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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

activity states. The vast number of analytical approaches currently available has been extensively reviewed and descriptions of these are beyond the scope of the current review (for examples see [20–36]). A strong proponent for the use of human qEEG in psychiatric and pharmaco-EEG research has been TM Itil and collaborators (e.g. [33–36]). This body of work and work by others has described the use of qEEG to predict the effects of pharmacological agents as well as to classify disease states. Neurobiologically, this approach is supported by the fact that the activity of a number of subcortical neurotransmitter systems from several brain regions outside the thalamus can directly impact cortical activity patterns. These neurotransmitter systems are generally targets of pharmacological intervention or participate in neurological disease states. Reviewed below, the impact of psychoactive drugs has been shown to have similar effects on the EEG patterns of animal models and humans for a number of drug classes.

An additional approach to characterizing spontaneous EEG changes is to analyze cortical activity potentials evoked by experimental perturbations as a means of assessing deterministic signal processing within the brain. These evoked potentials/event related potentials (EP/ERP) are characterized by a series of stimulus-dependent peaks and negativities in EEG activity observed by summation or averaging many trials of stimulus presentation. EP/ERP activity can be elicited through a number of sensory modalities including auditory evoked potentials (AEP), visual evoked potentials (VEPs), and sensory or somatosensory evoked potentials (SEPs or SSEPs). Specific neural pathways involved in detecting, processing, and filtering this information are responsible for producing EP/ERP patterns. Importantly, these pathways and EP/ERP response patterns are relatively conserved, similar, and robust across a number of mammalian species. As such, translatable patterns of evoked activity can be extracted from EEG signals of mice and rats (e.g. [37–42]) or non-human primates (e.g. [43–48]), to humans, principally differing in the temporal domain due to species differences in brain size. For example, the well-described human auditory evoked potential P50 or P1 has a consistent and positive evoked peak in the EEG that occurs 50 ms after a stimulus is presented. The correlative evoked peak in mice occurs at 20 ms (P20; P1) [49,50]. Importantly, the impact of a number of psychoactive drugs on EP/ERP responses has shown similar effects across animal models and humans (reviewed below).

4. Use of EEG as viewed by the U.S. food and drug administration

Currently, the guidelines of the Food, Drug, and Cosmetic Act require that a drug must possess "substantial evidence of effectiveness". This must include "... evidence consisting of adequate and well-controlled investigations, including clinical investigations ..." and show that "... the drug has the effect it purports or is represented to have under the condition of use prescribed." [51,52]. Regularly compounds are approved based on a foundation of sound preclinical and clinical data that demonstrates effects directly related to clinical outcomes. Recently, surrogate biomarker endpoints have been explicitly permitted to be used to designate the efficacy of a compound to accelerate the approval process through adoption of Subpart H of 21 CFR 314.500 (Code of Federal Regulations) and as part of the FDA Modernization Act, Section 506(b). Acceptable surrogate biomarkers must be rigorously tested to empirically demonstrate validity as an indicator of clinical endpoints [53–56]. Adoption of these new regulations permits well-established surrogate biomarkers to be used as an endpoint for one of two appropriate and well-controlled clinical trials demonstrating substantial evidence of effectiveness for FDA approval. Importantly in some cases, a non-established surrogate endpoint could be used as one of the two clinical endpoints [57,58]. For example, a surrogate biomarker used in this manner is the measure of serum cholesterol [59]. This marker can be used to predict coronary artery disease and measure the impact of medication on this clinical endpoint. Likewise, EEG measures of cortical activity have been used to predict psychiatric disorders in humans, such as depression, and the therapeutic effects of treatments. These data are buttressed by findings that EEG measures of cortical activity within the brain of animal models have been shown to detect similar EEG changes in human following administration of therapeutic compounds (see below). Together, this large body of evidence indicates the putative utility and validity of EEG as a surrogate biomarker.

5. Translational biomarker promise of EEG

The anatomical and functional organization of CNS neural pathways that generate EEG signals are similar between species used in preclinical drug discovery and humans. As such, both EEG activity and EP/ERP patterns are also generally translatable from rodent to human. Interestingly, brain volume differences often account for the majority of discrepancies in frequency shifts or latency differences between EP/ERP signatures observed across these species [60]. Thus, similarities in spontaneous EEG and EP/ERP measures from rodents to humans provide a solid foundation for the use of EEG in the pursuit of finding translatable biomarkers.

An important advantage of EEG methods is that similar recording techniques can be used in both preclinical and clinical studies. Moreover, in many mammalian species EEG monitoring can be performed in a relatively non-invasive, stress-free, and pain-free manner. These recordings can be performed during normal daily activities or while sleeping through the use of telemetric or ambulatory methods [61–65]. Advances in technology continue to enhance signal quality and durability of recording from patients (e.g. [33–36,66,67]). As such, EEG recording protocols easily fall in alignment with industry guidelines for studying CNS activity in preclinical and clinical settings [2].

Another important advantage of EEG methodologies is that EEG signal processing and analyses can be identical across these species. Identical computational algorithms can be used to generate both qualitative assessment of EEG (stages of sleep/wake [17]) and quantitative measures of the EEG signal (e.g. spectral/frequency components). The "signature" generated from the combination of EEG measures reflects the overall state of the subject. This signature can change between baseline and other experimental conditions. For example, these experimental protocols frequently involve recordings during baseline conditions followed by administration of an experimental compound, which can occur under conditions where the subject is quietly resting or conditions involving situational and/or behavioral paradigms. When recorded with sufficient numbers of electrodes, additional topographic analyses such as Low Resolution Brain Electromagnetic Tomography (LORETA) can be used to produce three-dimensional "images" of cortical and subcortical EEG signal generators. Although these later techniques are extremely powerful and promising, they are not directly translatable to preclinical models that are limited to a few electrodes by size of the mouse and rat skull. Nevertheless, a wide breadth of qEEG assessment tools, as well as those related to EP/ERP measures of CNS signal processing, are available to identify biomarker signatures. As such, analyses limited to a few channels may have a higher likelihood of translating results from preclinical evaluation to human.

In summary, the above evidence supports the use of EEG based approaches in the pursuit of finding valid, predictable, and translatable biomarkers. The degree to which these methods are

predictive for identifying drug action or treatment efficacy across species is reviewed throughout the following sections. Each section provides an overview of the current state of preclinical and clinical EEG research from a few critical areas in CNS drug discovery. These studies indicate the promise of EEG methods to aid in the development of new therapeutic compounds, the potential to assess the progression of clinical encephalopathies, and the ability to test the impact of therapeutic intervention. Although to date EEG approaches have yet to be elevated to surrogate biomarker status, these techniques do allow small clinical studies to be conducted in which healthy volunteers can be exposed to varying doses of a compound, bringing early dose-ranging into Phase I, instead of Phase II [68]. This approach allows the early comparison of clinical findings to preclinical work thereby improving the Go/No-Go decision-making process.

6. Depression and sleep

In humans, clinical diagnosis of depression is essentially based on identification of depression-like symptomology (e.g. Hamilton Rating Scale for Depression; DSM-IV). Preclinical models of depression (e.g. swim test; [69]) and other preclinical biomarkers including electrophysiological markers (e.g. serotonin neuron discharge properties; [70]), and genomics/proteomics (e.g. 5HT-2a receptor allele; [71]) may be predictive of therapeutic efficacy, but are difficult to directly translate to clinical populations and are relatively low-throughput measures. However, EEG measures of cortical activity do have the potential to be an extremely powerful surrogate biomarker of depression that is translatable across species. Since the early studies using EEG, certain hallmarks were noted in patients with depression [36,72–74]. Today, a large body of literature exists documenting EEG biomarkers in affective disorders including depression and the pharmaco-EEG effects of antidepressants across current compound classes (for reviews see [20,75,76]. However, as mentioned above the translatability of pharmaco-EEG signatures across species has not been well documented, thus making it difficult to assess the utility of these markers for preclinical screening of compounds.

Several notable exceptions exist regarding the effects of antidepressants on quantification of EEG activity changes. Principally, a number of studies have demonstrated strong evidence that one of the most important predictors of depressive episodes are disturbances in sleep and EEG measures of sleep. Humans with depression generally display a disinhibition of REM sleep that results in a shorter latency from sleep onset to the first REM period, a longer time spent in REM, and an increased REM intensity (demonstrated by increased eye movements). Overall, from humans to rats antidepressants suppress REM sleep. Certainly, there are a few exceptions where antidepressant compounds do not show REM suppression [77]. However, this lack of effect may be due to differences in receptor affinities between antidepressants. Within the frequency domain, fewer studies have directly compared the effects of an antidepressant in rodents to clinical outcomes. The tricyclic clomipramine has been shown to increase EEG power in the delta band and decrease theta power in mice [75]. These effects (as well as others across the entire spectra) were similar to what was observed in humans and were predictive of individuals who responded to treatment. Interestingly, another study demonstrated the delta/theta ratio was increased in patients responding to antidepressant treatment (MAOI and monocyclic; [78]). This idea of normalizing the delta/theta ratio for comparison across subjects has been further refined as a measure of cordance. Cordance indeed may provide a superior biomarker over spectral power alone [79,80].

Of interest, serotoninergic tone within the cortex has been shown to relate to 'loudness dependency' of the N1/P2 complex of auditory evoked response potentials. (LDAEP; [81–83]). Recently, two major reviews outline the status of LDAEP and the use of this biomarker as a predictor for antidepressant treatment responsiveness [84,85]. In brief, it has been demonstrated that high basal levels of 5HT in the CNS are related to a suppression of ERP responsiveness to auditory tone intensity. Conversely, low 5HT levels are reflected in the facilitation of tone intensity-ERP response curves. This relationship has been demonstrated in normal rodents, felines, and humans [82,83,86,87]. Importantly, this measure has also been shown to predict SSRI vs. NERI responsiveness in the treatment of depression. Nonetheless, a number of studies have cast doubt on the usefulness of LDAEP as a biomarker, citing no treatment effect on LDAEPs or non-specificity of the LDAEP for 5HT. Treatment regimes, subject selection parameters, and other variables are likely to account for these variable and negative results. Regardless, it is generally agreed that the LDAEP in animal models may be a useful preclinical biomarker to screen novel pharmaceutical compounds for antidepressant activity.

7. Attention deficit hyperactivity disorder

Attention-deficit hyperactivity disorder (ADHD) is characterized by inattentiveness and/or hyperactivity and impulsiveness. A number of lines of evidence indicate that function of the prefrontal cortex (PFC), important for regulating these cognitive functions, is impaired in individuals with ADHD [88–91]. Pharmacological treatments of ADHD share the important ability to optimize catecholamine (norepinephrine and dopamine) levels preferentially within the PFC [88]. This effect is strongly linked to the cognition-enhancing effects of these treatments and occurs in both patients with ADHD as well as normal subjects. Moreover, strong evidence links optimization of PFC catecholamine levels to specific changes in signal processing abilities of PFC neurons [88,92,93]. Thus, development of novel compounds that target either catecholamine systems or entirely different mechanisms of action will need to account for cognition-related changes in PFC neuronal activity.

Currently, the only markers for cognitive enhancement are behavioral tasks that specifically test PFC dependent cognitive processes. One such example is the preclinical delayed spatial alternation task (T-Maze task). Although this task shows sensitivity to cognitive enhancers and is predictive of clinical indices of enhanced cognitive performance in humans and treatment of ADHD symptoms, this task requires a significant amount of experimenter time (the experimenter must interact with the animal on a trial-by-trial basis; [92,93]). Recently, a number of studies have examined qEEG differences in children, adolescents, and adults with and without ADHD. A meta-analysis of these studies by Snyder and Hall [94] indicated a consistent increase in theta power (3.5–7.5 Hz, mean = 132% of normal controls) during a resting state. Increased theta by patients with ADHD over controls during cognitive tasks has also been observed [95]. Complimenting increased theta in ADHD children, other low frequencies are also increased including delta [95]. In contrast, a decrease in beta power is generally observed during resting states (12.5–25 Hz, mean = 94% of normal controls; [94]) and during cognitive tasks [96]. However, in rare cases an excess in beta activity is observed that occurs in a subset of ADHD patients (approximately 15–20% of children with combined inattentive and hyperactivity type and 2% of the inattentive type; [97–100]). This excess beta is also observed with affective disorders including depression and anxiety [101,102]. Overall, the major traits observed are that ADHD patients consistently exhibit an increased theta/beta ratio [98,103].

Analysis of the effects of methylphenidate (MPH; Ritalin) principally used in the treatment of ADHD has demonstrated a

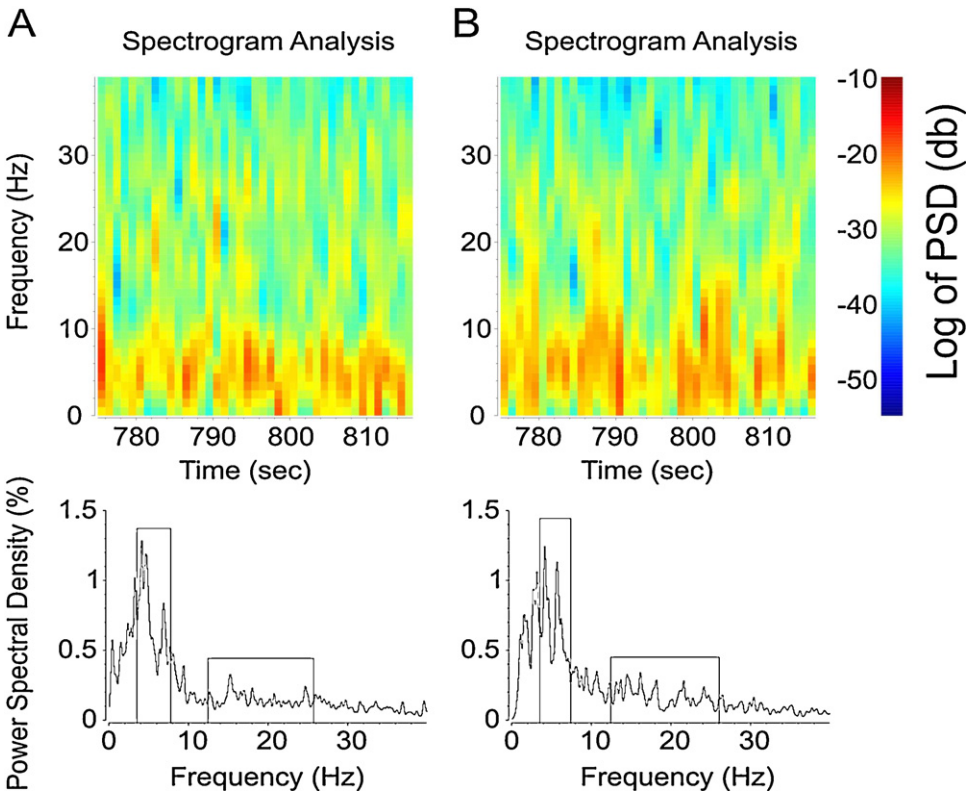

Fig. 1. ECoG recorded from the frontal cortex of the awake, freely-moving rat ($n = 1$) demonstrates spectral changes following clinically-relevant doses of methylphenidate similar to those observed in humans. ECoG segments from two files (A) Baseline and (B) following 0.25 mg/kg were subjected to FFT analysis (sliding 1 s window, 1 Hz resolution, Hann window) and plotted as a spectrogram (top; smoothed with 5 bin Gaussian kernel) or as a percent of total spectral power (bottom). Quantification of the total power within the theta band (3.5–7.5 Hz) and beta band (12.5–25 Hz) indicated a 10% decrease in theta and an 18% increase in beta. In this animal 0.25 mg/kg produced the greatest cognitive enhancement in a spatial delayed alternation task.

normalization of theta and beta frequencies in ADHD patients [104,105]. In general, psychostimulants including MPH increase alpha and beta activity [106,107] and decrease activity in the delta and theta frequencies [108]. Surprisingly, few studies have looked at EEG changes in the rodent or other preclinical models following treatments for ADHD. One such example demonstrated that in the anesthetized rat, near-clinically relevant doses of MPH (0.1 mg/kg i.v.) demonstrated a significant increase in theta (5–10 Hz; [109]). However, these seeming incongruent results likely are an artifact of anesthesia and higher than clinically relevant doses of MPH. Results from Devilbiss and colleagues did not show significant changes in EEG following clinically-relevant doses of MPH in the awake rat [93], although this study was not designed to specifically address band-power changes following dosing. However, recent preliminary data from Devilbiss and colleagues suggests that similar to humans, clinically-relevant doses of MPH increase beta power and decrease theta activity (Fig. 1).

Outside of determinations of EEG power as a surrogate marker for improved cognitive performance there have been a number of approaches that have yielded mixed results. For example, measures of inter-electrode coherence have demonstrated differences between normal subjects, patients with ADHD, and the effects of MPH principally in the delta and alpha frequency bands [110,111]. However, as the authors suggest, data recorded in the resting state with eyes closed may not reflect functional differences and instead may reflect structural or developmental differences in ADHD brains. Studies examining evoked potentials have examined the impact of MPH treatment on the differences in ADHD subjects [112,113]. Overall, stimulus sets and significantly related changes in ERP components were unique to each study making it difficult to evaluate the predictive value of ERP analysis as a surrogate biomarker for developing treatments of ADHD. Lastly, a number of methods exist for localizing EEG signal sources in the spatial domain including LORETA (Low Resolution Tomography), LCMV (Linearly Constrained Minimum Variance) spatial filtering, and MUSIC (Multiple Signal Classification) dipole scan. Recently, LORETA has been used to identify brain regions altered by methylphenidate administration in addition to antidepressant actions [108,114–116]. Although LORETA has been applied to primate EEG patterns [117], currently the usefulness of these spatial analyses is limited in rodent model screens for novel compounds.

8. Schizophrenia

Patients with schizophrenia present a number of classical positive and negative symptoms (e.g. hallucinations, thought disorders) relating to altered cognitive function. Although the neurobiological etiology of this disease is poorly understood, two well-supported theories suggest that (1) abnormal development of cortical networks may underlie the emergence of psychotic episodes and (2) sensory information processing is impaired in schizophrenic patients [118]. The support for these theories emanates from abnormalities in EEG frequency band power and measures of "sensory gating" including components of the AEP (P50-N100, mismatch negativity, and the P300 response). These and other electrophysiological endophenotypes of impaired sensory gating have been well characterized over the last several decades both clinically and preclinically [119–139]. Key elements of this literature are reviewed below.

Abnormalities in EEG frequency band power as well as differences in synchronous activity across brain regions have provided support for abnormal cortical network function in schizophrenics [140–142]. Although schizophrenic patients ex-

hibit altered EEG power in a number of frequency bands, the most prominent characteristics are a decrease in gamma and high-gamma band power [143,144] and increased delta power in frontal and temporal regions [145,146]. Importantly, increased beta and gamma power is observed in sensory regions where hallucinations are experienced [147,148], and a reduction in synchrony occurs within these bands [149–151]. The effect of compounds used to treat schizophrenia on normal individuals is varied and not necessarily aligned with classification by typical/atypical, but rather on their sedative/non-sedative actions [36,152,153]. For example, haloperidol, which is classified as a major neuroleptic/non-sedative neuroleptic, increases alpha and beta frequency power, whereas quetapine, which is a major neuroleptic/sedative, elicits a decrease in alpha activity. Second generation antipsychotics, such as clozapine/olanzapine have been demonstrated to increase power in the gamma frequency range of schizophrenic patients. Interestingly in rats, increases in alpha and beta frequency power have been observed following administration of chloropromazine and risperidone and a decrease in alpha power following quetapine [154,155]. Outside the use of typical/atypical antipsychotics, Knott et al. [156] reported that absolute and relative EEG power indices were influenced by transdermal nicotine with the resultant EEG profile of power reductions in slow-wave frequencies and power augmentation in fast-wave frequencies, particularly in high alpha and beta, described as "vigilance promoting" effect.

Impairments in sensory gating are considered one of the hallmarks of schizophrenia [49,157,158]. As such, patients diagnosed with schizophrenia exhibit impairments in the ability to inhibit responses to redundant stimuli and facilitate responses to novel or salient stimuli. This deficit can be assessed by measuring the suppression of the P50 and/or N100 components of an AEP between an initial conditioning tone (S1) and the second test stimuli (S2). The human P50-N100 component of the AEP is comprised of a positive deflection at 50 ms post-stimuli followed by a large negative deflection in the EEG around 100 ms. Generated by neural populations in the primary and association auditory cortices, this complex is elicited by an unpredictable stimulus in the absence of task demands [159–161]. Impairment in the brain's normal function to inhibit responses to subsequent stimuli that are presented within a short interval (approximately 500 ms) reflects the impairment in sensory gating observed in schizophrenic patients [136,162–165].

Sensory stimulus processing functions have also been extensively studied in preclinical animal models using AEPs [166]. The AEP in mice is comprised of P20, N40, P80, P120 and slow wave components and demonstrates similar morphologies to the human P50, N100, P200, P300 and slow wave [50]. In fact, Siegel and others have shown that the mouse P20 and N40 bear similarity to the human P50 and N100 in relative latency and orientation [50,163,167–172]. Importantly, the mouse P20/N40 waveform is gated following repeated stimuli similar to the human P50 and N100 components. Additionally, an index of mismatch negativity (MMN) between stimulus types can also be determined from AEP's and provides a biomarker of impaired sensory gating. Lastly, the late cognitive potentials (e.g. P300 reflecting target detection cognitive processes and N400 representing indexing context integration during recognition) can be used to monitor the probable location, timing and intensity of brain activation during cognitive tasks [173,174]. Together, the P50/N100, MMN, and P300 responses are potential candidates for objective investigation of pre-attentional and/or attention-dependent processing and have been found to be altered in schizophrenia [112,124,126].

In unmedicated schizophrenia patients, the magnitude of both P50 and N100 responses to the initial stimuli (S1) is generally diminished compared to normal subjects [175–182]. Nonetheless, some studies have demonstrated a number of AEP phenotype variants in schizophrenic patients including a reduced N100 amplitude [183–186] or reduced N100 response to the first stimulus (S1) but not S2 [175,187–191], similar N100 response amplitudes for both S1 and subsequent test stimuli (S2; [192]), and increased responses to only S2 [114,193]. To date it remains unclear whether these differences represent methodological discrepancies or reflect certain subpopulations of schizophrenics.

Schizophrenics present a reduction in the P300 amplitude that appears to correlate with severity of the disease and exhibits strong heritability [112,126,194,195]. P300 has been shown to be increased in 50% of schizophrenic patients being treated with quetiapine (Seroquel) in a trail of 10 patients treated for 16 weeks [196], accompanied by an improved clinical outcome for the group studied as assessed using PANSS, MADRS, Bf-S, SCL-90 and CGI-S instruments. Similarly, it has recently been demonstrated in a 16 patient 6-month trial of olanzapine that P300 source intensity, using LORETA, was significantly increased in the left superior temporal gyrus, and these changes were found to correlate with improvements in negative symptoms and verbal learning memory.

Mismatch negativity, another putative marker of schizophrenic populations, is determined from the difference in EP/ERP elicited by rare auditory events versus those evoked by stimuli repeated with higher frequencies [161]. Measurements of MMN differ from those of the other AEP components' amplitudes since the procedure utilizes deviant tones that are either attended or unattended in an oddball paradigm that embeds infrequent targets and distracters into the stimulus train. This well studied measure in schizophrenics is believed to be dependent on cortical circuit function. Additionally, the MMN is likely caused by a mismatch in neuronal activity between the deviant auditory input and a sensory-memory trace representing the standard stimuli. In other words, results from MMN studies suggest that MMN is a reflection of sensory memory, in that if there is repetitive auditory stimulation of one tone than an occurrence of a different novel or unprecedented tone, the subject elicits an MMN response. Schizophrenics tend to generate impaired MMN reflected in a smaller magnitude difference between the conditioned and oddball stimuli [68,197,198]. Furthermore, across many studies schizophrenic patients consistently show deficits in measures of MMN [199].

Although EP/ERP based approaches are very promising as translational biomarkers, bridging the gap between preclinical and clinical findings remains challenging. Among the AEP biomarkers of MMN deficits, P300 amplitude, and P50 gating, the P50 paradigm is uniquely placed for translatability from rodent to human. For example, MMN is well studied in schizophrenia patients, however the general lack of a rodent counterpart to the human task and failure of the atypical antipsychotics clozapine [200,201] and olanzapine [202] to reverse MMN deficits in schizophrenic patients challenges the ultimate use of this measure as a translatable endpoint. Moreover, recent work testing NMDA antagonist-induced MMN disruption at a neuronal circuit-level showed rodent auditory cortex unit responses failed to show the novelty correlate established for the human MMN [203]. In contrast, models of the P50 sensory gating deficit are well validated in mice and rats and can be easily assessed in patients. Clozapine has been shown to improve P50 gating in humans [204]. Moreover, second generation antipsychotics such as olanzapine have been reported to increase the amplitude of the P20, N40, and P80 components of the mouse AEP [205]. Clozapine and olanzapine further improve deficient sensory inhibition in DBA/2 mice [206,207]. Interestingly, haloperidol did not enhance AEP components or rescue deficient DBA/2 mice [205–207]. Moreover, work by others suggests that a number of antipsychotics including sulpiride, risperidone, clozapine, olanzapine, and haloperidol have been shown to exert no significant impact on P50 gating [193,208].

Nonetheless, some of the best evidence to suggest translatability of AEP endpoints has come from work with nicotinic acetylcholine receptor agonists and measures of P50/P20 sensory gating [209,210]. For example, Adler et al. [211] demonstrated that nicotine-containing gum increased P50 sensory gating to near normal levels within 30 min of administration with the gating of P50 returning to baseline levels within 1 hour in non-smoking relatives of schizophrenics with abnormal sensory gating compared to placebo administration. Administration of the alpha7 nicotinic receptor agonist DMXB-A (GTS-21) improves deficient sensory inhibition in DBA/2 mice [212]. Additionally, DMXB-A altered human AEP by reducing the P50 response to S2 compared with placebo [209]. Importantly, the impact of DMXB-A on AEP correlates with improved clinical ratings of negative symptoms of schizophrenics that are generally resistant to treatment with dopamine antagonist antipsychotic drugs [213]. Nicotine also modulated the later AEP response components. Nicotine-enhanced MMN amplitudes in both nonsmokers and smokers from baseline to post-drug recording greater than placebo [214], while transdermal nicotine increased P300 component to paired auditory stimuli, suggestive of increased attention and arousal [156,215].

9. Pain

EEG signals recorded from the brain can be modulated by somatosensory signals stimulated in peripheral nerves. This is conceptually similar to AEPs described previously, except that the incoming signals are generated by touch, heat or electrical stimulation peripherally. These somatosensory evoked potentials (SEPs or SSEPs) are carried to the brain by Aδ/Aß (for touch and electrical stimuli) or by Aδ/C fibers (heat, i.e. laser stimuli). Similar to AEP waveforms, these signals in response to painful stimuli are processed by averaging to extract the first negative (N1) and second positive (P2) components. In early studies with this technique, the N1 signal was reduced more by peripherally acting agents, while the P2 component was reduced mainly by central agents [216,217], which agrees with subsequent studies linking longer latency waveforms with central signal processing.

The most controllable stimulus to evoke SEPs is an infrared laser, specifically a constant duration CO_2 laser. This nociceptive, contact-free stimulation method efficiently and rapidly raises skin temperature, thus directly activating the heat receptors located on free nerve endings. While the depth of penetration is shallow, power settings can be individually adjusted for the subject. The resulting precise stimuli can be repetitively applied without habituation onto either normal or hypersensitive skin. In general, laser-evoked somatosensory evoked potentials (LSEP) show strong similarity to SEP's in humans and animal models. Delivery of pairs of laser-stimuli at sufficiently short intervals leads to suppression of the second response, which correlates with a loss of nociception of the second stimulus [218]. Moreover, LSEP like SEP response amplitudes are modulated by the level of attention/vigilance [219,220]. Although LSEPs and SEPs have been recorded in both human and animal studies, to date much of the work with LSEP has been performed in the clinic. Backward translation of these results to preclinical animal studies has been promising, however more studies are needed to fully determine the capabilities of this method.

In humans, LSEP measures are standardized across subjects via a common vigilance task such as an adaptive pursuit-tracking task. Under these standardized conditions, pharmacological activity modulation of LSEPs have been reported for a wide variety of anti-inflammatory agents (NSAIDs, ASA, and acetaminophen), opioids, anesthetics, antihistamines, and other common pain medications [221]. Encouragingly, B1 and NK1 antagonists, both of which have yet to show clinical efficacy in chronic pain conditions [222,223], were inactive in this model. Moreover, LSEP are absent or significantly altered in patients suffering from neuralgia that cause deficits in pain sensation [219,224–226]. Paired with capsaicin or UV irradiation as a sensitizer, these pharmacological treatments can be quantitatively evaluated for effects on the LSEP and SEP parameters. The reduction in pain score (as measured by the VAS instrument) to UV-induced hypersensitivity correlates well with the reduction in N1-P2 amplitude as measured by LSEP across these agents. Lastly, LSEPs also show a positive correlation with the unpleasantness of the laser stimuli applied to evoke the SEP in both humans [227] and rats [228,229].

Animal studies have shown that LSEP are significantly altered by general anesthetic agents [230,231]. For example, Qiao et al. [232] measured multi-channel LSEP in conscious rats to investigate its spatio-temporal features, an important advance needed to translate this technique. In these studies, laser stimulation of either the tail or hindpaw was performed on awake behaving animals. Laser stimuli were delivered to minimally overlapping skin areas among the trials. In most studies the primary somatosensory cortex has been implicated as a substrate of pain perception and perhaps even initial pain processing. Importantly, morphine treatment reduces the slower/later signals in these animals, due to C-fiber activation and pain processing, similar to data from human studies.

10. Alzheimer's disease

The progression and pathology of Alzheimer's disease (AD) is characterized by a number of neurobiological and cognitive changes. Clinical diagnostic criteria (DSM-IV, ICD-10 and NINCDS-ADRDA) are used to identify patients with Alzheimer's disease and provide clinical trial primary endpoints. However, these criteria rely on overt signs of dementia and measure only the symptoms of the disease, such as cognitive and functional impairment that correspond to neuropathologically advanced disease states [3]. Outside of impaired cognitive functions, neurobiological changes associated with AD progression can additionally present as altered physiological functions including sleep patterns, changes in EEG activity (spectral shifts) and EP/ERP responses, as well as an increase in epileptiform and/or seizure activity. Over the past several decades there has been considerable effort in exploring the utility of polysomnography, qEEG, and EP/ERP measures as useful clinical markers of early disease or progression biomarkers of AD [233,234]. Seizure activity and/or epileptiform discharges as measured by EEG have the additional promise as a novel biomarker for AD. As such, EEG based measures of neurological function offer a number of translatable, physiological endpoints that are likely indicative of disease progression in both AD patients and animal models.

As AD progresses, polysomnography reveals that patients demonstrate a loss of stage 2 sleep features including sleep spindles and K-complexes [235] as well as deficits in REM sleep due to shorter REM epoch durations without changes in latency [236,237]. These deficits are likely specific to AD and are not generally observed with normal aging processes or other cognitive disorders that involve REM sleep changes (depression: see above). Pharmacological treatments for AD, including the acetylcholinesterase inhibitor donepezil and the NMDA antagonist memantine, have been shown to restore REM sleep in human and animal models [238,239]. Moreover, in the human patient population, donepezil dependent changes in REM activity were significantly correlated with cognitive improvement ratings on the Alzheimer's Disease Assessment Scale (ADAS-cog) compared to baseline cognitive function and placebo group.

Recent mounting evidence suggests that qEEG measures of cortical activity may be used to classify and distinguish AD patients

from normal healthy volunteers (HV) (see [240–243]). EEG patterns demonstrate increased power in theta range (4–8 Hz) early in the progression of AD, and as the disease progresses, a decrease in alpha (8–13 Hz) and beta (13–40 Hz) powers followed by an increase in delta power (1–4 Hz) [240–247]. This cortical slowing, associated with cognitive decline, continues late into the disease associated with a slowing of the dominant occipital rhythm, and increased diffuse slow activity [248–251]. This evidence is supported by good correlation between the severity of these EEG abnormalities [252], and cognitive impairment [253]. Moreover, cerebrospinal fluid (CSF) markers of AD progression including measures of total tau protein, phosphorylated tau levels, and phosphorylated-tau/beta-amyloid(1–42) protein ratios exhibit strong correlation with increased theta frequency measurements and decreases in cognitive speed [254].

The N200 and P300 ERP components, indicative of executive cognitive control such as perceptual and attentional processes, have also been suggested as likely biomarker candidates for the progression of AD and predictive of decline from mild cognitive impairment (MCI) into AD [234,240–243]. Patients that progress from stable MCI to AD demonstrate significantly prolonged N200 latencies in their AEPs as well as higher CSF beta-amyloid(1–42) levels [255]. Moreover, reductions in amplitude and delay in peak latency of P300 is observed in AD patients compared to control subjects [256–258]. P300 latencies are significantly correlated with mean ADAS-cog scores and Mini Mental State Examination (MMSE) scores both before and after therapeutic treatments [259–262].

Seizure activity and/or epileptiform discharge in EEG recordings has been documented in AD patients since the 1970s. AD patients exhibit seizures and myoclonus, individually or together, as well as epileptiform discharges and triphasic waves [263–265]. Although currently a definitive link between seizures and AD remains unclear, studies have demonstrated higher seizure prevalence in patients presenting mild-to-moderate AD [266]. Also, there is an increased risk for spontaneous seizure activity in individuals with more severe AD compared with others of the same age [266–268]. Moreover, it has been suggested that there is a causal relationship between dementia pathology and the development and maintenance of seizures: AD patients with a younger age of dementia onset are particularly susceptible to seizures [264–265]. More subtle forms of non-convulsive seizures also likely go undiagnosed [269] and the amount of epileptiform abnormalities on EEG and complex partial seizures seem to differ between sporadic Alzheimer's disease and some familial forms of AD [270–272]. These findings support the notion that seizures can be a part of the natural history of AD. Although more research regarding a causal linkage is necessary, there is enough evidence to suggest utility of investigating these phenotypes both clinically and preclinically.

In animal models, introduction of familial mutations associated with AD result in altered amyloid precursor protein (APP) processing and elevations in amyloid beta (Aβ, Abeta) peptides and plaques. These mutants demonstrate a number of qEEG and cognitive changes paralleling AD patients. For example, qEEG measures of transgenic mice overexpressing both the mutant human APP695 gene (APPswe) found in a Swedish family with early-onset AD and the Presinillin genes revealed shifts from delta to theta activity during waking conditions [137–138]. Additionally, both Tg2576 and PSAPP transgenic mice demonstrate neuronal hyperexcitability associated with excessive synchronous neuronal activity accompanied by consistently higher dominant frequencies typically around 8 Hz [137–138,273–274]. This aberrant high-theta rhythm is not coupled to locomotor activity or stereotypies but rather dominated the electrical activity of the brain for about 50% of the recorded time in these transgenic mice compared to wildtype mice who exhibit similar frequencies less than 20% of the time in a typical recording session [137–138]. Importantly, this theta rhythm was present in mice that later developed Aβ deposition and eventual and measurable cognitive decline [273–274]. These and other data suggest that the specific presence and/or overexpression of APPswe and resultant elevated levels of Aβ would drive the underlying factors that cause subsequent EEG changes (but see: [275]). Thus it is posited that aberrant excitatory neuronal activity resulting from Aβ deposition may contribute to the EEG changes and cognitive deficits that characterize AD mouse models [137–138,273–274,276–280]. Together this preclinical and clinical data suggest that changes in EEG, including abnormally high theta power, may provide an early marker for the accumulation of Aβ and early stages of AD. Nevertheless, much work on the relationship between the neurobiological changes, network or regional circuitry (e.g. hippocampal) dysfunction and cognitive deterioration remains to be done.

Transgenic mouse models of AD additionally demonstrate epileptiform and seizure activity similar to AD patients. In general, APP and PS1 expression in mice increases seizure activity and EEG abnormalities with phenotypes ranging from abnormal spiking events (large transients) to interictal spiking and spontaneous seizures [276–277,281–283]. Moreover in mice prone to seizure and premature mortality by Fyn tyrosine kinase mutations (associated with dysfunctional N-methyl-D-aspartate (NMDA) receptors), these symptoms are exasperated by the expression of human APP [284–286]. Recently a study by Ittner et al. [287], demonstrated that deficiencies in the tau protein rescues Aβ induced memory deficits and shortened lifespan [287]. This tau deficiency additionally decreases seizures induced by the Aβ-mediated overstimulation of excitatory NMDA receptors in a transgenic hAPP mice [288].

Together the above evidence indicates that polysomnographic, qEEG, ERP, and epileptiform activity indices of nervous system function are likely candidates as biomarkers for the progression of AD or markers of clinical efficacy of developmental compounds. As such, progressive amyloidopathy likely disrupts normal neuronal function that increases in propensity and severity in an age-dependent manner causing impaired learning and memory and cognitive function [278–279]. Importantly, these characteristic abnormalities in EEG often precede the appearance of distinctive clinical features, even at the earliest stages of dementia. Thus although relatively new in identifying AD progression, EEG measures of paroxysmal activity may be an important translational biomarker for testing therapeutic strategies in the treatment of AD. Moreover, the combination of this marker with other high probability EEG derived predictors of dementia including alterations in sleep architecture and the continued changes in EEG frequency components will likely be important tools in the identification of AD progression and efficacy of treatments.

11. Conclusion

A wealth of information can be derived from analyzing patterns of spontaneous and stimulus-evoked EEG activity from rodents to humans. A number of these analyses exhibit a high level of congruence between species, thus representing multiple candidates for translatable biomarkers in drug discovery. The next challenge to be faced is the selection and validation of endpoints that provide for a set of truly translatable biomarkers bridging preclinical and clinical programs. In this regard, single channel qEEG analyses appear to be the most translatable and best tested of these approaches.

EEG measures in normal subjects can initially provide evidence of CNS penetration and drug-target engagement. For example, compound classes or families have been shown to exhibit a unique electrophysiological signature. The highly preserved sleep archi-

tecture observed across species allows for a direct comparison of compound effects indicated for sleep disorders or sleep deficits co-morbid with other conditions such as depression. In contrast, the current lack of definitive antipsychotic or procognitive activity predictability based on ability of antipsychotic drugs to normalize sensory gating deficits in schizophrenia suggests that the P50/P20 endpoint is close to, but not sufficient for, a surrogate biomarker of schizophrenia. The same can be said for the use of LSEP in pain, where clinical data provides some promise for this approach even in the absence of significant rodent data to fully support translatability. Nonetheless, the evoked potential endpoints are important to facilitate the early decision making process around new candidate advancement in the clinic.

Determinants of cortical activity through EEG measures permit a generic biomarker strategy with potential for broad utility across multiple CNS disorders. This strategy is independent of disease pathophysiology, and advantageous in the absence of the ability to directly interrogate a known endophenotype of disease. As such, EEG-based signatures represent promising preclinical screens to quickly determine CNS penetration, evidence of efficacy, pharmacokinetic/pharmacodynamic profile, CNS toxicity and pro-convulsant risk. Exploiting a strategy that compares the profile of a new drug candidate and a library of these signatures has the promise to further facilitate early decision-making processes and provide multiple indications for a single compound. Likely, an aggregate of biomarkers including EEG/ERP measures will be needed to both fully classify individual cognitive disorders as well as predict the therapeutic actions of compound families. Moreover, imaging methods such as Positron emission tomography (PET), functional Magnetic Resonance Imaging (fMRI) and Magnetoencephalography (MEG) may also prove to be an important adjunct to accurately and precisely identify changes in neurological function. MEG may offer similar promise as EEG but is still emerging.

The above approaches perhaps provide the most likely roadmap for using EEG methodologies as putative biomarkers to translate preclinical and human studies and fully bridge bench to bedside. The prospect of finding translational EEG (tEEG) biomarkers not only promises efficacy measurements in preclinical and clinical trials, but also earlier detection of disease processes. This potential for early intervention, effective and intelligently designed therapeutics, and the possibly of more individualized treatment will certainly provide better patient outcomes and reduce institutionalization.

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