Pharmaco-EEG Studies in Animals: An Overview of Contemporary Translational Applications

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\textbf{Abstract}  
The contemporary value of animal pharmaco-electroencephalography (p-EEG)-based applications are strongly interlinked with progress in recording and neuroscience analysis methodology. While p-EEG in humans and animals has been shown to be closely related in terms of underlying neuronal substrates, both translational and back-translational approaches are being used to address extrapolation issues and optimize the translational validity of preclinical animal p-EEG paradigms and data. Present applications build further on animal p-EEG and pharmaco-sleep EEG findings, but also on stimulation protocols, more specifically pharmaco-event-related potentials. Pharmaceutical research into novel treatments for neurological and psychiatric diseases has employed an increasing number of pharmacological as well as transgenic models to assess the potential therapeutic involvement of different neurochemical systems and novel drug targets as well as underlying neuronal connectivity and synaptic function. Consequently, p-EEG studies, now also readily applied in modeled animals, continue to have an important role in drug discovery and development, with progressively more emphasis on its potential as a central read-out for target engagement and as a (translational) functional marker of neuronal circuit processes underlying normal and pathological brain functioning. In a similar vein as was done for human p-EEG studies, the contribution of animal p-EEG studies can further benefit by adherence to guidelines for methodological standardization, which are presently under construction by the International Pharmaco-EEG Society (IPEG).

\textbf{Introduction}  
The present paper complements the papers on human pharmaco-electroencephalography (p-EEG) in this International Pharmaco-EEG Society (IPEG) special issue with an update on contemporary animal p-EEG applications, which can be subdivided in spontaneous versus stimulation- or event-related EEG recordings. The importance of control of vigilance level, the use of pharmacological challenges, and present restrictions and chal-
lenges will be outlined, emphasizing the need for preclinical methodological standardization [1].

Animal p-EEG Applications

The development of more advanced analysis algorithms opened up new potential for both clinical and preclinical p-EEG applications [2], such as using the gamma band for the subgrouping or stratification of schizophrenic patients [3], for the characterization of glutamatergic drugs (e.g. [4, 5]), in support of safety pharmacology (e.g. [6]), and for investigating neurocognition (e.g. [7, 8]). Furthermore, EEG topography helped to reintroduce EEG by means of theta band as a diagnostic marker for depression [9] and as a personalized treatment-response biomarker for antidepressants [10, 11]. EEG has also become important as a research and clinical tool in the diagnosis and treatment of developmental disorders such as attention deficit hyperactivity disorder [12] and for monitoring the functional (cognitive) decline in Alzheimer’s disease (AD), also being both a preclinical and clinical functional readout of brain substrates such as loss of synaptic plasticity and impaired neuronal connectivity [13–15].

Changes in behavioral sleep and waking are the most prominent modulators of the EEG. Consequently, the confounding effects of changes in vigilance behavior should be eliminated as much as possible before analyzing the effects of a drug on the EEG of free-running animals [16]. The use of animal p-EEG effects during EEG-defined sleep for the prediction of their potential therapeutic scope and efficacy has been shown to be a valuable tool, which, however, needs careful interpretation: when compared to human p-EEG, animal p-EEG and pharmaco-sleep EEG poses specific problems, which are discussed elsewhere in this issue [17].

p-EEG in Modeled Animals

Animal p-EEG can be used very effectively to demonstrate functional antagonism of psychotropic drugs. Antagonism can be used to specifically address or model a functional disturbance or aspect of a psychiatric or neurologic disorder. For example, a scopolamine-induced delta power increase, which appears to be a hallmark of cognitive decline, is prevented by donepezil – a cognition enhancer – while the antipsychotic olanzapine ‘neutralizes’ the gamma power disruption induced by the psychotomimetic PCP [7]. Both academia and the pharmaceutical industry have identified and implemented event-related potentials (ERP) and quantitative time-frequency analysis of the EEG as usable and valid measurement tools or biomarkers to study the pathophysiology, phenomenology, and response to behavioral or pharmacotherapy in psychiatric and neurological disorders [18–20]. ERP and EEG reliably recruit and measure the neuronal systems underlying the affective and cognitive domains that are of pathophysiological significance, such as in schizophrenia [21], AD [22], autism [23], attention disorders [24] and other neurodevelopmental and neurodegenerative brain diseases.

An intimate relationship exists between neurotransmitter tones, EEG activity, brain network communication, and functional disturbances. Earlier preclinical p-EEG studies have demonstrated that different types of drugs can be separated with respect to their action on cerebral field potentials. Modulation of cholinergic, noradrenergic, serotonergic, dopaminergic, or opioidergic-mediated neurotransmission elicited particular changes in EEG frequency bands which were employed to characterize the specific modulator drugs [25–29]. The investigation of brain oscillatory activities by looking at changes in frequency-specific measures can be done during a defined vigilance state, such as resting or in a given task. Synchronization of EEG oscillatory rhythms at multiple temporal and spatial scales represents a core mechanism in brain communication networks, while disturbances in neural synchrony are postulated to underlie the cognitive processing deficits in various neurological and neuropsychiatric disorders [30–36].

Oscillations within the theta frequency range are, for instance, critical to establish precise temporal interactions for the propagation and coordination of the flow of information across widely distributed neuronal networks in the subregions of the hippocampus and the entorhinal cortex [37]. Oscillatory activity in the gamma frequency range has (a) its primary generators in the cortex where subsets of inhibitory GABAergic interneuron circuits modulate glutamatergic pyramidal cell activity, (b) is involved in the establishment of synchronization with great precision in short distance local cortical networks [38], and (c) has repeatedly been shown to be associated with neurocognitive processes in normal subjects [39–43].

Cholinergic Scopolamine Model

Typical EEG alterations in AD are associated with a general slowing and decrease of alpha activity which leads to increased delta and theta activities [44]. Additionally, reduction in higher EEG frequency components in oc-
cipital and temporal areas correlates with cognitive decline and the severity of the disease [44–49]. Altered functional and effective EEG connectivity among long-range cortical networks (i.e. frontoparietal and frontotemporal) were recently described in AD patients. Brain cholinergic neurons are believed to be involved in memory and cognitive dysfunction in AD. Scopolamine is a nonselective muscarinic receptor antagonist, which is widely used in preclinical as well as clinical research to simulate the EEG and cognitive abnormalities of AD, albeit without the pathological, progressively degenerative aspects of AD [50]. Scopolamine impairs the activity of hippocampal and cortical fast network oscillations, leading to memory deficits combined with enhanced slow EEG oscillations in the delta frequency band [26, 51–54].

In rats instrumented with multichannel EEG electrodes, cognition enhancers such as donepezil, rivastigmine, tacrine, galantamine, and memantine, which have been approved for the symptomatic treatment of dementia, enhanced cortical slow theta (4.5–6 Hz) and gamma (30.5–50 Hz) oscillations and functional slow theta network connectivity in parieto-occipital areas, between cortical hemispheres, and in corticohippocampal networks [7]. When combined with scopolamine, the cognition enhancers attenuated the leftward shift in coherent slow delta activity combined with altered slow theta and gamma oscillations (see fig. 1 for a case study with rivastigmine), which were induced by scopolamine [7], and reduced the theta-gamma phase amplitude coupling and speed modulation of theta frequency by scopolamine [55]. Oral administration of AC-3933, a benzodiazepine receptor partial inverse agonist indicated for symptomatic treatment of AD, resulted in the amelioration of scopolamine-induced amnesia in rats, as well as in a shift in EEG relative power (i.e. power decreases in 1–4, 8–10, and 10–12 Hz bands, and power increases in 4–6, 6–8 and 20–14 Hz bands) characteristic of procognitive cholinergic activators, such as donepezil [56]. In another study, nicotine reversed scopolamine-increased EEG theta frequency to the control level [57]. In anesthetized rats, scopolamine significantly decreased the power (by 68%) of the brainstem stimulation-induced theta oscillation [58]. Scopolamine reduced both the rate of hippocampal pyramidal place cell discharge inside firing fields and the spatial coherence of the fields [59]. In mice, the scopolamine-induced larger slow wave activity revealed the potential role of α1 adrenergic and dopamine D1 and D2 receptors in the EEG desynchronized effect of modafinil [60]. Collectively, these data show that the scopolamine EEG model in the rat is a useful translational model for assessing putative (acetylcholine-mediated) cognitive enhancers for the treatment of AD.

**Glutamatic N-Methyl-D-Aspartate Models**

Abnormalities in functional connectivity for the gamma frequency rhythm generator have been consistently found in schizophrenic patients, in which failure in gamma oscillatory synchrony seems to be a specific functional component underlying the cognitive deficit and other symptoms of the disorder [61, 62]. Clinical reports have described complexity in gamma oscillatory response in schizophrenic patients, i.e. opposite changes in gamma oscillations have been linked to chronic versus psychosis states of the disease. A deficit in gamma power is generally correlated with negative symptoms, whereas an increased propensity for gamma oscillations is found during psychotic episodes and hallucinations [63–67]. Further support for the role of N-methyl-D-aspartate (NMDA) and GABAergic dysregulation in the genesis of perturbed gamma rhythm comes from consistent findings across species. Network oscillation and connectivity in the gamma frequency range can be readily observed, both experimentally and clinically, and may generate essential data concerning the pathophysiological processes underlying the dysfunction in the integrity of glutamatergic, dopaminergic, and GABAergic neuronal circuits in schizophrenia.

Glutamate NMDA receptor antagonists such as PCP, ketamine, and MK-801 have utility in modeling the positive, negative, and cognitive deficits of schizophrenia in healthy man and laboratory animals [68–72]. In preclinical studies, acute administration of PCP elicited aberrant network oscillations in the higher gamma frequency range [73–75]. A reduction of theta oscillations [76] and functional connectivity observed with PCP [75] correlates with the associated deficit in cognitive process (see fig. 2 for a case study on PCP with risperidone reversal). In the case of ketamine, the enhanced gamma network oscillation was independent of hyperlocomotion [75, 77, 78]. For MK801, the enhanced higher gamma oscillatory activity was associated with peak functional coherent activity in slow α1 oscillations in the frontoparietal cortical area [75, 78]. The effect on slow alpha oscillatory rhythm has been correlated earlier to serotonergic control mechanisms elicited by hallucinogenic drugs such as lysergic acid diethylamide (LSD) and the serotonergic phenethylamine hallucinogen [1,2,5-dimethoxy-4-methylamphetamine (DOM)] [79].

The atypical antipsychotics decreased EEG slow alpha and beta spectral power, especially within the striatum [80], and functional connectivity in slow alpha and higher gamma oscillatory rhythms in multichannel EEG-in-
Fig. 1. a Time course of the effects of combined subcutaneous administration of vehicle/vehicle, vehicle/scopolamine (0.16 mg/kg), rivastigmine (3 mg/kg)/vehicle, and rivastigmine (3 mg/kg)/scopolamine (0.16 mg/kg) on the EEG spectral patterns in frontoparieto-occipital cortical areas (only the right hemisphere is presented and the red dot on the brain diagram marks the brain region in which the drug effects are displayed, n = 8 for each condition) during each 15-min block of the recording session in rats. Mean EEG spectra were expressed as a percentage of the mean spectra in the baseline period. Rivastigmine elicited peak changes in both slow theta (4.5–6 Hz) and gamma (32–48 Hz) frequency oscillations, whereas scopolamine enhanced delta power (0.5–4 Hz) for 2 h after administration. Changes from baseline are presented as a heat map with cold dark blue to warm red color indicating an order increase in the magnitude of oscillatory power density in particular frequency. b Changes in the delta frequency power (0.5–4 Hz) during the first 2 h after combined subcutaneous administration of rivastigmine and scopolamine (only the right hemisphere is displayed). Color coded bars above and underneath the curves indicate intervals in which oscillatory activity difference differed from vehicle and scopolamine, respectively (mixed-model ANOVA). c Network coherence changes at baseline T0’ and at 45 min after pharmacological treatment of scopolamine elicited coherent activity in the delta frequency range in comparison with that of the control group (green arrowhead), whereas rivastigmine enhanced coherent activity in slow theta (4.5–6 Hz) and gamma (32–48 Hz) frequency oscillations (blue arrowhead). d Functional network coherence changes from baseline in each frequency band of interest derived from consecutive 4-second epochs concatenated and averaged in the first 15-min block (upper panel). The width of the edges between pair electrodes is drawn proportional to the weight of changes in coherent activity from baseline (0–50, 50–100, and 100–150%). Red color represents increases and blue color indicates decreases. Average networks derived from the first session’s recording session in each pharmacological condition and for each frequency band of interest: δ (0.5–4 Hz); θ 1  (4.5–6 Hz); θ 2  (6.5–8 Hz); α 1  (8.5–11); α 2  (11.5–13); β 1  (13.5–18 Hz); β 2  (18.5–30 Hz); γ 1  (30.5–50 Hz); γ 2  (50.1–100 Hz). Time-evolving dominant coherent activity in the frontoparietal and occipital structures indicated the potential of rivastigmine to attenuate scopolamine-induced most persistent δ frequency edges (for further details see Ahnaou et al. [7]). Data: Drinkenburg laboratory. Veh = Vehicle; Sco = scopolamine; Riv = rivastigmine.
Fig. 2. a Time course effects of combined subcutaneous administration of vehicle/vehicle, vehicle/PCP (2.5 mg/kg), risperidone (2.5 mg/kg)/vehicle, and risperidone (2.5 mg/kg)/PCP (2.5 mg/kg) on the EEG spectral patterns in fronto-parieto-occipital cortical areas (only the right hemisphere is presented and the red dot on the brain diagram marks the brain region in which the drug effects are displayed; n = 8 for each condition) during each 15-min block of the recording session in rats. Mean EEG spectra were expressed as a percentage of the mean spectra in the baseline period. Peak changes were elicited in higher gamma frequency oscillations for 2 h after the administration. Changes from baseline are presented as a heat map with cold dark blue to warm red color, indicating an order increase in the magnitude of oscillatory power density in particular frequency. b Changes in peak gamma 2 frequency (50.1–100 Hz) during 2 h after the combined treatments (only the right hemisphere is displayed, n = 8 for each condition). Color coded bars above and underneath the curves indicate intervals in which oscillatory activity difference differed from vehicle and PCP, respectively (mixed-model ANOVA). Risperidone was potent enough to significantly attenuate the aberrant high gamma oscillations in PCP-treated rats. Data: Drinkenburg laboratory. Veh = Vehicle.
Amphetamine is a widely used psychomotor stimulant for modeling positive symptoms of schizophrenia in rodents, and it is known to elicit prominent motor activity, during which the firing rate of neurons in the hippocampus is rhythmically modulated at a ~8-Hz ‘theta rhythm’ [85]. Amphetamine mainly induced an increase in EEG power and coherence in the higher theta and alpha bands. Increases in alpha power correlated with increases in locomotor activity [7, 86]. Pretreatment with the atypical antipsychotic olanzapine consistently attenuated the amphetamine-induced pathological enhancement of oscillations and functional connectivity at the slow alpha frequency range [81].

While it has been proposed that insufficient NMDA-R drive of fast-firing parvalbumin GABA-expressing interneurons is a prime mechanism of the disturbances in gamma oscillations seen in schizophrenics, in addition nonphysiological changes in terms of prolonged entrainment and increased gamma oscillatory activity have also been reported after administration of amphetamine or the dopamine agonist apomorphine, thus emphasizing the intricate relationship between hyperdopaminergia, hypogluta tematnergia, and GABA system dysfunction in schizophrenic symptomatology [87, 88].

Other Models
Deregulated levels of excitation and inhibition leading to abnormal EEG network oscillations and connectivity represents an effective strategy to assess the efficacy of novel drugs targeted at strengthening plasticity and inter- and intrahemispheric connectivity. Perturbations in the mechanisms underlying structural and functional developmental processes have also been useful to test pharmacological responses in disrupted cortico-cortical and cortico-subcortical oscillatory synchrony. For instance, clozapine was effective in reversing the deficit in long-range EEG theta network connectivity between the prefrontal cortex and the hippocampus in rats exposed to maternal immune activation, known as a risk factor for schizophrenia [89, 90]. Another example is the destabilization of neuronal networks and the increased incidence of epileptiform activity associated with pathologically elevated amyloid beta and the microtubule-binding protein Tau. Seizure phenotype (spikes and sharp waves) is most often noticed in models carrying the Swedish mutation, including Tg2576, APP23, hAPPJ20, APdE9 [91, 92], and apolipoprotein E4 [94], which strongly contribute to impaired functional connectivity across brain regions. Antiepileptic drugs that block sodium channels suppressed neural hyperactivation and epileptiform discharges in APdE9 [95]. The antiepileptic drug levetiracetam effectively suppressed abnormal spiking activity in hAPP mice and reversed their behavioral abnormalities and cognitive impairments [96], whereas cessation of levetiracetam treatment was accompanied by the reappearance of the recurrent aberrant network activity, dysfunctional epileptiform network, and behavioral abnormalities [96]. This potential mechanistic convergence of the effects of elevated amyloid beta and Tau makes EEG networks and functional connectivity strong functional markers for assessing novel disease interception therapeutics.

It is important to note that abnormalities in other EEG frequency bands than theta, alpha, and gamma have been well documented in a number of brain disorders and have been paralleled by preclinical animal disease models. While beyond the scope of this review, it is necessary to highlight the difficulty of parsing out the specific implication of a deficit in oscillations in a single frequency band because of the interdependence of neuronal oscillatory activity in different frequencies such as delta-gamma, theta-gamma, and delta-beta cross-frequency coupling [97–99].

Pharmaco-Event-Related Potentials
ERP and event-related oscillations are extensively used to study the disruption of neuronal circuits underlying sensory encoding, information processing, and attention

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Neuropsychobiology 2015;72:151–164

Drinkenburg/Ruigt/Ahnaou
in neuropsychiatric and neurodegenerative disorders. To date, several sensory-level ERP measures, including the auditory P50 paradigm, mismatch negativity (MMN), and P300 responses have been validated in both human clinical investigations and animal models [100–102].

**P50 Gating Paradigm**

The ability of the central nervous system to inhibit the response to incoming irrelevant sensory input is a fundamental protective mechanism that prevents the flooding of higher cortical centers with irrelevant information. The auditory paired-stimulus P50 paradigm is a prominent neurophysiological tool used to index preattentive auditory processing underlying stimulus detection. Abnormalities in P50 suppression have been related to dysfunctional auditory information evaluation and speed processing in cognitive tests in AD and schizophrenic patients [103–105].

Changes in the amplitude of auditory-evoked potential (AEP) responses in humans and animals can be demonstrated in the double click paradigm, in which two identical auditory tones are presented in a time window of 500 ms. Normal subjects have a smaller response to the second stimulus tone (S2) compared to the first stimulus tone (S1), and the ratio measure (S2/S1) is used as a quantitative index of sensory gating. Lower ratio numbers reflect stronger attenuation of irrelevant input and thus better gating capability. Modeling sensory-gating deficits in experimental animals often involves the perturbation of their normal physiological gating processes by the use of different pharmacological challenges (scopolamine, amphetamine, PCP, MK-801, and ketamine).

Scopolamine disrupts sensory gating in rats by increasing N50 amplitude for the S2 stimulus, whereas donepezil reversed such gating deficit index by increasing the N50 amplitude of the S1 stimulus [106].

The translation between animal and human pharmacological AEP components requires special attention in order to appreciate possible discrepancies in peak latencies and consequent labeling. The methodological approach including epidural versus indwelling electrode positioning can account to a large extent for discrepancies in the definition of the human P and N wave equivalents in rodents. Latency differences may also relate to species (e.g., rat versus mouse), but regardless of such differences when using a gating paradigm, for example, one can find a consistent and highly replicable reduction of the amplitude of the S1 stimulus [106]. Again, these AEP discrepancies underline the necessity of careful consideration of choice of methodology and where possible adherence to future animal guidelines for standardization of p-EEG and pERP use, especially when studies from different research groups are to be compared.

Amphetamine and PCP elicit a reduction in both the amplitude to the first stimulus and the gating index [107–109]. Likewise, the dopamine receptor agonist apomorphine dose-dependently reduced the amplitude response to S1 stimuli and thereby increased the S2/S1 ratio as well as the gating deficit in rats [110]. The antipsychotic clozapine prevented the auditory gating deficits induced by PCP in the CA3, dentate gyrus, and medial prefrontal cortex [111].

The P50 gating deficit models have been useful to characterize the effect of novel drugs and the relevance of novel biological targets. Nicotinic acetylcholinergic receptors (nAChR) have been implicated extensively in human and animal studies of attention, learning, and memory, and are recognized as attractive targets for drug development in cognitive and neurodegenerative disorders. The selective α7-nAChR agonist PNU-282987 and the positive allosteric modulator PNU-120596 improved the auditory gating deficit caused by amphetamine in rats [108, 112]. Likewise the selective α4-nicotinic acetylcholine receptor partial agonist JN403 restored the auditory gating deficit in the DBA/2 mouse model [113]. The α4-β2-nicotinic-acetylcholine receptor agonist AZD3480 was useful to reveal the influence of this subunit of the nicotinic receptor on event-related gamma oscillation [114].

Reduced intracellular cAMP and/or cGMP levels in frontal and temporal cortex have been involved in cognitive deficits, suggesting the potential therapeutic utility of phosphodiesterase inhibitors (PDE2, PDE4, PDE5, PDE9, PDE10) for improving cognitive processes [115]. The PDE4 inhibitors RO-20-1724 and rolipram increased the amplitude for the P20 and N40 AEP components, and reversed the disruptive effect of amphetamines on AEP and gating in mice [116]. The PDE2 inhibitor BAY 60-7550 increased the P1 peak amplitude to S1 stimuli, whereas the PDE10 inhibitor PQ-10 increased the N1 peak amplitude [117], but in our hands PQ-10 failed to prevent disruptive effects of amphetamine and PCP on AEP morphology and aberrant EEG oscillations, which limits interpretation of the procognitive potential of this compound [75].

Similarly, ketamine impaired auditory gating indices and elicited aberrant high-frequency oscillations in rodents [118–120]. This effect was normalized by systemic administration of an antipsychotic or by prior inactivation of the medial septum by the GABA agonist muscimol [120].

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**p-EEG Studies in Animals**

Neuropsychobiology 2015;72:151–164

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The P50 gating paradigm has also been used to examine the disruptive effects of other pharmacological challenges, both in neurodevelopmental models of schizophrenia and in transgenic mouse models of AD. For instance, cannabinoid receptors (CB1) and endocannabinoids have been linked to psychiatric disorders. The CB1 receptor agonist CP-55940 significantly disrupted auditory gating as well as neuronal theta and gamma network oscillations in the hippocampus and entorhinal cortex in anesthetized and freely moving rats [121, 122]. In the neonatal ventral hippocampal lesion model of schizophrenia, sensory gating function is impaired and is associated with a prolonged latency from S1 to N1 and reduced phase-locked theta and gamma oscillations, particularly at S1 [122, 123]. Finally, in transgenic mouse models of AD, information processing deficits are associated with an altered excitation-inhibition balance in brain-wide neuronal networks. For instance, transgenic mice carrying human APPswe and PS1-A246E transgenes show impaired auditory gating, which is associated with the overproduction of Abeta42 [124], while APPswe/PS1E9 AβE9 mice display aberrant AEP as reflected by larger cortical and thalamic amplitudes of different AEP components to both S1 and S2 stimuli with a paired stimulus index, indicating that the earliest cortical component N1 was less suppressed in AD-modeled mice than in wild-type animals [125].

Passive Oddball MMN Paradigm

MMN is typically measured with a passive oddball and is a neurophysiological index of the ability of the brain to extract relevant information from an irrelevant background, i.e. by comparing the incoming stimuli to a short-lived sensory memory trace of preceding sounds. NMDA receptors have been implicated in the generation of the MMN response and hence the MMN has been proposed as an index of NMDA receptor (dys)function. The non-selective channel blockers of NMDA reliably diminish automatic deviance detection in human subjects as well as in animal models [126, 127]. Local application of the NMDA antagonist PCP disrupted MMN in the wake monkey auditory cortex in a layer-specific manner [127]. MMN-like activity can be observed in mice in both duration and frequency deviance paradigms [128], and was attenuated by ketamine [129]. In rats, ketamine affected AEP latencies and attenuated deviance by increasing the amplitude to standard stimuli. CP-101,606, a highly selective antagonist at the NR2B subunit of the NMDA receptor, abolished the MMN response by inhibiting the N1 amplitude of the deviant stimulus [130]. Similarly, in rats the deviance detection associated with MMN-like responses (see fig. 3a, b, c for a case study on MK-801) as well as evoked oscillations (see fig. 3d for a case study on MK-801) was dose-dependently affected by MK-801 [131].

Active Oddball P300 Paradigm

The P300 and P3-like AEP typically measured in an active oddball paradigm is a positive wave in the ERP that occurs 300 ms or more after the stimulus involving voluntary action after a low-probability, task-relevant stimulus presentation. The P300 and P3-like AEP amplitude has

![Fig. 3](image-url)
Amplitude (μV)

Time (ms)

MMN amplitude

Time (ms)

MMN latency

Vehicle MK801 (mg/kg)

0.16 0.64 2.5

Standard Deviant Standard-deviant

MK801 (mg/kg)

0.060

0.050

0.040

0.030

0.020

EEG frequency oscillations (Hz)

0.0 – 20.0

– 40.0

– 60.0

– 80.0

– 100.0

0.0

– 50

50

100

150

200

250

300

350

400

500

100.0

80.0

60.0

40.0

20.0

0.0
been proposed to represent allocation of attentional resources and memory processing [132]. In monkeys, scopolamine prolonged the latency of the late P300-like potentials in the cortex and hippocampus, whereas the novel benzodiazepine inverse agonist S-8510 reversed the scopolamine-induced deficit [133]. Rats performing an active discriminant task displayed larger amplitudes in target trials compared to nontarget trials [134–136], and repeated methamphetamine administration in this model reduced the amplitude of P3-like AEP, indicating that changes in catecholamine transmission may affect the P3 generation [136], whereas modafinil, a drug used for improving alertness, lowered behavioral performance, decreased P3-like latency, and slightly affected its amplitude [134].

As exemplified above, the growing interest in network oscillations and stimulus-induced changes in sensory processes, which are phylogenetically well conserved, can provide opportunities for designing useful translational biomarkers of functional target engagement and thereby for the discovery of novel therapeutics.

Conclusion

Animal EEG research has made valuable contributions to neurophysiological science: as animal neurophysiological studies are open to invasive brain recording and stimulation paradigms as well as other in vivo techniques (e.g. multi- or single unit recordings, optogenetics), the neuronal circuits and oscillation-generating systems underlying the EEG can be studied in detail. The use of animal p-EEG has been and still is instrumental in drug discovery and development: it is generally applied to characterize the functional effect or potential efficacy of test compounds, to assess pharmaco-dynamic characteristics, and to monitor side effects (e.g. sedation) and toxicity (e.g. epileptic seizures). Over the past decade p-EEG has evolved much more as a pharmaco-dynamic biomarker for specific pharmacological activities (e.g. benzodiazepines, glutamatergic compounds, etc.), rather than as a pharmaco-therapeutic predictive marker with specificity for every type of treatment efficacy: the translational validity of applications of animal p-EEG and pharmaco-sleep EEG is dependent on the psychoactivity and/or neuronal substrates under investigation: for studying effects of drugs on sleep-wake and neurocognitive processes, rodent p-EEG has shown high predictive and (back-)translational validity, while reversal of several challenge models has been successfully validated as well.

p-EEG is thus thought to have significant potential as a translatable, intermediate biomarker of central pharmaco-dynamic activity; however, its full potential could not yet be realized due to poor standardization of methodology, especially between academia and industry research, rendering data pooling and meta-analyses flawed and assessment of translatability problematic [137]. Therefore, the animal p-EEG review papers in this special issue essentially form a prequel to novel IPEG guidelines for animal p-EEG and animal pharmaco-sleep EEG studies.

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Neuropsychobiology 2015;72:151–164

Drinkenburg/Ruigt/Ahnaou
p-EEG Studies in Animals


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Neuropsychobiology 2015;72:151–164
DOI: 10.1159/00042210
163


