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Review

Aligning strategies for using EEG as a surrogate biomarker: A review of preclinical and clinical research

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ABSTRACT

Electroencephalography (EEG) and related methodologies offer the promise of predicting the likelihood that novel therapies and compounds will exhibit clinical efficacy early in preclinical development. These analyses, including quantitative EEG (e.g. brain mapping) and evoked/event-related potentials (EP/ERP), can provide a physiological endpoint that may be used to facilitate drug discovery, optimize lead or candidate compound selection, as well as afford patient stratification and Go/No-Go decisions in clinical trials. Currently, the degree to which these different methodologies hold promise for translatability between preclinical models and the clinic have not been well summarized. To address this need, we review well-established and emerging EEG analytic approaches that are currently being integrated into drug discovery programs throughout preclinical development and clinical research. Furthermore, we present the use of EEG in the drug development process in the context of a number of major central nervous system disorders including Alzheimer's disease, schizophrenia, depression, attention deficit hyperactivity disorder, and pain. Lastly, we discuss the requirements necessary to consider EEG technologies as a biomarker. Many of these analyses show considerable translatability between species and are used to predict clinical efficacy from preclinical data. Nonetheless, the next challenge faced is the selection and validation of EEG endpoints that provide a set of robust and translatable biomarkers bridging preclinical and clinical programs.

Contents

Abbreviations: 5HT, 5-hydroxytryptamine: Serotonin; Aβ (Abeta), Amyloid Beta peptide; APP, Amyloid Precursor Protein; AD, Alzheimer's disease; AEP, auditory evoked potential; ASA, acetylsalicylic acid; ADAS-cog, Alzheimer's disease assessment scale (cognitive part); ADHD, attention deficit hyperactivity disorder; B1, bradykinin-1 receptor; Bf-S, Befindlichkeits-Skala; CGI-S, clinical global impression-severity; CNS, central nervous system; ECoG, electrocorticograph; EEG, electroencephalography; EP, evoked potential; ERP, event-related potential; HV, healthy volunteers; LCMV, linearly constrained minimum variance; LDAEP, loudness dependent auditory evoked potential; LORETA, low resolution brain electromagnetic tomography; LSEP, laser-evoked somatosensory evoked potentials; MADRS, Montgomery-Åsberg depression rating scale; MAOI, monoamine oxidase inhibitors; MCI, mild cognitive impairment; MDD, major (clinical) depressive disorder; MMSE, mini mental state examination; MPH, methylphenidate; MUSIC, multiple signal classification; NK1, neurokinin-1; NMDA, N-methyl-D-aspartic acid glutamate receptor subtype; NREM, non-rapid eye movement; NSAIDs, non-steroidal anti-inflammatory drug; PANSS, positive and negative syndrome scale; PS1, presinillin-1; PSAPP, presinillin/amyloid precursor protein; qEEG, quantitative EEG; REM, rapid eye movement; SCL-90, symptom checklist-90; SEP, sensory evoked potential; SSEP, somatosensory evoked potential; tEEG, translational EEG; VAS, visual analogue scale; VEP, visual evoked potential.

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1. Introduction

Over the last decade, electroencephalography (EEG) methodologies have emerged in preclinical and clinical research programs of pharmaceutical companies as useful tools for screening and development of novel therapeutics. For example, EEG is a well recognized methodology in safety pharmacology programs to measure adverse central nervous system (CNS) effects such as pro-convulsant risk and tolerance liability of experimental compounds [1,2]. Within drug development programs, EEG measures are now being used to provide evidence of CNS penetration, target engagement, and to determine pharmacokinetic and pharmacodynamic (PK/PD) properties of experimental compounds. EEG measures may also contribute to knowledge necessary to gauge mechanism of action and drive decisions for lead optimization or candidate selection. Clinically, EEG measures offer promise for patient stratification and predicting disease status. Additionally, EEG methodologies and analyses are generally straightforward and easily implementable in both clinical and preclinical settings. EEG and its analytic endpoints promise to provide surrogate measures of drug efficacy as well as have the potential to predict the impact of development compounds on endophenotypes associated with the disease process. Ultimately, these approaches may provide a high degree of predictability of therapeutic efficacy in the clinic. Yet, the degree to which EEG methodologies and analyses are useful as biological markers of drug action remains under debate. Importantly, a number of EEG biomarker candidates are readily used and have demonstrated the ability to translate preclinical findings into clinical observations. In summary, finding biomarkers that are predictive, translational, and are accessible both preclinically and clinically is a critical step in development of novel therapeutics that could have significant impact on early cost–benefit decision making of compound development, reducing economic burden on the health-care system, and improving patient quality of life [3–6].

2. Definition of a biomarker

The definitions of a biomarker, clinical endpoint, and surrogate endpoint have been formalized by the "Biomarkers Definitions Working Group" within the context of drug discovery [7,8]. A biomarker is an objectively measured index of pharmacological response or biological process that is quantifiable, precise, and reproducible. This biomarker may be used to diagnose or stage a disease process or predict a clinical response to treatment [9]. When used as a substitute for a clinical endpoint, a biomarker may be elevated to the status of a surrogate biomarker.

In drug discovery, a number of preclinical models are used to screen compounds under development. Ideally, these models meet the definition of a biomarker and indicate normal biological or pathological processes or a response to therapeutic intervention [7]. Moreover, the biomarker should reflect a critical path between compound-target engagement and its impact on disease processes, demonstrating that a measurement observed preclinically will predict, or translate to, therapeutic efficacy in the clinic. Preclinical CNS biomarkers employed to develop therapeutics are generally not used as surrogate biomarkers. Indeed, actual clinical endpoints have remained the standard for evaluating efficacy and safety of novel therapeutics in the prevention or treatment of these diseases. Current animal models provide a solid foundation for the discovery and early characterization of new drug candidates. However, ultimately these models need to be used in combination with well-validated and translatable biomarkers to allow a robust translation of preclinical observations into early clinical development.

3. EEG has characteristics of a biomarker

The history of recording EEG activity extends across a time line dating back to Galvani's experiments in 1791 with "animal electricity" [10,11]. Since then, important landmarks have included Richard Caton's observations of "continuous spontaneous electrical activity" and sensory evoked responses [12]. Additionally, work by Hans Berger with human scalp recordings were essential in the evolution of EEG methods, during which the term "Elektrenkephalogramm" was established [13–15]. EEG recordings of electrical activity of the human brain are traditionally acquired with non-invasive electrodes placed on the scalp. In animal models, electrocorticograph (ECoG) recordings are most frequently used where electrodes are placed on or below the dura or directly within the cortex. These recordings reflect the gross electrical activity emanating from synaptic currents of individual neurons across large cortical areas. Given similarities in brain structure and conserved neurobiological systems across the phylogenetic mammalian hierarchy, it is reasonable that measures of cortical activity within the brain are generally translatable across species. The acronym EEG will be used to indicate both ECoG and EEG for the remainder of this article, although it is recognized that subtle differences do exist between data obtained from each of these methods.

The EEG exhibits a spectrum of oscillation frequencies, which are modulated across the sleep-wake axis. Low-frequency synchronous activity of cortical neurons is predominantly observed during sleep. These low-frequency oscillations are thought to result from reciprocal firing patterns within the recurrent circuitry of the cortex, thalamus, and the reticular nucleus [16]. During periods of cortical activation, waking, and higher EEG frequencies, neurons display increased excitability and exhibit more asynchronous discharge. These patterns of spontaneous EEG activity observed throughout the circadian cycle can be classified into a number of states. The most prominent distinctions are those observed within the ultradian cycles of sleep. Descriptions of each stage using polysomnographic recordings have been formally standardized by Rechtschaffen and Kales [17] and later by the American Academy of Sleep Medicine [18]. These states include periods of waking, progressively deeper levels of sleep (Stages 1–4 [17]), and periods of Rapid Eye Movement (REM). These classes of EEG activity are observed in humans and animals of lower phylogenetic orders [19], although the number of non-REM stages differs across species. This conservation of sleep/wake architecture observed in a number of mammalian and non-mammalian animals supports the translatability of EEG recordings across species.

Quantification of spontaneous EEG (quantitative EEG, qEEG) in the temporal, frequency, and spatial domains, whether within waking states or across sleep stages, offers additional measures of