this into consideration, it seems to be all the more necessary to define the state – of – the – art and to discuss both the possibilities and limits of EEG in clinical – pharmacological research. EEG is well accepted as a tool for describing the effects of psychotropic drugs. It also has been used sucessfully for revealing and describing the undesirable effects of drugs – including those which are not primarily psychotropic – on the central nervous system.

A further important field of application, which, in fact, was also discussed in our symposium, involves its use in clinical pharmacology. Until now we have been accustomed to describing

bioavailability in terms of the existence of substances and their metabolites in the blood circulation, their actual and theoretical distribution in the organism and their excretion. Frequently, however, it is impossible to obtain a sufficiently clear picture of metabolism, so that we must ask whether, in the case of certain substances – especially those which are centrally active, it might be useful to describe the dynamics of an effect parameter. This should become a major future use of quantitative EEG in pharmacological research. Routines should be developed to such a degree of sophistication that a clear description of the effect of certain drugs is possible.

It is interesting to note that our American colleagues of the College of Neuropsychopharmacology attached significance to the aspect of effect kinetics in the Final Task Force Report on Biovailability and Bioequivalency of Psychotropic Drugs.

Finally, I would like to express the hope that our symposium and this book will document our interest in, and contribute to, defining the state – of – the – art and in discussing the possibilities and the limits of EEG in drug research.

Introductory remarks

W. M. Herrmann

The choice of the subject for this symposium, electroencephalography in drug research, can be attributed to two factors. First, there is the increasing importance of the method of electroencephalography in discovering and evaluating the effects of drugs and the risks they involve. Second, the Institute of Drugs of the German Federal Health Office regards one of its tasks to be the cooperation with the scientific community in establishing guidelines for research and encouraging new methods, especially in those areas of drug research in which new developments are occurring rapidly and in which there are no internationally recognized conventions.

H. Berger, who is considered to be the founder of EEG in drug research, was a psychiatrist. Since then, electroencephalography has been mainly utilized by psychiatrists, neurologists and neurophysiologists, so that it is understandable that in drug research, electroencephalography was initially concerned almost exclusively with psychotropic drugs and drugs for neurology. We therefore felt that it would be of particular interest if a more detailed account could be given of so-called non-classic psychotropic drugs. Reports will be provided on the EEG effects of lithium, hypnotic drugs, β-blockers, opiates, endorphines and enkephalines.

In recent years, several new fields of application have been opened up. Among these areas is the evaluation of the toxicity of drugs in the CNS, especially of those drugs that are not in use in neurology or in psychiatry. With the aid of the EEG it is possible to determine whether a particular drug has an effect at the functional level of the EEG at a relatively early stage of the development of drugs. Hopefully, this information will lead to hypotheses for the assessment of risks involved with specific drugs and thus, perhaps, an improvement of drug safety at the place of work and in traffic.

Prof. Schnieders has already drawn attention to the newly recognized importance of the EEG in the evaluation of the bioavailability and bioequivalency of drugs. The EEG also appears to me to be a viable instrument and one which will occupy a permanent place in the evaluation of bioavailability and bioequivalency of substances that affect the functions of the brain.

Progress in the areas of identifying and characterizing drug effects on the CNS has led to hope that substances can be allocated to clinically defined psychotropic classes on the more objective basis of the functional level of the EEG. It is felt that an account of the latest findings and in particular, a definition of a theoretical position would be of great use. Therefore, W. M. Herrmann's thesis for «Habilitation» at the Free University of Berlin is presented in this book. Another important area of research is the aspect of vigilance. Since M. Matejcek worked extensively on this subject for his doctoral dissertation, this work is also included.

New methods have also been introduced. In the visual evaluation of the past, the qualitative aspects played a particularly important role. Quantitative evaluations were difficult; not much mention is made of them in the literature. Although the quantitative evaluation of the EEG is now firmly established, at the time of the symposium, June 1980, I thought that it would require many years to develop minimum standards for the quantitative and statistical methods of pharmaco-EEG studies covering the areas of fields of application, planning of experiments, methods

of quantitative analysis, and evaluation of the validity of the results obtained from investigations of the effectiveness of specific drugs and the risks they involve. Now, less than two years later, this task has been accomplished; the guidelines worked out by an expert committee are presented in this book. Although these guidelines have the consent of an important group of experts, there is still much work to be done until they are generally accepted and applied.

Over the past ten years electroencephalography in drug research has given rise to a number of expectations, but it has also resulted in some disappointments. I remain convinced that the EEG has a great future in drug research. At the same time, I am equally certain that much still remains to be done before the EEG can take its rightful place: We must propagate and apply the guidelines, train personnel and obtain research funds for method-oriented projects from the public sector as well as from the pharmaceutical industry.

We hope that this book will contribute to fulfilling these tasks by documenting the present state of knowledge, stimulating further fruitful investigations, and suggesting methods and standards which could make results cumulative.

Guidelines for Pharmaco-EEG Studies in Man

Expert group, organized at the Federal Health Office, Institute for Drugs, Berlin, West Germany

Coordination

G. Stille
W. M. Herrmann

Members of the Expert Group

D. Bente, Berlin, West Germany
M. Fink, Stony Brook, New York, USA
T. M. Itil, Tarrytown, New York, USA
W. P. Koella, Basel, Switzerland
St. Kubicki, Berlin, West Germany
H. Künkel, Hannover, West Germany
J. Kugler, Munich, West Germany
M. Matejcek, Basel, Switzerland
H. Petsche, Vienna, Austria

Preamble

The goal of these guidelines, developed by an expert group, are to present the minimum standards for the methods of pharmaco-EEG studies.

It is anticipated that these guidelines will be modified as the science of the pharmaco-EEG develops.

The goal of these guidelines, developed by an expert group, is to present the minimum standards for *quantitative and statistical* methods of pharmaco-EEG studies.

Empfehlungen für Pharmakoelektroenzephalographische Untersuchungen am Menschen

Expertengruppe, gebildet beim Bundesgesundheitsamt, Institut für Arzneimittel, Berlin, Bundesrepublik Deutschland

Koordination

G. Stille
W. M. Herrmann

Mitglieder der Expertengruppe

D. Bente, Berlin, Bundesrepublik Deutschland
M. Fink, Stony Brook, New York, USA
T. M. Itil, Tarrytown, New York, USA
W. P. Koella, Basel, Schweiz
St. Kubicki, Berlin, Bundesrepublik Deutschland
H. Künkel, Hannover, Bundesrepublik Deutschland
J. Kugler, München, Bundesrepublik Deutschland
M. Matejcek, Basel, Schweiz
H. Petsche, Wien, Österreich

Präambel

Diese Empfehlungen sollen dazu beitragen, Mindestanforderungen einer Expertengruppe an die Methodik pharmakoelektroenzephalographischer Untersuchungen zu präzisieren.

Sie müssen fortlaufend der wissenschaftlichen Entwicklung angepaßt werden.

I. Fundamentals

(1) The pharmaco-EEG concerns the description and the quantitative analysis of the effects of substances on the central nervous system by means of neurophysiologic methods. The methods are within the framework of clinical and experimental pharmacology, neurotoxicology, therapeutic research, and associated disciplines. Pharmaco-EEG studies use quantitative methods of data reduction and statistical analysis.

(2) Pharmaco-EEG studies are applicable when there are indications that a substance may, at the therapeutic doses used, have an effect on brain function.

(3) The methods provide descriptions of the direct and indirect effects of substances on brain functions and reflect the pharmacodynamic and pharmacokinetic properties of the substances.

(4) Pharmaco-EEG studies require:

a) a design which is relevant to the aims of the study, including a placebo control when indicated, and

b) the use of quantitative methods of data collection and reduction, and statistical means for the data analysis to achieve the aims of the study.

(5) Pharmaco-EEG studies are indicated in all phases of clinical research and, in addition, contribute to monitoring the course of drug treatment. Depending on the objectives, either patients or normal volunteers may be examined. Pharmaco-EEG studies answer questions in clinical pharmacology as well as in therapeutic research.

II. Requirements of the Investigator of neurophysiologic studies

The responsible investigator should:

(1) Understand the range of normal and abnormal variability of the methods used, based on sufficient experience of several years.

(2) Be acquainted with the literature and methods of neurophysiology and biosignal data analyses which are the basis for the interpretations of the results of the study.

(3) Be responsible for the planning, organization, execution, and interpretation of the results of the study.

I. Grundlagen

(1) Die Pharmakoelektroenzephalographie befaßt sich mit der Erfassung und Analyse von Pharmakonwirkungen auf das Zentralnervensystem durch neurophysiologische Methoden im Rahmen der klinischen und experimentellen Pharmakologie, Neurotoxikologie, therapeutischen Forschung und verwandter Gebiete.

(2) Pharmakoelektroenzephalographische Untersuchungen sind dann sinnvoll, wenn aufgrund der vorliegenden Erkenntnisse zu erwarten ist oder vermutet werden kann, daß das Pharmakon mittelbar oder unmittelbar im therapeutisch relevanten Dosisbereich die Funktion des Gehirns beeinflußt.

(3) Pharmakoelektroenzephalographische Untersuchungen ermöglichen Aussagen über direkte oder indirekte Wirkungen auf das Gehirn unter Berücksichtigung von Pharmakokinetik und Pharmakodynamik.

(4) Pharmakoelektroenzephalographische Untersuchungen erfordern:

a) eine am Untersuchungsziel orientierte biometrische Prüfungsplanung, ggf. unter Einschluß einer Plazebokontrolle und
b) eine dem Untersuchungsziel angemessene Erfassung, Verarbeitung und Auswertung der Daten.

(5) Pharmakoelektroenzephalographische Untersuchungen sind in allen Phasen der klinischen Prüfung indiziert und können darüber hinaus der Therapiekontrolle dienen. Je nach Fragestellung erstrecken sie sich auf Probanden oder Patienten. Sie dienen damit sowohl der klinischen Pharmakologie als auch der therapeutischen Forschung.

II. Anforderungen an den Leiter der neurophysiologischen Untersuchungen

Der Verantwortliche muß:

(1) die physiologische und pathologische Variationsbreite der angewendeten neurophysiologischen Untersuchungsmethoden kennen und hierzu über eine mehrjährige ausreichende Erfahrung verfügen.

(2) Kenntnisse und Erfahrungen auf dem Gebiete der neurophysiologischen Meßdatenverarbeitung und Biosignalanalyse besitzen, die ihn zu einer am Untersuchungsziel orientierten Auswertung der neurophysiologischen Daten und Interpretation der Ergebnisse befähigen.

(3) für die neurophysiologische Planung, Durchführung, Auswertung und Interpretation verantwortlich zeichnen.

III. Important environmental, situational, and subject variables in patients and volunteers

(1) Since there are many factors that affect the functions of the central nervous system, and consequently, neurophysiologic measures, it is necessary to control these factors as much as possible. At a minimum, if such variables cannot be excluded, they should be documented. These factors include:

a) The environment of the recording, such as
- room temperature
- humidity
- sound level and light intensity
- intermittent disturbing events
- organization of the laboratory rooms

b) Situational factors, such as
- position of the subject
  (standing, sitting, leaning, lying flat)
- amount and nature of sensory stimulation
  (eyes closed, eyes open without a specific place to attend, eyes open with attending to a visual task)
- social isolation
  (degree of interaction with personnel; personal relations with technical staff)
- adaptation to the situation
- state of vigilance and its control
  (It is essential that the instructions for maintaining vigilance be explicit, as «Sit quietly and relaxed, but do not fall asleep!» and/or sensorimotor or cognitive tasks given during the examination. Random and undefined interactions between the subject and the technician during the recording (as changing the electrode placement or posture, additional instructions or stimulation) should be minimal, and if such interactions occur, they should be documented)
- time of recording
- meal-times
  (type of food and times of administration)

c) Personal data, such as
- demographic data
  (age, sex, socioeconomic status)
- medical status
  (state of health, history of prior illnesses, use of medication and drugs, sleep history, EEG characteristics)
- use of tobacco, coffee, tea, and alcohol, before and during the days of examination
- personal characteristics
  (e.g., emotional lability, neuroticism, extraversion/introversion)
- important psychophysiological characteristics
  (emotional state, such as anxiety or fatigue, reaction to stress, bladder or bowel problems, etc.)

(2) It is necessary to document the degree to which these factors have been used as inclusion and exclusion criteria.

III. Zur Bedeutung umgebungs-, situations- und personenbedingter Faktoren bei Patienten und Probanden

(1) Da eine Reihe von Faktoren die Funktion des Zentralnervensystems und damit auch die neurophysiologischen Meßergebnisse beeinflußt, müssen diese Faktoren soweit als möglich kontrolliert, zumindest aber protokolliert werden. Hierzu gehören:

a) Umgebungsbedingungen, z. B.

- Raumtemperatur
- Luftfeuchtigkeit
- akustische und optische Einflüsse
- passager auftretende Störeinflüsse
- räumliche Konfiguration des Labors

b) Situationsbedingungen, z. B.

- Position des Untersuchten
  (stehend, aufrecht sitzend, zurückgelehnt, liegend)
- Art und Ausmaß des Umweltkontaktes
  (Augen geschlossen, Augen geöffnet ohne gerichtete Aufmerksamkeit, gerichtete Aufmerksamkeit bei Durchführung von Aufgaben)
- sozialer Bezug
  (Grad der Isolation vom untersuchenden Personal und Konstanz bzw. Bekanntheit der untersuchten Personen)
- Bekanntheitsgrad der Untersuchungssituation
  (Grad der Adaptation)
- Vigilanzdynamik
  (Zweckmäßig sind hier standardisierte Verhaltensinstruktionen, wie «Sitzen Sie ruhig und entspannt, aber schlafen Sie nicht ein!» und/oder sensomotorische und kognitive Aufgaben während der Untersuchung; unsystematische Interaktionen zwischen Untersucher und Untersuchtem während der Ableitung, z. B. Verbesserung der Elektrodenposition, Haltungskorrektur, Zusatzinstruktionen oder Weckreize sollten möglichst vermieden, jedenfalls aber protokolliert werden)
- Uhrzeit der Untersuchung
- Mahlzeit
  (Art und Uhrzeit)

c) personenbezogene Bedingungen, z. B.

- demographische Daten
  (Alter, Geschlecht, sozioökonomischer Status)
- biomedizinische Daten
  (Gesundheitszustand, Krankheitsvorgeschichte, Genußmittel-, Drogen- und Arzneimittelanamnese, Schlafanamnese, EEG-Befund)
- Nikotin-, Koffein- und Alkoholgebrauch während des Untersuchungstages und am Vortage
- Persönlichkeitsmerkmale
  (emotionale Labilität bzw. Neurotizismus, Extra-/Introversion sowie andere für die Fragestellung relevante Persönlichkeitsdimensionen)
- Merkmale des aktuellen psychophysischen und vegetativen Zustandes
  (Befindlichkeiten, wie Angst, Müdigkeit, Stimmungslage, etc.; Streßmomente; Harn- oder Stuhldrang, etc.).

(2) Im einzelnen muß dargestellt werden, ob und wie die unter (1) genannten Einflußgrößen in die Ein- und Ausschlußkriterien eingegangen sind.

IV. Technical details of the study

(1) The standards for recording the EEG as proposed by the following sources are recommended: Chapter 3 of the American EEG Society («Minimum technical requirements for performing clinical electroencephalography» – 1980) and the standards for clinical practice in EEG of the International Federation of Societies of EEG and Clinical Neurophysiology (Chapter B – «Equipment»; and Chapter D – «Recording»).

(2) EEG electrodes should be applied according to the 10–20 system. If alternative placements are used, their locations should be accurately defined and the justification for the use stated.

(3) Electrode resistance and channel amplification should be calibrated and recorded before and after the recording. If more than one channel of EEG is recorded, amplification of all channels should be identical.

(4) Differences in topographic recording should be considered, since EEG activity may vary between the anterior and posterior parts of the scalp, between temporal and parietal regions, and between the two hemispheres. Hence, multichannel recordings are encouraged.

(5) An adequate and necessary documentation of the biosignals requires that the signals may be examined from the paper record. It is necessary that records be maintained of the date, time, duration of recording, electrode montage, and time constant of the equipment, among other significant variables, and that the record be signed by the recorder.

(6) Biological and technical artefacts (e.g. EKG, electrode, movement, and sweating) must be identified and excluded from the final analyses of the recordings. To the extent that artefact rejection is done automatically, the criteria and methods for rejection must be defined. The number and times of rejected samples should be identified, so that their relation to the original recording can be determined.

V. Data analysis

(1) When the signal is reduced by digital means, the following aspects must be considered:

- adequate sampling rate of the analog to digital converter in relation to the variations of the signal
- attention must be paid to the relations between the frequencies of interest, filtering and acquisition rate in order to avoid errors due to folding frequencies.

These parameters of signal reduction should be recorded.

(2) The type of data reduction (e.g. interval analysis, spectral analysis) and the methods of their statistical analysis should be recorded. Also, the procedures used to derive the measures from the reduced data should be stated explicitly. This is essential, since these procedures determine and limit the interpretations of the results which are obtained.

(3) The technical aspects of the study and the basis for the interpretations should be clearly stated and justified.

The Expert Group requests suggestions, opinions and comments on these Guidelines, if possible, within two months of publication.

IV. Anforderungen an die Untersuchungstechnik

(1) Zur elektroenzephalographischen Untersuchungstechnik wird auf Kapitel 3 (Minimum Technical Requirements for Performing Clinical Electroencephalography) der Guidelines der American EEG Society (1980) und andere Standards (z.B. Standard of Clinical Practice in EEG der International Federation of Societies for EEG and Clinical Neurophysiology, Kapitel B. Equipment und D. Recording) verwiesen.

(2) Die EEG-Elektroden sollen nach dem 10–20-System angelegt werden. Abweichende Elektrodenpositionen müssen in Relation hierzu definiert werden; die Abweichung sollte begründet werden.

(3) Die Elektrodenübergangswiderstände sollen vor und nach jeder Untersuchung gemessen und dokumentiert werden. Das gleiche gilt für die Verstärkungseichung zu Beginn und am Ende der Ableitung. Werden mehrere EEG-Kanäle in die Auswertung einbezogen, so gewinnt eine vergleichende Verstärkungskontrolle besondere Bedeutung.

(4) Im Hinblick auf die topographische Differenzierung des EEG ist eine Mehrkanalableitung anzustreben, so daß je nach Fragestellung das Beurteilen der elektroenzephalographischen Aktivität im Bereich der vorderen und hinteren Schädelhälfte und der parietalen und temporalen Hirnregionen, gegebenenfalls auch im Seitenvergleich möglich ist.

(5) Die notwendige Dokumentation der Biosignale erfordert, daß die Daten jederzeit bei Bedarf auf Papier wiedergegeben werden können. Dabei müssen Angaben zur Person des Untersuchten, Datum, Uhrzeit und Dauer der Registrierung, Kanalbelegung, obere und untere Grenzfrequenz (Zeitkonstante) dokumentiert und durch die ableitende Person unterzeichnet werden.

(6) Biologische und technische Artefakte (z.B. EKG-, Elektroden-, Bewegungs- und Schwitzartefakte) müssen gekennzeichnet und von der weiteren Verarbeitung ausgeschlossen werden. Soweit der Ausschluß mit automatischen Verfahren erfolgt, müssen deren Funktionskriterien dargestellt werden. Der Zeitanteil und die Zeitstellen eliminierter Segmente sind zu kennzeichnen, so daß ihr Bezug zum originalen Ablauf jederzeit erkenntlich ist.

V. Verarbeitung und Auswertung der Meßdaten

(1) Sofern die Signale digital erfaßt werden, müssen bestimmte Grundsätze der digitalen Signalverarbeitung beachtet werden:

- ausreichende Auflösung des AD-Wandlers in Relation zur Dynamik des Signals
- Beachtung der Zusammenhänge zwischen interessierendem Frequenzbereich des Signals, Filterung und Abtastrate, um Verfälschungen des Signals gering zu halten.

Diese Parameter der Datenerfassung müssen dokumentiert werden.

(2) Die für die Meßdatenverarbeitung verwendeten Verfahren (z.B. Intervallanalyse, Spektralanalyse) und die für sie charakteristischen Schritte müssen dokumentiert werden. Ebenso sind die Verfahren, die zur Bildung von Variablen führen, zu erläutern, da von ihnen die Aussage- und Interpretationsfähigkeit der Ergebnisse wesentlich abhängt.

(3) Das biometrische Vorgehen soll beschrieben und begründet werden.

Die Expertengruppe bittet um Meinungsäußerung und Stellungnahme, möglichst innerhalb von 2 Monaten nach Veröffentlichung.

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