Guidelines for the Recording and Evaluation of Pharmaco-EEG Data in Man: The International Pharmaco-EEG Society (IPEG)

Marc Jobert[a]   Frederick J. Wilson[b]   Gé S.F. Ruigt[c]   Martin Brunovsky[d]   Leslie S. Prichep[e]
Wilhelmus H.I.M. Drinkenburg[f]   The IPEG Pharmaco-EEG Guidelines Committee

[a]International Pharmaco-EEG Society, Berlin, Germany; [b]Pharmatherapeutics Precision Medicine, Pfizer Ltd,
Sandwich, UK; [c]Clinical Consultancy for Neuroscience Drug Development, Oss, The Netherlands; [d]Psychiatric Center, Department of Psychiatry and Medical Psychology, Charles University, Prague, Czech Republic; [e]Brain Research Laboratories, Department of Psychiatry, University School of Medicine, New York, N.Y., USA; [f]Neuroscience Discovery, Janssen Research and Development, Pharmaceutical Companies of Johnson and Johnson, Beerse, Belgium

Abstract

The International Pharmaco-EEG Society (IPEG) presents updated guidelines summarising the requirements for the recording and computerised evaluation of pharmaco-EEG data in man. Since the publication of the first pharmaco-EEG guidelines in 1982, technical and data processing methods have advanced steadily, thus enhancing data quality and expanding the palette of tools available to investigate the action of drugs on the central nervous system (CNS), determine the pharmacokinetic and pharmacodynamic properties of novel therapeutics and evaluate the CNS penetration or toxicity of compounds. However, a review of the literature reveals inconsistent operating procedures from one study to another. While this fact does not invalidate results per se, the lack of standardisation constitutes a regrettable shortcoming, especially in the context of drug development programmes. Moreover, this shortcoming hampers reliable

Co-authors (in alphabetical order):
Claudio Babiloni: Department of Biomedical Sciences, University of Foggia, Foggia, Italy; ***Peter H. Boeijinga:*** FORENAP Research and Development, Rouffach, France; ***Dominic H. ffytche:*** Institute of Psychiatry, King's College London, London, UK; ***Jon Freeman:*** Brooklyn Strategic Consulting, New York, N.Y., USA; ***Joop M.A. van Gerven:*** Center for Human Drug Research, Leiden, The Netherlands; ***Koichi Hirata:*** Department of Neurology, Dokkyo Medical University, Tochigi, Japan; ***Ulrich Hegerl:*** Department of Psychiatry, University of Leipzig, Leipzig, Germany; ***Toshihiko Kinoshita:*** Department of Psychiatry, Kansai Medical University, Moriguchi, Osaka, Japan; ***Verner J. Knott:*** Institute of Mental Health Research, University of Ottawa, Ottawa, Ont., Canada; ***Fernando H. Lopes Da Silva:*** Center of Neuroscience, Swammerdam Institute for Life Sciences, Amsterdam, The Netherlands; ***Milos Matousek:*** Department of Clinical Neurophysiology, Göteborg, Sweden; ***Armida Mucci:*** Department of Psychiatry, University of Naples SUN, Naples, Italy; ***Judith F. Nottage:*** Institute of Psychiatry, King's College London, London, UK; ***Sebastian Olbrich:*** Department of Psychiatry, University of Leipzig, Leipzig, Germany; ***Bernd Saletu:*** Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria; ***Andrej Stancak:*** Department of Experimental Psychology, Institute of Psychology, Health and Society, University of Liverpool, Liverpool, UK; ***Werner K. Strik:*** University Hospital for Clinical Psychiatry, Bern, Switzerland; ***Richard G. Wise:*** Cardiff University Brain Research Imaging Centre, School of Psychology, Cardiff University, Cardiff, UK.

Marc Jobert
E-Mail publications@ipeg-society.org

comparisons between outcomes of studies from different laboratories and hence also prevents pooling of data which is a requirement for sufficiently powering the validation of novel analytical algorithms and EEG-based biomarkers. The present updated guidelines reflect the consensus of a global panel of EEG experts and are intended to assist investigators using pharmaco-EEG in clinical research, by providing clear and concise recommendations and thereby enabling standardisation of methodology and facilitating comparability of data across laboratories.

Introduction

Pharmaco-electroencephalography (pharmaco-EEG) concerns the description and the quantitative analysis of the effects of substances on the central nervous system (CNS) by means of neurophysiological and electrophysiological methods used within the framework of clinical and experimental pharmacology, neurotoxicology, therapeutic research and associated disciplines. For the remainder of this article, the acronym pharmaco-EEG strictly refers to human quantitative electroencephalography (QEEG) in the context of drug testing. Separate guidelines for pharmaco-sleep studies in man are in preparation for publication by the International Pharmaco-EEG Society (IPEG). Evoked potentials (EPs)/event-related potentials (ERPs), in which the time-locked EEG signal resulting from a specific event is examined, represent another area of study and will be the subject of dedicated guidelines.

In the 80s and early 90s, several guidelines were published with the goal to standardise the acquisition and processing of data collected in pharmaco-EEG studies [1–3] or to provide procedural recommendations for the recording and quantitative analysis of EEG activity in research contexts [4].

The initial pharmaco-EEG guidelines were complemented in 1995 by another guideline paper providing the framework to build standard operating procedures (SOPs), identifying the key components and minimum requirements for data acquisition, amplification and filtering, the validation of hardware and software, artefact treatment and fast Fourier analysis [5]. This framework constituted the basis for setting up laboratory-specific SOPs. This attempt was driven by the mandatory need for compliance to good clinical practice, an international quality standard launched by the International Conference on Harmonisation (ICH), an international body defining standards that governments can transpose into regulations for the registration of pharmaceuticals and for the conduct of clinical trials involving human subjects. Good clinical practice requires SOPs to be available to document all methods and procedures in use during drug development.

In parallel, several organisations published recommendations and guidelines for the use of EEG in various clinical fields [6–8] in an effort to improve standardisation and facilitate the proper utilisation of the technique in clinical practice.

EEG is a non-invasive method which directly reveals the spontaneous synchronised postsynaptic neuronal activity of the human cortex with high temporal resolution. While EEG parameters are among the biomarkers with the highest heritability [9–12], they show at the same time a very high sensitivity to changes in both environment and internal states (state-modulated traits). The sensitivity to such factors, which are extraneous to the objective of many studies, means that a high degree of quality control and detailed SOPs are required in order to decrease the effect of confounders in the analysis of the data.

While pharmaco-EEG has demonstrated its value in the development of CNS-active compounds in many instances, and while validated quantitative methods have been available for a long time to study the effects of drugs on brain functions in patients and volunteers [13], there is still reluctance to apply this method in large-scale clinical trials or for pivotal drug studies. There are a number of reasons contributing to this situation:

(1) While there is evidence indicating the putative utility and validity of EEG as a biomarker relevant to a range of drug classes covering several therapeutic indications, it has not yet been generally accepted as such. Further, the translatability of pharmaco-EEG signatures is not universal across the spectrum of CNS-active drugs, but depends on the pharmacological mechanism and the preclinical species used. Hence its use as a translational biomarker for the preclinical screening of compounds and the development of new drugs requires careful interpretation [14].

(2) Despite the fact that pharmaco-EEG has been used in research laboratories for several decades now [15, 16], operating procedures have not yet been standardised to an extent facilitating reliable comparison of datasets and results across units, making it difficult (or even impossible) to share datasets between sites or to pool results from different clinical trials.

(3) This lack of standardisation constitutes a difficult obstacle for the design and interpretation of clinical trials due to the difficulties in comparing results across the literature.

(4) The large inter-individual variability observed in EEG records, some of which may be attributable to the lack of standardisation, can be compensated by increasing the sample size, provided that the behavioural and awareness state of the subjects is tightly controlled. However, trial costs quickly become prohibitive as the sample size increases and hence improvements in standardisation which enable sample size reductions will make routine application more attractive. Despite this, EEG is still one of the cheapest of the various methods that can be used as a window into the brain's activity, and also has the advantage that it can feasibly be integrated into first-in-human studies.

(5) For a long time, the amount of data generated by recording EEG signals from multiple electrodes quickly overwhelmed the storage capacity of computers and the processing techniques were constrained by CPU power. These limitations have now disappeared as a consequence of vastly increased computing power and storage capacities.

In this context, one of the crucial steps is to enhance the standardisation of the operating procedures, not only to improve the ability to compare EEG data and results generated in different laboratories by reducing variance but also to facilitate the creation of a centralised repository where a large number of records could be stored and shared. Such a repository would enable the following endeavours:

(1) Constitute reference datasets (i.e. both the raw EEG signals recorded against a unipolar reference and the derived parameters) obtained under standardised conditions from different studies using various drugs (with emphasis on reference drugs and including placebo) and study populations (healthy volunteers and various patient populations) under standardised behavioural conditions, enabling comparative analyses.

(2) Identify EEG parameters and properties that could be exploited as potential (translatable) biomarkers and quantify their validity on large populations.

(3) Facilitate the transition of novel compounds from preclinical to clinical research and development programs by enabling the early comparison of results obtained in preclinical screening and early clinical experiments, thereby improving the decision-making process as well as de-risking and accelerating the development of new CNS-active compounds.

Pharmaco-EEG Studies

Fundamentals

Pharmaco-EEG studies are applicable when there are indications that a substance may have an effect on the CNS at therapeutic or pharmacologically relevant dose levels. Pharmaco-EEG studies are indicated in all phases of clinical research and may answer questions in clinical pharmacology as well as in therapeutic research. It is the consistency and nature of the empirical observations captured by the pharmaco-EEG method, particularly in the realm of clinical psychopharmacology, which have established this technique as a suitable means for a complete quantitative description of the effect of a drug on the function of the brain in humans [17, 18]. Pharmaco-EEG data can be exploited to classify psychotropic substances [19, 20] and to assess drug-drug interactions or to monitor side effects and toxicity [21]. The use of quantitative methods for data reduction and statistical analysis provides quantitative descriptions of the direct and indirect effects of active compounds on brain functions [22] hence generating pharmacodynamic (PD) outcome measures which, along with separate pharmacokinetic (PK) data (e.g. drug concentration from blood samples), can be used to study the PK-PD relationship [23–25].

Pharmaco-EEG studies need to be designed in accordance with the objectives of the study (including placebo control and/or reference drug and test-retest design when indicated, and always keeping the behavioural and awareness state of the subjects under well-controlled standardised conditions) and require appropriate statistical methods adapted to the study design and the investigated hypotheses. Dependent upon the study objectives, either patients and/or normal volunteers may be examined. Although a given psychotropic drug tends to produce similar and replicable EEG profile changes in different populations at the group level, per-subject differences in EEG response profiles have also been shown to be a useful indicator of the biological variability and therapeutic potency of a compound. Less potent psychotropic drugs often exhibit higher biological variability (as seen in individual EEG response profiles), while more therapeutically potent compounds (i.e. with low biological variability) generally produce very similar EEG profile changes in the majority of subjects tested [26]. In patient populations, clinical response to drugs has shown to be a source of variation with different patterns observed in responders versus non-responders [27, 28]. This illustrates the potential utility of EEG for patient selection in clinical trials or as a companion diagnostic

Table 1. Minimum set of subject metadata to be filed in pharmaco-EEG trials

Demographics	Age, gender, handedness
Medical history	State of health, prior or current illnesses, psychiatric history
Screening EEG	Abnormalities, high/low α power
Medication status	Current use of drugs, use of drugs in the past 4 weeks Use of alcohol, tobacco, illicit drugs

to certain drug therapies, thus facilitating a personalised medicine approach.

All clinical trial programmes must follow the ICH guidelines aimed at 'ensuring that good quality, safe and effective medicines are developed and registered in the most efficient and cost-effective manner. These activities are pursued in the interest of the consumer and public health, to prevent unnecessary duplication of clinical trials in humans and to minimize the use of animal testing without compromising the regulatory obligations of safety and effectiveness.' The ICH guidelines cover a broad range of activities related to drug development [29, 30].

In addition, the responsible investigator should: (a) be acquainted with the literature and techniques of EEG data processing which are the basis for the interpretation of the results; (b) understand the range of normal and abnormal variability of the neurophysiological methods used, and (c) be responsible for the planning, organisation and execution of the study.

Subjects

Due to the broad spectrum of neurophysiological domains where pharmaco-EEG studies are applicable, it is not possible to provide an all-inclusive standard for subject-related data which should be collected in pharmaco-EEG trials. The type of subject data to be collected may depend upon the objectives, targeted population, pathology (by patients) and other attributes of a specific trial.

The following factors should be considered when compiling inclusion and exclusion criteria for a particular study and documented routinely: demographic data (age, gender, handedness and socioeconomic status); medical history [state of health, prior illnesses, presence of any metabolic syndrome, hyperglycaemia or thyroid disorder, use of drugs (including medication and recreational substances, particularly cannabis), sleep quality and behaviour, and EEG characteristics]; psychiatric history (DSM or ICD diagnoses), and use of tobacco, coffee, tea, energy drinks and alcohol (before and during the days of examination). If relevant, more personal characteristics are to be filed: emotional lability, neuroticism, extraver-

sion/introversion; important psycho-physiological attributes such as emotional state (anxiety or fatigue), reaction to stress, bladder or bowel problems and menstrual cycle, for example. Where possible, standardised rating scales should be used to quantify characteristics and subjective descriptors should be avoided.

Table 1 summarises the set of subject metadata to be recorded in pharmaco-EEG trials.

Given the profound effect of nicotine, caffeine and alcohol consumption on the EEG signal, it is generally recommended to restrict the use of these products in clinical EEG trials, for instance by excluding subjects if they meet any of the following conditions within the previous 6 months:

- History of regular alcohol consumption exceeding 2–3 units/day for females and 3–4 units/day for males [31]
- History of regular use of tobacco or nicotine-containing products exceeding the equivalent of 5 cigarettes per day
- History of regular consumption of caffeine exceeding the equivalent of 4 cups of coffee per day, a level that approximates health-related criteria [32]

In addition, subjects should refrain from alcohol and caffeine for at least 24 h, and from tobacco or nicotine products for at least 4 h (preferably 8 h) prior to an EEG recording.

Stricter exclusion criteria or restrictions may be applied on a study-by-study basis where required.

Phenotyping and/or genotyping of the participants is acquiring increasing importance for safety and PK reasons; since drugs can be primarily metabolized through specific cytochrome P_{450} (CYP) isoenzymes, metabolic status could be defined accordingly in order to avoid potential accumulation/fast elimination during the washout phase, for example. If a drug is known to be subject to a major genetic polymorphism, studies could be performed in panels of participants of known phenotype or genotype for the polymorphism in question.

In addition, genotyping is becoming relevant for the EEG itself: it has been demonstrated that a low/high natural α rhythm can influence the interpretation of the

EEG response to drugs [33], and studies of twins conclude that the high inter-individual variability in α power and α peak frequency is largely genetically determined [9–12]. Today, the best candidate is a gene encoding catechol-*O*-methyltransferase. According to a recent study [34], the Val[158]Met polymorphism of the enzyme is highly predictive of individual α activity, with the Val allele carriers displaying lower α peak frequency and lower α activity compared to the Met allele carriers. If this variability is likely to have an effect on a particular study, then suitable subjects could be selected either by genotyping or by screening for low/high EEG α rhythm. Alternatively, genotyping data could be collected for post hoc analysis.

Pharmaco-EEG – Data Acquisition

Digital Recording

Digitising is the conversion of an analogue (continuous) signal into a digital (discrete) representation (i.e. a sequence of numbers). Analogue-to-digital (A/D) converters usually have a resolution of 16 bits, meaning that the analogue amplitude of each discrete point is represented by a value ranging from 0 to 65,535 (0 to $2^{16} - 1$). The sampling rate (T_S) corresponds to the time interval between two subsequent points and determines the resolution in time. The sampling frequency (F_S) expresses the number of samples digitised per second and is the reciprocal of the sampling rate ($F_S = 1/T_S$). With a sampling frequency of 500 Hz, the resolution in time (Δs) corresponds to the sampling rate and is given by the reciprocal of the sampling frequency, i.e. 2 ms.

From a theoretical point of view, the sampling frequency must be at least twice the highest frequency present in the signal to be digitised (Nyquist-Shannon sampling theorem). Conversely, frequency components higher than half the sampling frequency (also called Nyquist frequency, $F_N = F_S/2$) must be removed using analogue filters before digitising to avoid aliasing effects. Errors introduced in the digitised signal by aliasing cannot be detected and corrected afterwards. Because of imperfections in the analogue filters, the sampling frequency is in practice at least fourfold the analogue filter (anti-aliasing) cut-off frequency.

From a practical point of view, the following applies for pharmaco-EEG studies: Sampling frequency must be at least 500 Hz (i.e. 500 samples per second) and be a multiple of 50 or 64 [e.g. 500 or 512 Hz (currently in neurocognitive studies and in epilepsy, EEGs are being recorded with a wider frequency band to allow the study of high γ band components or, more generally, high frequency oscillations; in this case, sampling has to be at rates >2 kHz. This is discussed in the section on High-Frequency (γ) EEG Activity below)]. The A/D converter must have a digital resolution of at least 16 bits and resolve changes in the EEG below 0.2 μV. Prior to sampling, an anti-aliasing low-pass filter set at 70 Hz (with a roll-off of at least 12 dB/octave) must be used and the high-pass filter should be set below 0.5 Hz (time constant >2 s; recommended 0.01 Hz). Ideally, digital recordings should be made with minimal filtering (as above) and additional filters applied post hoc. This enables the effect of the filtering step to be evaluated. In particular, the use of a notch filter (50 or 60 Hz) during recording should be avoided as it can potentially disguise an electrode problem, while the mains noise can be eliminated off-line at the data processing stage.

The electrode impedance (or resistance) should conventionally be maintained below 5 kΩ. However, modern amplifiers with high internal resistances are able to record at higher scalp impedances (e.g. without using conductive gel). Similarly, MRI compatible EEG caps have inbuilt safety resistors that set a minimum impedance of around 10 kΩ. In these cases, higher impedance is acceptable, but in all cases it is important to balance impedance across electrode sites. The preamplifier input impedance must be over 100 MΩ. As the rejection of cross-talk between channels is important for coherence or other measures of relationships between electrodes, a cross-talk rejection of at least 90 dB is required and better is recommended.

Comprehensible overviews on technical aspects related to the digital recording of EEG signals have been published elsewhere and provide additional insight on specific details [35–37].

Calibration

Recording accuracy (how far the sample varies from the 'true' signal value) is dependent upon system calibration. The calibration procedure is aimed at testing the performance of the entire hardware and must be carried out before each measurement. Calibration is also essential to achieve a reference potential of known voltage against the absolute amplitude of the recorded signals. To pick up possible time-dependent fluctuations of amplifiers, due to thermic effects for example, it is recommended to re-check the calibration at the end of each measurement session.

Nowadays, most EEG machines have internal hardware calibration and the procedure may be carried out

automatically. Verification is made that the same input signals (sine waves with known amplitude and frequency) applied to all channels are present with the same amplitude at the output of the amplifiers and are subsequently correctly transmitted to the A/D converter. If internal calibration is not available, then an external device should be used to generate stable test waves that are relayed through the electrode sockets.

Ideally, standardised calibration procedures should include sine waves of stable amplitude (e.g. 100 μV) at two different frequency ranges (e.g. at 1 and 10 Hz) whether internally generated or from an external source. Verification of the calibration signal should be performed with digital callipers utilising as long a duration of the calibration signal as possible (e.g. 1 min per frequency). Although no definitive data currently exist on the amount of tolerable deviation for pharmaco-EEG signals, a maximum acceptable variance of ±2% in signal amplitude at both frequencies is recommended. Between-channel differences suggest an amplifier imbalance and channels with >±2% variance should be eliminated from analysis.

Electrode Positions

While demonstration has been made in the past that it is possible to trace the effects of specific compounds with a limited number of electrodes (e.g. using the bipolar fronto-central and occipito-temporal derivations, F_z-C_z and O_z-T_6), it is no-longer state-of-the-art and inappropriate for advanced investigations. Instead, a configuration of 21 electrodes placed according to the international 10–20 system [38] is the recommended minimal electrode configuration. If additional EEG electrodes are used (e.g. for mapping or localisation studies), then the international extended 10–20 electrode placement system (also known as 10% system [39–41]) should be utilised. The nomenclature of the electrodes must follow these standards.

Many laboratories use electrode caps (as opposed to measuring individual electrode positions) for ease of application of dense electrode arrays. However, cap electrode positions only approximate the 10–20 locations and are rarely measured accurately. It is important to ensure that the electrode location does not deviate from the standard when using caps.

As a matter of principle, recording against one reference electrode is recommended (e.g. against C_z, A_1 and A_2) or the arithmetic mean of A_1 and A_2 [$(A_1 + A_2)/2$] (i.e. a mathematically generated 'linked-ear' or 'linked-mastoid' reference). Without resistors between them, two linked electrodes (e.g. A_1 with A_2) connect two brain regions, thereby changing the electrical potential distribution over the scalp. Hence, although the resulting distortion of potential may be negligible in many or even most cases [42], physically linking the electrodes is not recommended. A linked reference may also be problematic if the impedance of one or other electrode varies differentially during a recording (for example if one of the electrodes becomes dislodged). The data must be stored in a format permitting conversion from the recording reference to any other reference (common average reference, current source derivation or other channels as reference, for example). Active electrode systems can be used in pharmaco-EEG studies provided that active electrodes would not distort any frequency components in the frequency range 0.05–40 Hz.

In addition, EOG (electrooculography) must be recorded (vertical and horizontal, bipolar) to aid in identifying artefacts and to correct off line the interference captured in the EEG using appropriate data processing algorithms. The recording of both ECG (electrocardiography) for assessment of the activity of the autonomous nervous system and EMG (electromyography) as additional marker for vigilance stages or artefacts is recommended. The recording of other vital parameters, such as blood pressure and respiration, is optional.

Environmental Conditions

There are many environmental factors affecting the function and activity of the CNS and, as a result, also affecting neurophysiologic readouts of brain activity. It is therefore necessary to control these factors to the best possible extent. If deviations from normal, pre-existing or pre-defined conditions are observed, then these should be recorded as metadata. In clinical trials, it is mandatory to document the degree to which these factors have been used as inclusion and exclusion criteria.

Adaptation. EEG measurements are subject and sensitive to adaptation effects. Consequently, at least one pre-examination EEG recording (apart from the screening EEG) should ideally be performed on a separate day to carry out one (or several) blank or habituation measurement(s). Such a procedure allows the subject to become familiar with the environment, apparatus and recording protocol. When this additional subject visit is not feasible, then a period of acclimation should be included in the protocol on the study day itself before the actual recording session is started.

Room. The recording should occur in a separate, sound-attenuated room with constant light (approximately 40 lx), regulated temperature (20–23°C/68–73°F)

and normal humidity conditions. Intermittent disturbing events must be avoided. Random and undefined interactions between the subject and the staff during the recording (as for changing the electrode placement or posture, or giving additional instructions or stimulation) should be limited and documented. Typically, clinical neurophysiology studies are carried out with the subject sitting in a half-reclined position to reduce neck muscle tension and with constant dimmed light (approximately 40 lx) and this is recommended in many cases. However, these conditions are not amenable to the presentation of a task and so resting data acquired in this way will not be suitable for comparison with subsequent task-related recordings forming part of the same study. Hence in studies involving both resting and task-related recordings, it is recommended that resting recordings be made in a situation that exactly replicates the recording conditions to be used when engaged in tasks (i.e. the subjects should be comfortably seated in a suitably supportive high-backed chair in an upright position). The ambient light level should be maintained at a similar level during resting and task-related recordings.

Time of Recording. Recording periods should be completed at the same time of the day and under the same conditions. If possible, having documentation of a subject's wake and sleep history (e.g. around 1 week of consistent bed- and rise-time) is advisable to assist in recognising circadian influences on the EEG (subjects with highly disrupted sleep should be carefully evaluated and potentially excluded from the study). Whenever possible, the recording should preferably occur in the morning (between 9:00 and 13:00 h) to avoid interference with meal times and postprandial vigilance fluctuations. This aspect is to be taken into consideration for the design of studies with repeated measurements following drug intake (e.g. at baseline and 1, 2, 4 and 8 h after medication). Also the type of food (breakfast and lunch) must be carefully selected.

Recording Conditions
For the purpose of standardisation and to ensure that results obtained in one laboratory can be compared with results obtained in another, pharmaco-EEG studies should be recorded under one or more of the following conditions:

(1) Vigilance-controlled EEG for 5 min (RT). During this recording session, the subjects must have their eyes open and the vigilance level should be controlled by a simple continuous performance task (e.g. creating a story out of given words or solving simple arithmetic prob-

lems), which incorporates a fixation point to minimise eye movement artefacts. The purpose is to stabilise the vigilance to a relatively narrowly defined level by means of the continuous mental exercise. The EEG should be monitored online by an EEG technician and short external interventions for vigilance stimulation are permissible if a decrease in vigilance is observed, for instance in case of intrusion of slow-wave activity in the EEG. However, the EEG segments in which the interventions occurred are labelled as artefacts and are excluded from the evaluation.

(2) Resting EEG with closed eyes for 5 to 15 min (RS_C). During this session, the EEG is recorded with closed eyes and fluctuations of vigilance are permitted without any restriction, the purpose of this recording condition being to examine the variations in vigilance over time. It is essential that the instructions should be explicit, such as 'Sit quietly and keep your eyes closed; there is no task to complete, just relax!' Limited external interventions should take place during the session and used only when necessary to help maintain consistency of state (e.g. eyes opening). Drowsiness EEG patterns or falling asleep are not a reason to intervene. While sessions of 5 min yielding a minimum of 2-min artefact-free signal are sufficient to quantify EEG activity and demonstrate pharmacological effects on spectral parameters [43], the recording may be extended to 15 min to assess the regulation of vigilance ('CNS arousal') and wakefulness, and to quantify drug-induced changes in these parameters (e.g. sleepiness) [44].

(3) Resting EEG with open and closed eyes for 5 min in each eye state (RS_{co}). Recordings of this type employ alternate periods with eyes open and closed of 1-min duration each in response to commands from the technician. Subjects should face a featureless wall in order to standardise the visual environment and reduce the effect of eye movements on the EEG during periods with open eyes. No additional vigilance control procedure should be used; in particular, fixation is not recommended as this in itself constitutes a task. Data in each of the two states should be separated prior to processing and the EEG activity analysed separately for segments with open and closed eyes.

Important Comments:
- The task to be used during the vigilance-controlled condition has deliberately not been tightly defined in order to encompass the range of currently accepted practice. One particular variation is to use a visual performance task undertaken at a computer terminal,

which has the benefit of also providing a measure of performance whereby epochs surrounding stimulus presentation and motor response or outside preset limits of 'normal' reaction time can be excluded from the analysis. There are also other accepted procedures for maintaining vigilance during EEG recording, including the use of a device which is sensitive to muscle relaxation. However, it is important to note that the results cannot be readily compared when different tasks or vigilance control methods are used as systematic differences in both the topography and frequency composition of the resulting EEG signals are to be expected. Hence, the method used must always be clearly described alongside the results.

- Continuous video recording synchronised with the EEG is recommended.
- It may not be possible to fully adhere to the standard procedures in cases where patients are uncooperative or unable to follow instructions (e.g. psychotic or severely demented patients). Any deviations from the standard must be clearly stated alongside the presentation of the results.
- EEG recording should always take place prior to additional testing (e.g. cognitive paradigms), since vigilance might be decreased after exhausting or time-consuming tests.
- Since the brain activity indicated by the EEG depends strongly on the present level of vigilance [45], care has to be taken that drug effects on vigilance regulation (e.g. more rapid decline to lower vigilance stages with sedating drugs) are separated from drug effects on EEG activity within the same vigilance level (e.g. increase in α frequency).
- With measures such as connectivity, phase and coherence, there is evidence that more data are necessary to converge to stable, reliable estimates, and hence the recording duration for any of the conditions may be extended if required to meet the objectives of the study.

Artefacts

Artefact identification and elimination is crucial for the proper quantitative analysis of EEG records. With optimal recording conditions, artefacts are only accidental and appear infrequently. Artefacts can have various physiological origins (ocular, cardiac, muscular, behavioural, sweating and respiratory) and can be identified and/or eliminated either on line during the recording or off line. Special care should be taken in those studies where higher frequency bands (i.e. β and γ) are of interest since the EEG signals may be contaminated by muscle activity.

Automated EOG artefact rejection is possible using appropriate algorithms [46–48]. However, when computerised algorithms are used, a semi-automatic procedure that includes additional visual inspection is recommended. Even new approaches such as the independent component analysis (ICA) used for the detection of eye movement or muscle artefacts [49] should be applied with caution. The risk of excluding components with mixed neurophysiological information of brain activity and artefacts should be minimised by careful inspection of topographic maps of the components and by using an appropriate number of components (equal to the number of channels of the input matrix).

Should the investigator doubt the validity of the procedure either because of the large percentage of EEG segments containing artefacts or because the kind of artefacts could be confused with the treatment effect, then a comparative biometrical evaluation and assessment of the artefact-free and complete data should follow.

Minimum Requirements

Table 2 summarises the minimum requirements for the recording of pharmaco-EEG studies.

Pharmaco-EEG – Data Processing

Representation in the Time Domain

In the time domain, the variations in potential after amplification are displayed as a function of time and signals are usually denoted by a function $s(t)$ [or $s(k\,T_S)$ (with $k = 1…N$) in its digital form]. The representation in the time domain is used for the visual inspection of EEG curves and for the evaluation of EEG activity resulting from external sensory stimulation for which the position in time is relative to the time point at which a stimulus occurs. Thus, time is considered as a variable of the observed phenomenon. The detection of patterns or transient activities in the EEG usually relies on processing algorithms operating in the time domain.

Representation in the Frequency Domain

The transformation of a signal $s(t)$ into the frequency domain using the fast Fourier transformation (FFT) implicitly assumes that $s(t)$ can be split up as a finite sum of weighted sinusoidal waveforms [denoted as $s(f)$]. The number of sinusoidal waveforms is dependent upon the window size (i.e. the number of points of the input signal) subjected to FFT. The resulting graphical representation displays the spectral characteristics of $s(t)$, which is then

Table 2. Minimum requirements for the recording of pharmaco-EEG studies

EEG recording equipment	Sampling rate	≥500 Hz
	A/D conversion	≥16 bits
	High-pass filtering	≤0.5 Hz (0.01 Hz recommended)
	Low-pass filtering	70 Hz (roll-off of at least 12 dB/octave)
	Notch filter	Usage avoided; otherwise 50 or 60 Hz (dependent on the power supply frequency)
	Pre-amplifier impedance	≥100 MΩ at 50 Hz
	Common mode rejection	≥90 dB
Electrodes	Electrode impedance	Balanced impedance across all electrode sites
	Number and placement	At least 21 electrodes placed according to the 10–20 system or the extended 10–20 system (10% system) in case >21 electrodes are used
	Type	Ag/AgCl or equivalent in terms of electrode drift and DC resistance
	Montage	Monopolar against a common reference
	Reference	Should be modifiable post hoc, (C_z, A_1, A_2, average mastoids)
	Ground	AF_z
	EOG	Vertical and horizontal for artefact identification
	ECG	Recommended
	EMG	Recommended
Experimental design and conditions	Adaptation	It is recommended to make the subject familiar with the recording conditions and procedures during a separate recording session
	Recording environment	Sound-attenuated room Constant dimmed light (approximately 40 lx) or light level defined by the computer monitor used for task presentation Constant room temperature: 20–23°C (68–73°F) Any major disturbances should be logged Subject in a (semi-)reclined comfortable position or in an upright position facing a computer monitor (for studies that also include a task)
	Design	Double-blind placebo-controlled cross-over design is recommended for acute studies in healthy subjects For multiple dose and patient studies, the design should be adapted according to the objectives
	Recording time points	Baseline and a number of post-drug recording time points to be driven by drug PK; at least one time point around T_{max} plus at least 3 time points covering the decline in the PK curve (usually multiples – e.g. 1, 2, 4 and 8 h) If T_{half} ≥12 h, then a 24-hour overnight time point should be considered
	Time of day	Preferably in the morning Cross-over repeat tests should be done at the same clock time and under the same conditions
	Recording conditions	RT (5 min vigilance controlled, eyes open) RS_c (5- to 15-min resting condition, eyes closed) RS_{co} (10-min resting with alternate eyes open and eyes closed)
Storage conditions	Local storage	The proprietary format of each EEG recording equipment
	Export/import format	European data format 'plus' [see ref. 50 for details]
	Signals	Raw data without transformation Automatic artefact rejection is optional

Table 3. Frequency ranges for spectral analysis in pharmaco-EEG studies

Nomenclature	Frequency range Hz	Units of the results
δ^F	1.5 to <6.0	µV/Hz
θ^F	6.0 to <8.5	µV/Hz
α_1^F	8.5 to <10.5	µV/Hz
α_2^F	10.5 to <12.5	µV/Hz
β_1^F	12.5 to <18.5	µV/Hz
β_2^F	18.5 to <21.0	µV/Hz
β_3^F	21.0 to <30.0	µV/Hz
Total power	1.5 to <30.0	µV/Hz
γ	30.0 to <40.0	µV/Hz
Dominant frequency	6.0 to <12.5	Hz
ASI	$\dfrac{\alpha_1^F + \alpha_2^F}{\delta^F + \theta^F}$	%
TBR	$\dfrac{\theta^F}{\beta_1^F + \beta_2^F}$	%

The α slow-wave index (ASI) is defined as the ratio between α activity and the sum of the activity in the δ and θ frequency ranges [54]. The θ/β ratio (TBR) expresses the ratio between θ activity and the activity in the two β frequency ranges. The γ band was included at a later stage and definition of additional frequency ranges >40.0 Hz is the subject of further work [see the section on High-Frequency (γ) EEG Activity].
[F] Refers to the factorial analysis used to define the ranges between 1.5 and 30.0 Hz.

depicted by peaks in the frequency domain. This kind of display is generally used for the evaluation of spontaneous EEG activity for which the position in time of events has no direct relevance.

The FFT (as an orthogonal transformation) is essentially a mathematical operation performed on time series data which does not alter the information content of the signal. Neither is any assumption made regarding the nature of the data nor any interpretation implied. Within the limitations of computational accuracy, the full reversibility of the transformation is implicit and given only as long as numbers are retained in their complex form and not averaged.

The resolution in the frequency domain depends upon the sampling frequency (F_S) and the number (N) of sampling points (size of the signal window) subjected to FFT. This resolution (denoted here as ΔF) is given by the ratio ($\Delta F = F_S/N$). Accordingly, the longer the signal window (N), the better the resolution of the frequency content.

When considering the results of an FFT applied to a signal window of N = 2,048 points (a number chosen because it corresponds to 2^{11} and facilitates a rounded-off length) with $F_S = 512$ Hz, then $\Delta F = 0.25$ Hz, which means that the frequency analysis can resolve 0.25 Hz (that is resolve 10.25 vs. 10.50 Hz directly). In this particular case, the signal window (called epoch) will have a length of 4 s.

To reduce the broadband artefact, known as leakage, the signal window must be tapered toward zero at their initial and final data points (this tapering is usually done using a windowing function). When the FFT is applied on sequential epochs, then discarding a proportion of the signal through windowing can lead to differences in spectra depending on the starting point of the epoch series. An alternative that results in a spectrum less sensitive to the starting point is to use partially overlapping epochs so that all data are represented.

Although computer-based analysis of scalp-recorded signals for pharmaco-EEG profiling has utilised a wide range of quantitative techniques, spectral analysis via FFT is currently the most common method of choice for the parameterisation of pharmaco-EEG studies.

Non-Stationarity
Many signals, including EEG, are non-stationary, which means that they have a time-varying frequency spectrum, although they can be considered locally stationary over short segments in which the parameters of interest vary minimally.

In practice, the choice of the segment length is a trade-off between frequency resolution (which suggests a longer epoch) and ensuring quasi-stationarity (which suggests a shorter epoch). For the pharmaco-EEG, epochs of 2- to 10-second duration are used.

Spectral Analysis
The traditional parameterisation of pharmaco-EEG activity is largely based on spectral analysis. To this end, the recorded signals are divided into epochs (2–10 s) which are subjected to spectral analysis using FFT. This transformation in the frequency domain and subsequent computation of the power spectrum allows a first data reduction.

The second step of data reduction consists in the extraction of spectral parameters. The frequency range is subdivided into frequency bands, and the spectral performance (area under the curve) is computed for each of them (expressed in µV/Hz; square root of absolute power) or using another transformation (e.g. the natural logarithm of ab-

solute power) to better meet the assumption of normal distribution [51–53]. The transformation should preferably be carried out prior to any other manipulations, such as averaging spectral parameters across several epochs.

Table 3 provides a summary of the frequency ranges to be used in pharmaco-EEG studies. These frequency bands were defined on the basis of factorial analysis of EEG records [55–57] and thereby constitute a very robust framework. It does not mean that other frequency ranges shall not be used for specific purposes [58]. However, to ensure that the results of a study can be compared with others published and therefore can provide useful reference material for other scientists, publications should always report the results obtained for this standard configuration (beside others if appropriate).

Absolute spectral EEG values are recommended as the primary outcome measures (endpoints) in the pharmaco-EEG profiling. Test-retest reliability investigations have shown that intra-individual EEG spectral measures can be treated as a stable trait [59]. Additional computed spectral parameters, such as relative values in frequency ranges, dominant frequency in the α and β frequency bands, peak skewness (asymmetry coefficient), peak kurtosis (peak shape) and the activity ratio between different frequency bands, should be interpreted in the light of absolute values [60]. These derived parameters may provide additional insight for the interpretation of the data.

Pharmaco-EEG Brain Mapping
Multichannel topography ('mapping') is widely used to display activity simultaneously recorded from several electrodes. Pharmaco-EEG brain mapping is suited to assess the topographical changes induced by CNS-active compounds. Usually, the topographical distribution of spectral parameters and error probabilities (probability mapping) are displayed [22, 61, 62]. Time-dependent changes of EEG activity can be investigated as a function of the recording condition or by analysing segments of records (e.g. for the evaluation of vigilance fluctuations).

Several authors have pointed out limitations and difficulties of the mapping technique which are related to reference problems, the influence of spatial artefacts and the clinical interpretation of mapping data. In particular, spectral brain maps derived from single electrode references have the disadvantage of being substantially distorted near the common reference site and are likely to be misinterpreted. This problem can be partially avoided by using reference-free derivations (e.g. spatial average references or current source density derivations; the latter is generally preferred) [63– 65].

The main advantage of mapping lies in its ability to easily visualise the spatial relationships of EEG data among the scalp recording sites, but it must be remembered that the majority (~99%) of the pixels displayed on the oval or circle may represent interpolated values, unlike the CT or MRI structural images upon which they are often overlaid, where 100% of the pixels display real data values resulting in a spatial resolution of several orders of magnitude greater than that of EEG topographic maps [22]. Advanced interpolation algorithms have been developed to improve the graphical representation of maps and the error made by properly chosen algorithms is usually small [66]. Lack of information about electrical activity at locations not covered with EEG electrodes needs to be taken into account as low spatial sampling may lead to spatial aliasing. This problem cannot be solved by interpolating spatially under-sampled data, rather by increasing the number of EEG electrodes that would offer comparatively short (e.g. 3–5 cm) inter-electrode distances. Last, investigators must be sensitive to the fact that vivid colour differences can draw their attention but may represent only subtle differences in data. To minimise such effects, it is suggested that colour coding of images should be based upon statistical probabilities, clearly indicated in the colour scale or legend provided with the maps.

In the case of coherence assessment, coherence should only be measured for data that have been re-referenced so that no pairs of electrodes tested for coherence share an electrode in common. Further, when comparing coherence in different conditions, the same number of trials should be used to calculate coherence in each condition.

For technical details on EEG brain mapping refer to the abundant literature and review papers published to date. Guidelines for the topographic analysis of EEGs and EPs have been published by the International Federation of Clinical Neurophysiology [63] and recommendations for evaluations in the context of pharmacological studies have been published by the IPEG [67].

Data Processing Strategies
In principle, the selection of trial design, recording conditions and duration, number of measurement points and approach for data analysis are dependent upon the ultimate objectives of the study. Consequently, the strategy selected for the EEG signal processing is to be adapted to each specific configuration. As the analysis can be very versatile, it is therefore not possible to define strict guidelines. Nevertheless, it is useful to provide some guidance on the strategies suitable for the processing of pharmaco-EEG records.
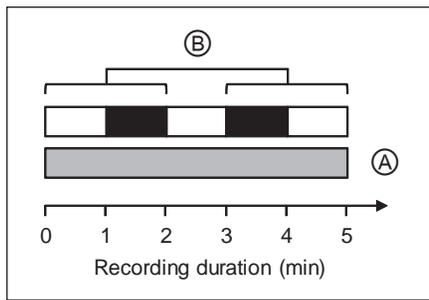
Fig. 1. Processing of 5 min EEG recorded under RT or RS_c conditions. Spectral activity is analysed over 5 min (A). A comparison of spectral activity for the segments at the beginning and the end of the recording (B) can be applied to capture time-dependent changes.

In the following and for the purpose of example, it will be assumed that the EEG signals are recorded with a sampling frequency of 500 Hz (F_S) and that the spectral parameters are computed for epochs of 4-second length (i.e. 2,000 samples), whereby the FFT are computed based on 2,048 (2^{11}) points, with the individual overlapping epochs being tapered digitally toward zero voltage at their initial and final 24 data points. This way, 1 min of EEG recording will produce 15 power spectra, each 4-second epoch providing a set of spectral parameters (table 3).

Considering an EEG signal recorded for 5 min under RT or under RS_c conditions, the 5-min recording is first divided into 75 epochs; artefact-marked epochs are eliminated, and the sets of spectral parameters are calculated. Then, the strategy for data processing involves two steps (fig. 1):

(1) For each spectral parameter, the activity over 5 min is quantified using the sample mean and its standard deviation (the median and its quartiles or the trimean can also be used). This procedure is straightforward and provides for each measurement point and each EEG channel a set of spectral values that can be compared with others. The main drawback of this approach lies in the fact that it does not allow changes that may occur during the 5-min recording to be captured [43], e.g. as a result of a sedative effect. This problem can be addressed by proceeding with a subsequent complementary assessment.

(2) The spectral activity at the beginning and at the end of the recording are quantified separately and the results compared. This assessment is particularly useful to verify the stability of the recording condition (as expected for RT) or to detect time-dependent changes (especially for RS_c).

Typically, the duration of the recording under RS_c is extended to up to around 15 min to assess the dynamics of vigilance fluctuations. In this case, the vigilance regulation can be explored and vigilance levels assessed over the whole duration of the recording session, from relaxed wakefulness to sleep onset [68–70]. When focusing on spectral activities only, the recording can be decomposed into segments of equal length (e.g. 3 min) and the spectral parameters quantified for each segment (fig. 2) using the sample mean and standard deviation or other suitable parameters as described above, following the elimination of epochs containing artefacts. Then, the results obtained for the segments at the beginning, the middle and the end of the recording can be compared to capture time-dependent changes.

The processing of EEG signals recorded in the resting state with alternate periods of RS_{co} requires separating the epochs corresponding to the respective eye states (fig. 3). Off-line treatment of EOG (blink) events occurring in the open-eye segments is mandatory and requires particular attention (e.g. using ICA or similar filtering techniques). Then, the spectral parameters can be quantified for each eye state separately using the same method as for the RT and RS_c recording conditions (fig. 1). Also, in this case, it is useful to verify the stability of the recording through assessment of any time-dependent changes.

In pharmacological trials aimed at assessing the effect of compounds on the CNS and on the EEG in particular, the study design as well as the selected recording conditions and related processing strategies will be dependent upon the profile of the compound under examination, whereby the hypotheses and targeted parameters will be defined upfront. Exploratory evaluations, however, may require more flexibility, especially when the potential effects are unknown. When documented and justified, the recording duration and the strategy selected for data processing can be adjusted if specifically needed for a particular study. However, such deviations may impede the ability to compare results with other studies.

Pharmaco-EEG – Statistical Analysis

The present guideline paper is not intended to discuss the statistical aspects of the design and analysis of pharmaco-EEG studies and especially of PD studies. To this end, reference is made to the corresponding IPEG guidelines [71], which provide a set of recommendations for the investigation of the PD characteristics of a compound
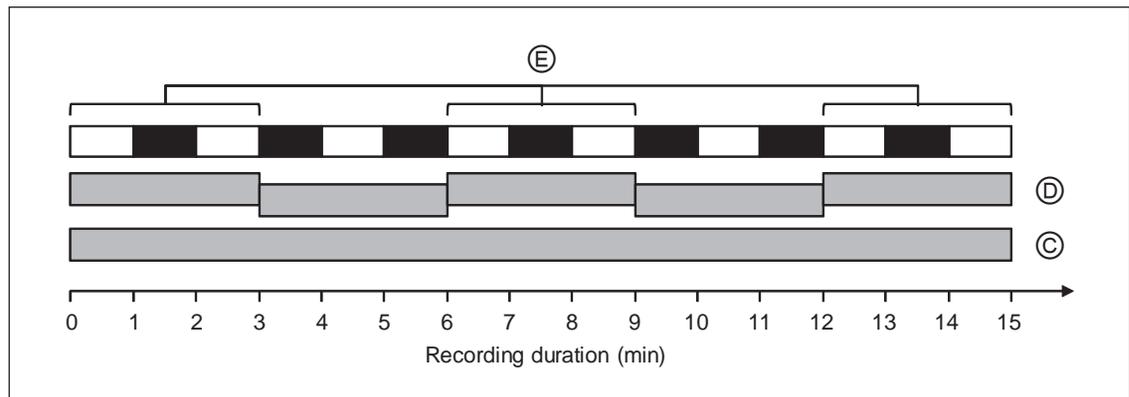
Fig. 2. Processing of 15 min EEG recorded under RS_c. The variations in spectral activity can be analysed over 15 min (C) or over consecutive segments (D). A comparison of spectral activity for segments of 3 min at the beginning, middle and end of the recording can be applied to capture time-dependent changes (E).
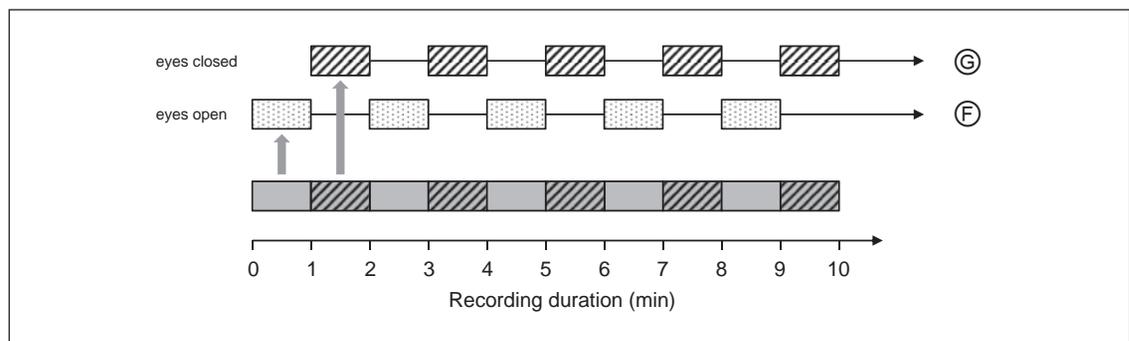
Fig. 3. Processing of 10 min EEG recorded under RS_{co}. During the recording session, the subject alternates between states with eyes open and closed every 60 s. The spectral activity is analysed over the 5 segments corresponding to (F) and (G) recording periods with eyes open and closed.

(e.g. time or dose effects) in the early phases of clinical drug development.

In summary, the key factors to consider during the planning include, but are not limited to, the suitable type of study design, the determination of the sample size and the randomisation. In PD studies, the investigator must address the problem of 'multiplicity' of tests resulting from a profusion of parameters (i.e. inferential statistical statements) to which a statistical comparison is applied. Further, the computation of a large number of statistical tests in a given sample may lead to false conclusions and must be used carefully [72]. In a paper published in 1987, Abt [73] distinguishes three levels of statistical approach based on probability computations: exploratory, descriptive and confirmatory statistical analyses. The descriptive data analysis suggests inspection of changes by studying the pattern of descriptive p values assessed for all pairwise tests for differences in time or treatment. This approach is particularly useful for the evaluation of topographical changes [74]. Valid alternatives to this method include randomisation and non-parametric permutation analyses, which are used in brain imaging studies [75, 76], including EEG source imaging.

Sources of multiplicity are several variables, time points and locations of measurement/observation, and comparisons of more than two treatments or different galenic formulations. Moreover, pharmaco-EEG profiles may also be examined in relation to behavioural changes assessed with rating scales, neuropsychological evaluations and computerised cognitive tests.

Whilst univariate models generally compare individual variables of between-group or within-subject datasets, multivariate statistics assess multiple factors to create discriminants. Some methods utilise linear combinations of EEG measures with other clinical, cognitive and affective ratings (neurometric analysis [77]). Methods based on EEG measures alone are less well developed but show future promise [78], and this field is advancing rapidly, driven mainly by the use of such techniques in functional MRI (fMRI).

Finally, it should be noted that careful modelling and precise correlation with independent parameters, such as PK factors, hormonal profile or metabolic status, are often needed to determine the particular electrophysiological change induced by a neuroactive drug, due to the inherent non-specificity of the electrophysiological effects [79].

Due to the complexity of most statistical analyses required for the evaluation of pharmaco-EEG studies, the assistance of an experienced statistician is highly recommended.

Use of Normative Databases

While not always available, when appropriate normative data exist [80], the data collected should be subjected to comparisons (e.g. z-transformation) with a normative data sample. The power spectrum of the EEG is extremely stable and highly replicable, distinctive for each brain region in a healthy, normally functioning individual, and is generally independent of cultural, ethnic or racial factors. Therefore, this predictable, known power spectrum can be used as a normative baseline that specifies the expected electrical activity of the healthy, normally functioning human brain across the human lifespan. Deviations from these norms can be described as standard scores, providing a reliable and objective metric for abnormalities of brain electrical activity [81–83].

Pharmaco-EEG – Advanced Topics

EEG Source Localisation

The ability to display the time course and localisation of brain activity based on extracranial measurements requires a mathematical solution to the inverse problem for the computation of images of electric neuronal activity based on the EEG signals recorded from the electrodes. In general, there is no unique solution to this problem. Inverse solutions critically depend on many a priori assumptions, including head models, solution spaces, regularisation parameters, the specific assumption on current density distribution and procedures used for statistical mapping (like normalisation or log transformation) and statistical thresholds. All these factors have a significant impact on the results that may vary drastically depending on the choices made and it is usually impossible to validate the correctness of the choices independently. Consequently, it is therefore absolutely necessary that all of these parameters and choices are fully presented and that the implications of the choices are explicitly discussed.

LORETA (low resolution electromagnetic tomography) provides 3-dimensional functional imaging of brain electrical activity based on multichannel surface EEG recording without a priori knowledge about the putative number of discernible source regions [84, 85]. It is important to notice that a reliable estimation of EEG sources depends upon the usage of a sufficient number of electrodes (at least 19) which are equally distributed. The spatial resolution is limited by the distances between electrodes in the input matrix and by the assumption of smoothness. LORETA can be used to locate the most probable cortical and subcortical sources for different frequency bands, and the time resolution of the EEG data can be exploited for functional mapping of brain activities, whereby the solution space is restricted to cortical grey matter. Finally, LORETA images can also be computed relative to normative voxel values, allowing sources to be evaluated as the deviation from age-expected norms.

The empirical validity of LORETA has been established in a large number of studies [86] covering various EEG research fields, such as psychiatry [87, 88], neurology [89, 90], neuropsychopharmacology [91] and sleep medicine [92]. Further, the co-registration of LORETA with other neuroimaging methods has shown good correspondence of effects [93, 94]. More recently, LORETA has been used to evaluate interactive functional dynamic connectivity in the brain, quantified by coherence and phase synchronization [95].

Despite the limitations of inherently low resolution and the need for a priori assumptions, source localisation techniques represent important advances in the utility of QEEG that are a useful addition to other available functional neuroimaging techniques, and EEG-based methods provide direct information on neuronal activity with high temporal but low spatial resolution. In contrast, fMRI has high spatial resolution but low temporal resolution that is confounded by the haemodynamic response function. Magneto-encephalography combines high spatial and temporal resolution with a direct measure of activity but is less well established and not readily available. Also, it is sensitive to tangential and insensitive to radial

sources, whereas EEG is most sensitive to radial sources, so the techniques may provide different but complementary information on brain activity [96].

Cordance

Cordance is a QEEG analysis procedure that combines complementary information from both absolute and relative power from the EEG spectrum, as well as information from neighbouring electrodes for each scalp electrode [97]. It has been reported to have a stronger correlation with cerebral perfusion as measured by positron emission tomography (PET) than either absolute or relative power alone [98], potentially providing a physiologic framework for the interpretation of findings.

Cordance has been used to assess neurophysiological changes and treatment outcomes in major depression [99] and to predict the response of treatments in patients with major depressive disorder [100–102] or bipolar depression [103]. Across studies of patients with major depressive disorder treated with various antidepressant medications, decreases in prefrontal θ cordance 1 week after the start of medication have consistently predicted response, with overall accuracy ranging from 72 to 88%. Examination of this measure in one randomized, double-blind, placebo-controlled trial has suggested it may be a specific indicator of medication efficacy but not placebo efficacy [104].

High-Frequency (γ) EEG Activity

Over recent years, there has been considerably increased interest in EEG activities in the frequency domain above 40 Hz. Prior to 2007, attempts to extract EEG activity in the γ band used traditional analysis methods. However, in 2007, Whitham et al. [105] demonstrated that a considerable proportion of the γ signal extracted in this way disappeared with temporary muscle paralysis. Subsequently, Yuval-Greenberg et al. [106] and Keren et al. [107] showed that most of the power in the widely reported induced broad-band γ peak at 200–300 ms after a visual stimulus did not originate in the brain and was in fact due to extra-ocular muscle activity during microsaccades.

Subsequently, methods have been developed to deal with these tonic scalp and neck muscle and extra-ocular muscle artefacts, hence enabling the true underlying EEG signal to be extracted [107–109]. These techniques require recording specifications that exceed those specified above, including in particular:

- Increased sampling rate (2–5 kHz)
- Higher low-pass filter cut-off (500–1,000 Hz)

- Improved amplitude resolution (0.1 μV or below)
- Additional EOG electrodes to record fully the extra-ocular muscle activity
- Additional electrodes to record exogenous noise (e.g. power-line noise) for regression-based artefact reduction

Enhanced signal processing techniques are also needed, such as:

- Shorter epoch lengths (typically 512 or 256 ms) to maintain the stationarity assumption of the FFT
- ICA- or regression-based methods for removal of exogenous artefacts (e.g. power-line noise or pick-up from computer monitors) that would be removed by the low-pass filter in traditional recordings
- ICA-, regression- or model-based methods for removal of tonic scalp and neck muscle and extra-ocular muscle artefacts.

This is an area of research in which techniques are developing rapidly and there is insufficient evidence at present to determine the optimal recording and analysis techniques for high-frequency EEG. However, it is clear that the choice of method will quantitatively change the results. Therefore, in studies including high-frequency EEG, full details of the recording specification and analysis techniques used, especially in relation to the artefacts discussed above, must be reported such that other laboratories can replicate, and potentially improve upon, the results, so the field can continue to advance.

In addition, the factor analysis used to define the frequency ranges presented in table 3 did not include coverage of frequencies above 40 Hz. Hence, until a formal factor analysis is undertaken to include the high γ frequency range, it is important that studies clearly report the frequency bands that have been used. In the absence of any other information, the following empirically chosen frequency ranges are suggested as a starting point for investigators: 30 to <65 ($γ_1$), 65 to <90 ($γ_2$), and 90 to <135 Hz ($γ_3$) [110, 111].

EEG Biomarkers and Translational Medicine

Within the context of drug discovery, the definitions of a biomarker, clinical endpoint and surrogate endpoint have been formalised by the Biomarkers Definitions Working Group [112]: A biomarker is 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention', whereas a surrogate endpoint is 'a biomarker that is intended to substitute for a clinical endpoint'. Put differently, a biomarker is an objectively measured index of

pharmacological response (or biological process) that is quantifiable, precise and reproducible. Biomarkers may be used to diagnose or stage disease processes or predict clinical responses to treatments [113]. In the future, implementation of panels of relevant biomarkers may well transform the process of development of new drugs [114].

In the simplest case, EEG can be used as a PD biomarker reflecting brain activity in healthy subjects without reference to a specific therapeutic indication. PK-PD modelling can thus be undertaken in different species using a similar outcome measure, hence enabling cross-species comparisons of the effects of a drug [115, 116].

While EEG has a long history of evaluation in various diseases of the CNS, evidence is only recently accruing of its putative validity as a useful and reliable biomarker for several therapeutic indications [14]. Recent reviews have, for instance, focussed on promising results indicating the relevance of QEEG as a reliable and sensitive biomarker in many areas, including:

- Prediction of antidepressant response [104]
- Early detection of mild cognitive impairment and Alzheimer's disease [117, 118]
- Application in major neuropathophysiological disorders [119]
- Characterisation of sleep disturbances in depression [120]
- Assessment of vigilance in affective disorders [121]
- As a marker of genetic risk for attention deficit hyperactivity disorder [122]
- As a biomarker for localizing epileptogenic foci in the brain [123]

In addition there is an increasing interest in the use of ERP biomarkers for characterisation of, for example, the cognitive disturbances in schizophrenia [124] or clinical depression [125].

Another important aspect concerns the translatability of pharmaco-EEG signatures for the preclinical screening and the development of CNS-active compounds. The goal of translational medicine applied to QEEG is to bring brain research from bench to bed and back. There are already several examples of successful contribution of preclinical EEG-based models in the discovery of psychoactive drugs [14, 126, 127]. These EEG models in animals have shown promise in improving the understanding of disease mechanisms and therapeutics (e.g. identification of central effects at a functional level and characterisation of central effects depending on the psychoactive class or therapeutic indication) or in studying the relationship between animal behaviour and EEG activity [128]. Recent papers have further shown the validity of EEG as putative translatable biomarker in depression [129] and Alzheimer's disease [130].

The major strength of using EEG in translational medicine is that most EEG parameters can be measured in a similar way in various animal species and human subjects, using broadly similar paradigms, recording techniques and signal processing algorithms: these similarities not only reflect face validity but also considerable construct validity. As similar QEEG methodology is applicable in different species, it has the potential to bridge the gap between preclinical and clinical research. However, the lack of reliable translational procedures applicable to both patients and experimental animal models is an obstacle for the advancement of basic research, the determination of the translational validity of the technology and ultimately the development of new compounds [131] for three main reasons:

(1) Lack of standardisation of animal EEG methodology (e.g. low lead density)
(2) Lack of specific guidelines on animal QEEG and pharmaco-sleep EEG recording
(3) Lack of valid animal models for psychiatric diseases.

In this context, it becomes crucial that efforts are made in the standardisation of experimental conditions and in the development of protocols facilitating the comparison of data collected in both humans and animals. Such a concerted harmonisation would also offer the potential to quickly acquire large databases that could be shared between research groups and hence enable a fuller study and understanding of translatability, including:

- Equivalence of electrode specifications, positioning and montage across species including man
- Equivalence of preclinical and clinical paradigms, such as vigilance control for example
- Equivalence of spectral bands in different species (both numerically and in terms of species physiology)
- Differences between human scalp EEG recordings and preclinical cortical recordings (including understanding differences between gyrencephalics and lissencephalics)
- Equivalence and differences of underlying neurological processes and drug effects in different species and strains (from mice to primates)

Specific guidelines for preclinical, animal pharmaco-EEG recording and analysis are in preparation for publication by IPEG. Together with the present guidelines for studies in man, these will address several of the above issues and hence should further contribute to optimisation of the translational value of QEEG.

Conclusion

QEEG and related methods have the potential to offer reliable biomarkers and will, in view of the recent developments in QEEG technology, play an increasingly important role in all phases of drug development. The evaluation and quantification of drug effects in pharmaco-EEG, sleep and EP/ERP studies provide a set of methods to capture the therapeutic benefits and the potential adverse effects that a drug induces in diverse patient populations. By combining various methods and their respective strengths, it is reasonable to argue that they will provide a more complete characterisation of the spectrum of pharmacologic CNS responses [132].

In this context, it is mandatory to enhance and standardise methodology and facilitate comparability of data across laboratories both in academia and in industry. To this end, investigators using pharmaco-EEG are urged to refer to and comply with the guidelines presented here when designing and conducting studies, and to reference the present paper when publishing study results.

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