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REVIEW ARTICLE

A roadmap for development of neuro-oscillations as translational biomarkers for treatment development in neuropsychopharmacology

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New treatment development for psychiatric disorders depends critically upon the development of physiological measures that can accurately translate between preclinical animal models and clinical human studies. Such measures can be used both as stratification biomarkers to define pathophysiologically homogeneous patient populations and as target engagement biomarkers to verify similarity of effects across preclinical and clinical intervention. Traditional "time-domain" event-related potentials (ERP) have been used translationally to date but are limited by the significant differences in timing and distribution across rodent, monkey and human studies. By contrast, neuro-oscillatory responses, analyzed within the "time-frequency" domain, are relatively preserved across species permitting more precise translational comparisons. Moreover, neuro-oscillatory responses are increasingly being mapped to local circuit mechanisms and may be useful for investigating effects of both pharmacological and neuromodulatory interventions on excitatory/inhibitory balance. The present paper provides a roadmap for development of neuro-oscillatory responses as translational biomarkers in neuropsychiatric treatment development.

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INTRODUCTION

New treatment development in psychiatry depends on the availability of biomarkers that permit translation between preclinical and clinical research. Event related potential (ERP)-based measures, such as auditory N1, mismatch negativity (MMN) or P300, have proven among the strongest biomarkers of brain dysfunction in schizophrenia [1, 2], but translational utility of these measures has been hampered by the significant differences in timing, polarity and scalp distribution across species. Here, we review the degree to which recent advances in the use of neuro-oscillatory approaches to analyze both human and rodent ERP data permits greater utility and rigor within translational research.

For ERPs, continuous electroencephalographic activity (EEG) is recorded along with the timing of "events," such as auditory/visual stimuli or motor responses. The continuous EEG is then segmented into discrete epochs relative to the timing tags. In traditional ERP approaches, the epochs are then averaged within the "time domain," giving rise to a series of positive and negative peaks that vary across time and scalp distribution. Peaks with consistent polarity, timing, scalp distribution and response to parametric manipulation (e.g. loudness, probability) are termed "components" (e.g. refs. [3, 4]). While effective, ERPs capture only a small portion of the information inherent in the EEG signal [5].

Oscillatory analyses of EEG/ERP data depend on the use of spectral decomposition or "time-frequency" (TF) analysis. In spectral analyses, data are analyzed as a function of amplitude (or power) over time within specific frequency-bands. While computationally more demanding than traditional ERP analyses, such approaches potentially provide greater insights into underlying physiological mechanisms, as well as greater ability to translate between human and animal studies in relationship to the oscillatory "connectome" [6]. Here we provide an overview of current translational usage of both time- and TF ("spectral") approaches for the analysis of ERP data, as well as a roadmap for studies needed to further validate translational neuro-oscillatory approaches to support novel treatment development.

COMPUTATIONAL ASPECTS OF NEURO-OSCILLATORY ACTIVITY

Neuro-oscillatory activity is typically analyzed in discrete frequency-bands that were originally described based on

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Table 1. Overview of typical frequency bands used for spectral analyses.

Frequency Band	Frequency (Hz)	Processes	Human ERP	Translational paradigms (rodent/monkey)	Local-circuit substrates
Delta	0.5–4	oscillatory entrainment, non-REM sleep	P300, late cognitive potentials	Entrainment, sleep	NR2C; T-type Ca^{2+} channels
Theta	4–7	Sensory response; memory integration	Auditory N1, MMN; Visual P1; Fixation-related potentials error related negativity	MMN, hippocampal memory encoding	Somatostatin (SOM) interneurons
Alpha	8–12	Brain "idling"; thalamocortical processing; pulvinar-cortex interaction	Ongoing alpha EEG amplitude eyes open/eyes closed; visual steady-state response; stimulus/attention-induced alpha ERD	Pulvinar modulation (monkey)	High-threshold thalamic interneurons
Beta	12–24	Motor processing; cross-region coordination, top-down information transfer	Pre-motor potentials; task-related beta suppression	Pre-motor potentials	Gap junctions; M-currents; Kc7-type K^{+} channels
Gamma	>24	Local circuit activation, bottom-up information transfer, binding	Induced gamma; auditory steady-state response	Auditory steady-state response	Parvalbumin (PV) interneurons

empirical observation and are named in order of discovery. Thus, alpha (8–12 Hz) rhythms, which predominate over occipital brain regions during wakefulness, were first described in the 1920s based upon changes in amplitude during eyes-closed vs. eyes-open conditions [7]. Beta (12–24 Hz) rhythms were described shortly thereafter based upon pre-movement activity over motor cortex [8]; gamma (>24 Hz) rhythms based on "psychical activation" [9], delta (1–4 Hz) rhythms based on sleep [10]; and theta (4–7 Hz) rhythms based on psychomotor seizures [11] (Table 1).

Despite the empirical origins of these rhythms, ongoing research has reified these definitions and has begun to characterize the underlying neural mechanisms [12, 13]. Given the limited number of frequency-bands relative to the number of potential cellular/network generation mechanisms, it is clear that multiple mechanisms may contribute to activity within each band. Specific generator mechanisms may also cross traditional frequency-bands [14]. Nevertheless, current nomenclature permits efficient communication of results [13].

EVOKED VS. SINGLE-TRIAL SPECTRAL ANALYSIS

Within each frequency-band, several measures are obtained that offer complementary information regarding underlying generator mechanisms (Fig. 1). Specific measures obtained from TF analyses include (1) evoked-power, (2) single-trial power, (3) intertrial coherence (ITC) [15]—also termed phase-locking factor (PLF) [16, 17], and (4) event-related desynchronization (Fig. 1a, left). These measures all provide mechanistic information that is lost in traditional time-domain ERP approaches.

Evoked-power ("power of the average") represents the spectral decomposition of the traditional ERP into the TF-domain and permits differentiation of spectral components that are superimposed in the traditional ERP. Any of a number of TF decomposition approaches may be used, including fast Fourier transform (FFT) or Wavelet decomposition (e.g. "Morlets" [18]). For wavelets, the number of cycles (typically 3–6) is tailored to specific frequency-bands [19, 20].

Single-trial power ("average of the power") is calculated by first decomposing each individual response into the TF-domain and then averaging the single trials (Fig. 1a, right). An additional measure, "induced power", may be obtained by subtracting or regressing evoked-power from total power [21, 22], isolating components that are not phase-locked. As with evoked-power, total single-trial power is typically represented in μV^2 (or single-trial amplitude as μV),

Intertrial coherence (ITC, PLF) represents the consistency of responses across trials, and is represented as percentage (0–1), or percent (0–100%) coherence across trials. Traditional evoked responses may reflect either pure phase-resetting of ongoing oscillatory activity, pure added power, or a combination, which can only be determined by single-trial analyses [23, 24]. Moreover, these processes may be differentially mediated by driver vs. modulatory inputs from thalamus to cortex (e.g. [25]).

Event-related desynchronizations (ERD) represent a reduction in ongoing power following stimulus presentation. Conceptually, surface-recorded oscillatory activity is largest when individual local-circuit ensembles oscillate in-phase with each other, leading to summation at a distance [26]. By contrast, when ensembles desynchronize as occurs when individual ensembles are brought "on-line" for cognitive operations, the surface-recorded activity decreases. ERD are particularly relevant for alpha activity, which increases with eye-closure and is thought to represent "idling" of the visual system. Alpha amplitude is reduced tonically during visual attention (vs. rest) and phasically by individual stimuli, leading to a stimulus-driven alpha ERD [27, 28].

Examples of these processes are shown in Figs. 1 and 2. Figure 1b shows a paradigm in which visual responses are

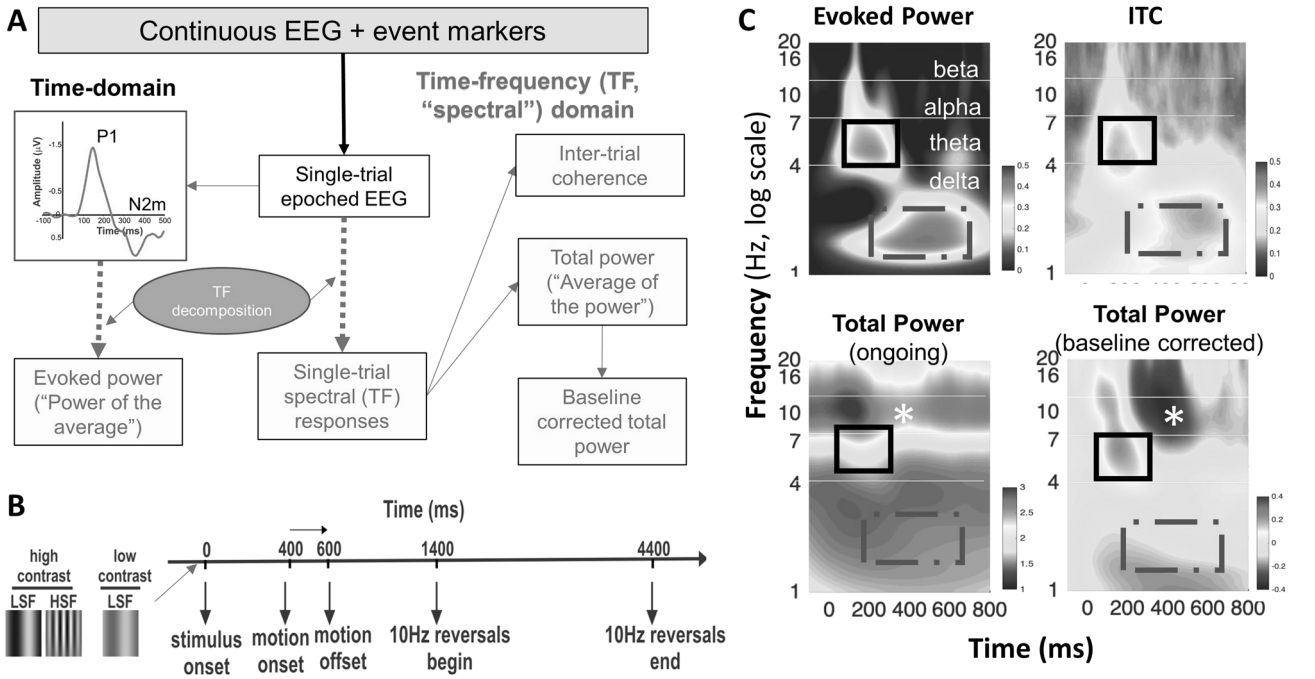

Fig. 1 Illustration of differential information obtained from evoked and single-trial analyses. a Schematic diagram of processing scheme. Unshaded boxes represent time-domain measures. Shaded boxes represent time-frequency (TF) domain or "spectral" measures. For time-domain measures, random EEG activity and waves that are not time or phase-locked to event onsets do not survive signal averaging across epochs and are not captured in the ERP (see also Fig. 2). TF decomposition can be applied either to averaged time-domain files, yielding evoked-power analyses, or to the single-trials prior to averaging, yielding separate assessments of intertrial coherence (ITC) and total power (evoked + induced). Estimation of power from the single trial epochs preserves and quantifies all of the neuro-oscillatory activity present, irrespective of whether the oscillations elicited by the event are "evoked" or "induced". Total ongoing power in humans tends to be dominated by ongoing alpha activity. Therefore, total power is typically baseline corrected to permit better visualization of stimulus-induced changes. **b** Cartoon of the recently developed interleaved visual presentation paradigm ("JH-Flkr") showing initial stimulus onset at 0 msec, followed by motion onset at 600 msec and steady-state stimulation onset at 1400 msec. **c** Time-frequency plots for Evoked-Power, Intertrial coherence (ITC, "phase locking"), Ongoing (i.e. non-baseline corrected) single-trial Total Power and Baseline corrected total power. Note that the response evoked by stimulus onset occurs primarily in the theta frequency range (solid box) and is accompanied by alterations in both ITC and total power. By contrast, the response evoked by motion onset occurs primarily in the delta frequency range (dashed box) and is associated with alterations only in ITC but not total power, suggesting differential underlying local circuit mechanisms. Finally, the stimulus-induced alpha event-related desynchronization (ERD) (asterisk) is not associated with alterations in either evoked-power or ITC but appears only in single-trial power analyses. Adapted from ref. [61] .

obtained both to the onset of a stimulus and its subsequent motion. In the traditional time-domain ERP both responses are represented simply as positive and negative peaks in the waveform (Fig. 1a). By contrast, in TF analyses, the two separate response types are resolved into different underlying frequency bands (Fig. 1c), suggesting that different local circuit ensemble types are involved. Similar representations are observed in evoked-power and ITC measures.

Total power measures provide complementary information. For example, in addition to the evoked activity, stimulus presentation also desynchronizes ongoing alpha activity (Fig. 1c, asterisk), which is thought to reflect bringing the region "on-line". This effect is further highlighted by correcting for baseline activity (Fig. 1d). Similarly, in gamma steady-state paradigms, presentation of auditory stimuli aligns ongoing gamma activity, leading to an increase in evoked-power and ITC. By contrast, stimulus-induced changes in gamma power that are not phase-locked will not appear in time-domain or evoked-power analyses and will only be detectable using single-trial measures (Fig. 2).

Significant coupling also occurs between frequencies. Typically, frequencies are hierarchically organized such that peaks of high-frequency activity occur at specific phases of the low-frequency cycle ("phase-amplitude coupling") [29–32]. In general, oscillatory activity represents an interplay between excitatory glutamatergic pyramidal neurons in cortex and local circuit GABAergic interneurons, modulated by additional neurotransmitter systems, and thus may be particularly useful as indices of excitation/inhibition (E/I) balance across disorders [26, 33–35].

CLINICAL FINDINGS

The majority of clinical studies using spectral decomposition approaches have focused on gamma activity, which may also be derived from narrow-band filtering of the traditional ERP. More recent studies have explored the spectral content of validated ERP measures such as auditory MMN, visual P1 or task-related P300. Single-trial analysis studies have also investigated alpha and beta ERD as measures of task engagement during sensory and cognitive processing.

Gamma

Gamma deficits have been studied extensively in schizophrenia using both auditory steady-state response (ASSR) and evoked-activity paradigms. For ASSR, stimuli are presented at 40-Hz permitting assessment of integrity of gamma-generating circuit elements. Deficits in ASSR have been widely replicated across the psychosis spectrum [36–43] and in relevant genetic risk syndromes (e.g. 22q11) [44], although literature in autism spectrum disorder (ASD) is conflicting [45]. Progressive reduction in auditory evoked gamma is seen over time in first-episode schizophrenia patients, but not in clinical high risk (CHR), suggesting that evoked

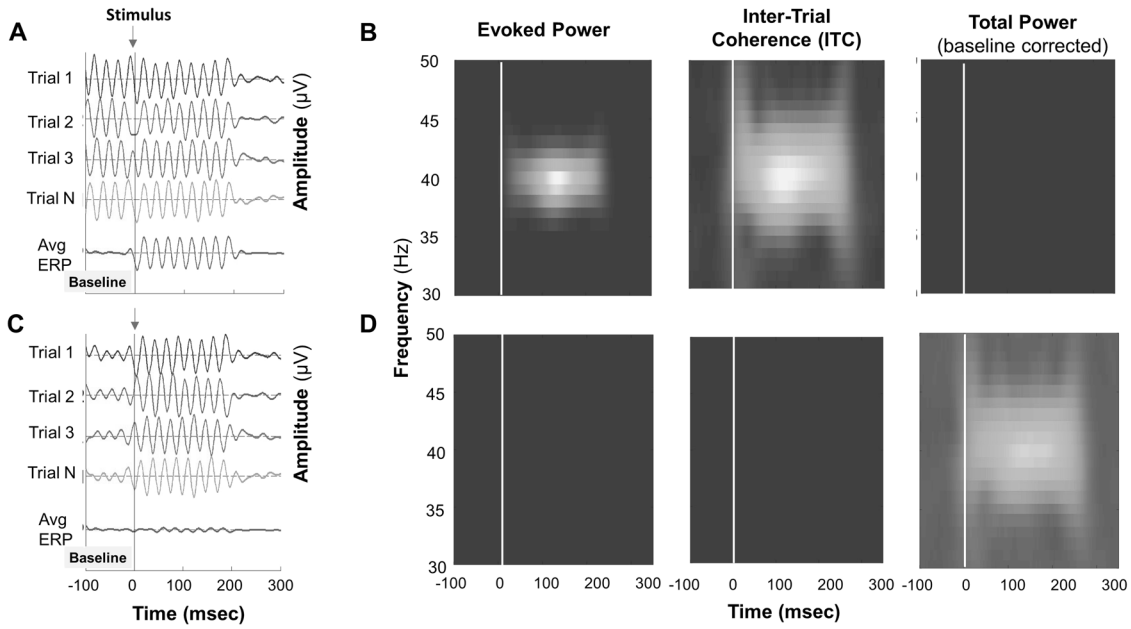

Fig. 2 Illustration of single trial event-related oscillations and corresponding time-frequency measures. a Stimulus evoked phase-resetting of ongoing gamma oscillations. Pure phase-resetting occurs when a stimulus evokes a change in the phase of the ongoing oscillations without evoking a change in the magnitude of the oscillations. Because the phase of the stimulus evoked-oscillation is reset in a consistent manner across trials, the single trial oscillations survive averaging and are evident in the ERP. Note that these oscillations are not evident in the pre-stimulus ERP baseline because their random phase leads to their being cancelled out when epochs are averaged to generate the ERP. In contrast, the oscillations show strong phase synchrony across trials for the first 200 msec post-stimulus and are therefore evident after averaging trials to derive the ERP. **b** In pure phase-resetting by a stimulus, the phase of ongoing oscillations is reset by the stimulus in a consistent manner across trials, resulting in high intertrial coherence (ITC). In this scenario, the TF analysis shows prominent gamma band evoked-power and ITC. However, because the stimulus does not evoke a change in the magnitude of the ongoing oscillations, there is no appreciable total gamma power response to the stimulus once baseline correction is performed. **c** Stimulus induced increase in the power of ongoing gamma oscillations with no phase resetting. As with **a**, oscillations during the prestimulus baseline period do not survive averaging during the generation of the ERP. In contrast to A, the stimulus induces an increase in the magnitude of oscillations, but because the post-stimulus oscillations are not phase synchronized across trials, very little of this activity survives averaging across epochs when generating the ERP. **d** With a stimulus-induced increase in power, but oscillations with random phase across trials, there is a clear increase in total power, but no appreciable evoked power or intertrial coherence. Adapted from ref. [17].

gamma may index progressive neurodegenerative processes that occur over the early course of the illness [46].

Theta

Deficits in theta frequency responses are observed prominently during both auditory and visual processing in schizophrenia. Deficits in early auditory processing, including impaired N1 [47] and MMN [48–50] generation have been demonstrated consistently in schizophrenia, including prodromal phases of the illness [51–53]. Both N1 and MMN were subsequently mapped into the theta-frequency-band using narrow spectral filtering [54] as well as more comprehensive TF approaches [33, 55–59] (Fig. 3).

In the visual system, sensory-driven P1 potentials also show prominent activity in the theta frequency range and are reduced in schizophrenia, particularly in response to low spatial frequency, magnocellular-biased stimuli [60–62]. Visual fixation-related potentials (FRP) also reflect primarily phase-reset of ongoing theta frequency rhythms and are also significantly reduced in schizophrenia [63]. Finally, theta activation over frontal regions may index adaptive cognitive controls [64, 65], including response inhibition [64, 66], and thus may index impairments of these processes in schizophrenia.

As opposed to the reductions observed in schizophrenia, increases in visual theta response have recently been observed in ASD, related to impaired face emotion processing [62]. Acute alcohol may disrupt theta generation across a range of processes including auditory N1 and MMN [67], especially in the context of bipolar disorder [68], visual sensory potentials, and cognitive activities such as visual P300 [69]. In individuals with chronic alcohol use disorder, reduced theta activation during reward processing has been found to correlate with increased impulsivity [69], consistent with the role of prefrontal theta in response inhibition.

Delta

Delta rhythms were initially defined in the context of slow-wave (non-rapid eye movement) sleep, in which thalamic neurons impose T channel-mediated slow coherent activity throughout cortex [70, 71]. During adolescence, there is a marked decline in delta-sleep activity [72, 73] that correlates with parallel reductions in cortical thickness and gray matter volume, all of which are thought to reflect age-related synaptic pruning [72, 74]. Reductions in delta amplitude during slow-wave sleep are well established in schizophrenia [75, 76] as are reductions in cortical thickness and gray matter volume, and thus support the potential role of erroneous- or hyper-pruning in schizophrenia [77].

During wakefulness, delta amplitudes are low, reflecting desynchronization of delta generators across cortex. However, during attention-dependent processing, regional delta rhythms become entrained to the rhythm of presented stimuli and increase in the selectivity and efficiency of local processing [78, 79]. Violations of these entrained rhythms may underlie the generation of the widely-studied P300 potential, which also shows spectral power within the delta range [80–82].

In schizophrenia, deficits in auditory delta entrainment [79] and steady-state delta response [83] correlate with impaired P300 generation, auditory perceptual abnormalities and working memory deficits. P300 deficits are observed consistently not only

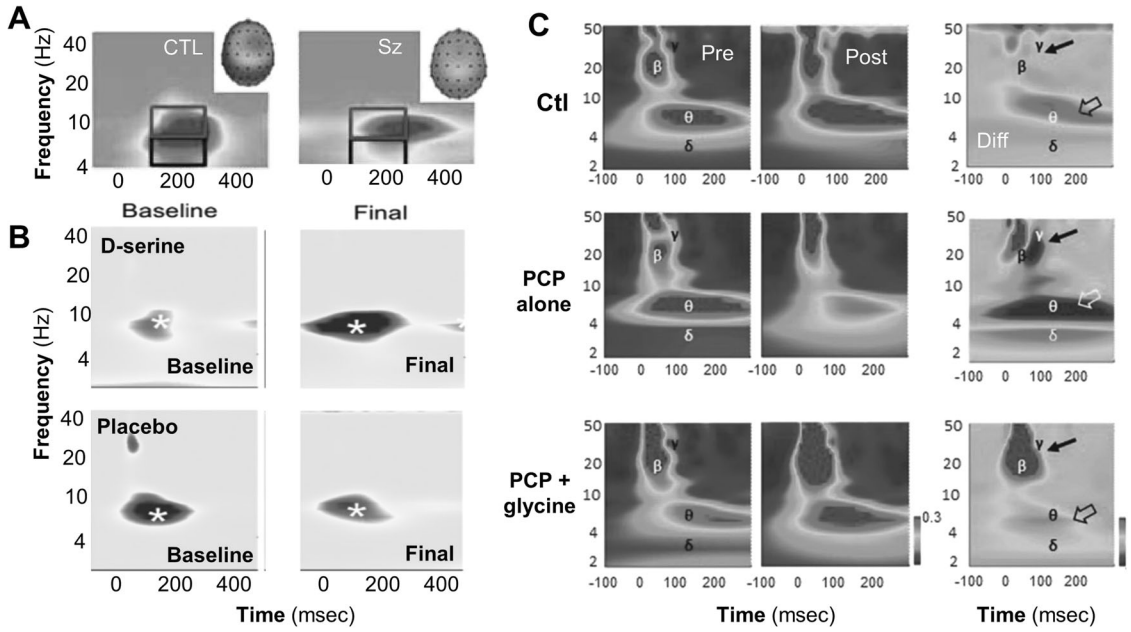

Fig. 3 Cross-species homology. a Mismatch negativity (MMN) in schizophrenia vs. control patients, showing deficits in evoked-power within the theta frequency range. From ref. [200]. **b** MMN prior to and following treatment with the NMDAR glycine-site agonist D-serine in schizophrenia (Sz) vs. placebo. From ref. [138], $*p < 0.05$. **c** MMN in rodents pre/post treatment with placebo (Ctl), PCP alone, or PCP + glycine in rodents. Note decrease in MMN-related theta activity pre/post PCP alone treatment, and prevention of the difference by simultaneous glycine treatment. From ref. [55].

across the illness course in schizophrenia [84] but also in the prodromal period preceding psychosis onset [85–87] other neuropsychiatric disorders including bipolar disorder [88], alcohol use disorder [89, 90] and neurodegenerative disorders [91].

Finally, in the visual system, the onset of motion elicits a characteristic negative potential with peak at ~200 ms termed the motion-N2 (N2m) [92]. As opposed to other stimulus-driven activity, N2m has recently been shown to have a spectral signature within the delta frequency range (Fig. 1c) and thus may be particularly useful for investigating underlying circuits. N2m/delta deficits have recently been reported in both schizophrenia and CHR [61] subjects.

Alpha/Beta

Alpha rhythms play a predominant role in coordination within the visual system whereas beta rhythms are particularly important with regard to sensory-motor processing and coordination of information across cortical regions [6, 93]. For both sets of measures, amplitudes are high during brain "idling," but are suppressed when brain systems are engaged [27]. Thus, posterior alpha is reduced in a "top down" fashion during sustained visual attention. Alpha "blocking" also occurs in response to stimulus presentation, leading to a stimulus driven ERD [28]. Both task and stimulus-induced modulation of alpha activity reflect in part reciprocal interactions between the pulvinar nucleus of the thalamus and visual regions of cortex [61, 94–97].

Deficits in alpha blocking in schizophrenia were initially discovered shortly after the discovery of the EEG itself [98], and were extensively replicated in the pre-ERP era (e.g. refs. [99, 100]). More recently, deficits in alpha/beta ERD over visual areas [101, 102] and beta ERD over motor areas [102, 103] have been observed during visuo-motor tasks, and shown to correlate with impaired task performance. By contrast to stimulus-driven activity, sustained alpha suppression during visual attention appears to be preserved [28, 79]. Alpha synchrony deficits in schizophrenia may also be studied using steady-state visual evoked potential (ssVEP) approaches [61, 104]. In children with ASD, reductions in ongoing alpha activity correlate with cognitive impairment [105], whereas in high-functioning ASD increases are observed in both resting alpha and ssVEP activity [62], suggesting involvement of alpha-generating circuits across pathophysiological disorders.

TRANSLATIONAL NEURO-OSCILLATION STUDIES

The characterization of oscillatory disturbances in neuropsychiatric disorders provides increased opportunities for cross-species translation. For many measures, particularly those utilizing passive sensory stimulation, paradigms are extremely similar across species, permitting direct cross-species comparison. Animal models can then be used to both dissect local circuit mechanisms and evaluate the effect of interventions, such as N-methyl-D-aspartate receptor (NMDAR) antagonists, that are known to produce schizophrenia-like deficits in humans.

GAMMA

Gamma activity, in general, is thought to reflect increased excitatory drive to specific cortical regions [106], which then can trigger rhythmic feedback inhibition from local fast-spiking parvalbumin (PV)-type basket interneurons [107] (Fig. 4). The characteristic frequency is imposed by the kinetics of AMPA-type glutamate receptors on the PV interneurons, as well as KV3.1/3.2K$^+$ channels that maintain narrow action potentials; and $GABA_A$ receptors, which drive the feedback inhibition of pyramidal neurons [108].

The cross-species translatability of the ASSR at this time requires further investigation. Whereas the ASSR in humans shows a consistent 40 Hz resonance, more variable results have been observed in rodents (e.g., refs. [109–111]. In some reports, NMDAR antagonism [112, 113] and genetic knockout of NMDAR on PV-expressing interneurons [114, 115] have been shown to decrease the 40 Hz ASSR in rodents, but in other studies the ASSR is increased by these manipulations [110, 111, 116].

In computational modeling, reductions in ASSR are most attributable to reductions of PV and GAD65 in PV interneurons [117], which may be a downstream consequence of NMDAR

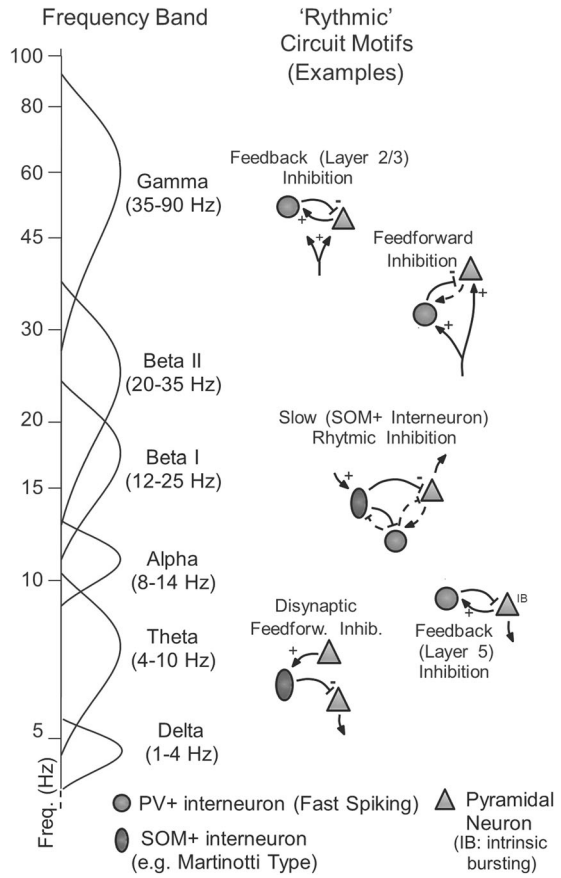

Fig. 4 Local circuit mechanisms underlying neuro-oscillatory measures. Frequency-bands and example circuit motifs whose activation is associated with frequency specific rhythmic activity in the neocortex. The frequency axis illustrates that oscillatory bands are partly overlapping (varying e.g. with excitatory and inhibitory drive). The circuit diagrams illustrate that activation of specific cells (e.g. fast spiking parvalbumim (PV+) expressing interneurons in superficial layers; somatostain (SOM+) interneurons) and their cortical connectivity are associated with rhythmic activity at bandlimited frequency-bands.

blockade [118], rather than to NMDAR dysfunction itself [117]. In rodents, effects of developmental NR1 knock-down may be reversed by $GABA_B$ agonists [119], although the applicability of this finding to humans has not been tested.

Task-related gamma modulation may also be observed in rodents. For example, cortico-hippocampal gamma synchronization transiently increases during working memory encoding [120] and retrieval [121]. In animal models, as in humans, gamma activity may also be extensively coupled to slower theta and delta rhythms [29, 30, 122–124]. Furthermore, in rodents, modulatory neurotransmitters such as dopamine may shift patterns of coupling [125]. Animal models thus provide an opportunity to determine the degree to which gamma deficits reflect dysfunction within specific gamma generating mechanism vs. the degree to which they are an indirect reflection of impaired generation of slower rhythms, or impaired cross-frequency coupling.

THETA

The MMN paradigm has also been extensively validated in both monkeys [126–129] and rodents [55, 113, 130–132], and as in humans depends strongly on NMDAR function. As in humans, rodent [55, 133] and monkey [134], MMN activity maps predominantly to the theta frequency range. Moreover, schizophrenia-like MMN deficits are induced by acute [135–137] and chronic [55] NMDAR blockade and prevented by the simultaneous administration of an NMDAR agonist [55], paralleling human studies [138] (Fig. 3c).

At the local circuit level, cortical theta rhythms depend primarily on the functioning of local circuit somatostatin (SOM)-type GABAergic interneurons [13] (Fig. 4). Moreover, in rodents both theta rhythms and MMN generation are selectively impaired by optogenetic silencing of somatostatin interneurons within cortex [139]. In rodents, increased theta synchrony, especially within the septo-hippocampal-entorhinal system [6], is also associated with working memory encoding [140] and retrieval [141, 142], and may thus serve as a model system for theta-related frontal cognitive deficits in schizophrenia.

DELTA

In animals, mechanisms underlying generation of delta rhythms have been studied most extensively in the context of sleep, in which thalamic neurons impose T-channel mediated slow coherent activity throughout cortex [70, 71]. Type 1 nitrergic cortical interneurons, which are known to co-express both somatostatin, neurokinin 1 (NK1) receptors, and NMDAR may also play a critical role in both NREM sleep generation and sleep-related consolidation [143], although the role of these cells in attention-dependent processing remains relatively unknown.

In monkeys, delta entrainment to stimulus regularities are observed that are similar to those in humans and are linked to synchrony between cortex and subcortical structures including the pulvinar [144–146]. P300-like activity is also elicited during active discrimination tasks in rodents. Furthermore, as in humans evidence suggests that cholinergic signaling in the medial septum (MS) and the nucleus basalis magnocellularis (NBM) may be important modulators of task-related delta activity of cortical ERP in the rat [147, 148] and can be modulated by pharmacological perturbation of cholinergic tone [149]. Additionally, selective lesions in the MS or NBM produce profound changes in both and synchrony in both cortical and limbic sites [150, 151].

ALPHA/BETA

In monkeys, as in humans, alpha rhythms within visual cortex appear to be driven by synchrony between pulvinar nucleus and cortex [96, 152], as well as feedback propagation from higher to lower tiers of the visual system [153]. Furthermore, NMDAR antagonists inhibit alpha while increasing ongoing gamma activity [153, 154], similar to the pattern observed in schizophrenia. Glutamatergic contributions to alpha generation may also be mediated, in part, by mGluR1 receptors [93] Other receptor systems involved in alpha generation, including muscarinic cholinergic [93, 155] and 5-HT2A [156] receptors, may be relevant for changes observed in neurodegenerative disorders and the effects of hallucinogenic psychostimulants, respectively.

In rodents, pulvinar nucleus is much less developed than in primates [157], and pulvinar contributions to neuro-oscillatory activity remains relatively unstudied [158]. Integrative beta function is also relatively unstudied in rodent schizophrenia models. Motor-related beta activity in rodents is critically dependent upon gap junction and M- currents mediated through Kc7-type potassium channels and may be modulated by both $GABA_A$ and NMDAR modulation [159, 160]. In rodents, NMDAR antagonists such as ketamine or PCP induce reductions in ongoing beta activity that may reflect impaired corticothalamic connectivity. Supporting this possibility, chemogenetic inhibition of the mediodorsal thalamus in mice decreases synchronization between mediodorsal thalamus and medial prefrontal cortex [161].

CROSS-SPECIES VALIDATION ISSUES

Despite the promise of neuro-oscillations as translational biomarkers, several methodological issues still need to be clarified before their widespread use for treatment development. The main "disconnect" between spectral activity obtained from human scalp-recorded activity and intracranially recorded oscillations in animals is the need for greater signal averaging in human recordings to differentiate task-related activity from background EEG.

A critical question, therefore, is the degree to which the oscillatory signature obtained from spectral decomposition of human ERP data reflects added energy "created" by the stimulus that coincidentally falls within specific frequency-bands vs. stimulus-induced activation/modulation of the same circuits that generate ongoing oscillatory brain activity.

This is especially the case with regard to conditions such as steady-state potentials, where the oscillatory structure is imposed by the eliciting stimulus, and by paradigms in which the exogenous stimulation evokes an increase in power that may therefore indicate a response that is superimposed on ongoing brain rhythms. In such cases, artifactual increases in ITC may be observed as well [32, 78]. Nevertheless, several translational measures, including ASSR, MMN [55, 162] and delta entrainment [79] involve primarily phase-reset of ongoing rhythms and thus appear to translatable across species [24, 163].

Further support for homology comes from the possibility that even continuously recorded endogenous potentials may, in fact, be synchronized to unmeasured events. For example, in humans and monkeys, saccadic eye movements lead to reset of ongoing theta rhythms not only within visual regions but also hippocampus [164, 165], a process termed "active sensing" [166]. The relationship can only be assessed, however, if eye movements are explicitly measured. In rodents, a similar relationship is observed related to whisker movement ("active whisking") [167], suggesting that even endogenous rhythms may, in fact, be synchronized to discrete events [168].

TREATMENT DEVELOPMENT

Current medication classes such as antipsychotics, antidepressants and anti-anxiety agents were discovered fortuitously and then "reverse engineered" primarily using radioreceptor approaches to translate across human and rodent models and demonstrate clinical target engagement. Many current treatment targets (e.g. ionotropic/metabotropic glutamate receptors) have low agonist affinity and thus do not support receptor-based approaches for determination of target engagement. Moreover, treatment development is increasingly focused on modification of circuit-level disturbances, such as impaired E/I balance, using multi-targeted treatment approaches. Neuro-oscillatory approaches specifically index local circuit activity and are translatable across rodents, monkeys and humans, supporting their use in development of next-generation treatment approaches.

For example, ASSR may be particularly related to chronic oxidative stress, which leads to downregulation of PV-type interneurons [169]. In rodents, both increases [109–111, 116] and decreases [113, 170] in ASSR are also reported, potentially explainable based on varying degrees of NMDAR occupancy across studies [112]. To date, the effects of manipulation of other receptor types such as Ca^{2+} permeable AMPA channels on local ASSR generation has not been assessed.

Even in humans, many aspects of the ASSR remain relatively unexplored, such as differential impairment of early (0–100 ms) vs. late (300–500 ms) response in CHR vs. first-episode schizophrenia [45], and differential effects of increasing interstimulus interval length/variability [37, 171], and stimulus duration [36] in controls vs. patients. Systematic exploration of the same parameter space in both humans and rodents, combined with rodent pharmacological and genetic studies are needed to refine the biomarker and increase its applicability across disorders.

By contrast, theta-band deficits such as indexed by MMN have shown significant sensitivity to NMDAR antagonists such as PCP, ketamine or MK-801 across rodent [133, 135], primate [126, 134] and human [172–174] models, suggesting NMDAR involvement within the SOM-containing E/I circuit [133]. Similar effects are also observed on theta activity within the paired click paradigm [175]. In rodents, as in humans, MMN generation may be modulated by NMDAR agonists such as glycine, D-serine or *N*-acetylcysteine [55, 138, 176, 177], suggesting utility for translational treatment development.

Nevertheless, in current animal models, MMN deficits are induced primarily by pharmacological challenge. Development of animals that more closely capture pathophysiological features of the disorder may lead to improved understanding of the basis for MMN deficits in schizophrenia and other disorders, and thus to improved treatments. Additionally, sub-chronic exposure to ketamine leads to lasting reductions in evoked theta activity, as well as cognitive performance that may rely on the networks that generate this rhythm [178–181].

The basis for these persistent changes needs to be understood, and may provide improved treatment targets for schizophrenia, alcohol use disorders, or others. Finally, development of translational biomarkers, in general, requires pre-competitive collaboration between industry, academia and government to support an FDA biomarkers approval [3]. Such a consortium has recently been established for MMN (www.erpbiomarkers.org), potentially paving the way for its use in patient stratification and outcome assessment.

Disturbances of alpha modulation are documented across a number of disorders including schizophrenia [62, 100, 101, 105] and ASD [62, 105]. Even though the alpha rhythm was first described almost 100 years ago, basic mechanisms underlying alpha generation remain unresolved. More etiological work is needed to understand and manipulate these circuits. Increasingly, subcortical structures such as pulvinar nucleus [61, 96] are implicated in alpha regulation and should be increased targets for treatment-related research.

Alterations in P300 generation, reflecting delta-band dysfunction, are caused not only by NMDAR antagonists [182] but also by other pharmacological agents including GABA agonists [182], 5-HT2A antagonists [183, 184], cannabinoids [185, 186] and muscarinic antagonists [187, 188]. The $GABA_B$ agonist gamma-hydroxyoxybutyrate may improve both delta-sleep time and cognition in schizophrenia [189], suggesting interactive contributions of multiple neurochemical pathways to delta generation. Although attention-dependent paradigms are difficult to implement in rodents, entrainment phenomena may be possible

Finally, oscillatory approaches may also be critical for demonstration of target engagement with non-invasive brain stimulation approaches, such as transcranial magnetic (TMS) or direct-current stimulation (tDCS), which target disturbances in intrinsic oscillatory activity [190, 191] in disorders such as schizophrenia [192–194] or depression [190, 191, 195–197]. For example, one interventional strategy involves entrainment of oscillatory activity at frequencies and phase relationships that are natural to the underlying neuronal circuits [13] and evident in the timing of cognitive processes [198, 199]. However, further exploration of these processes in both rodents and humans is required.

In summary, neuro-oscillatory approaches are ideally suited for integration across pre-clinical and clinical stages of new treatment development, especially for treatments targeting network level dysfunction and impaired E/I balance. Unanswered questions remain concerning the homology between specific oscillatory measures across human and animal models. Nevertheless, the strong conservation of the oscillatory frequencies across species provides novel opportunities for bidirectional cross-species

translation and assessment of target engagement by novel pharmacological and brain-stimulation-based approaches.

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AUTHOR CONTRIBUTIONS

DCJ participated in drafting the work or revising it critically for important intellectual content; final approval of the submitted version; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SJS participated in drafting the work or revising it critically for important intellectual content; final approval of the submitted version; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. KMS participated in drafting the work or revising it critically for important intellectual content; final approval of the submitted version; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. DHM participated in drafting the work or revising it critically for important intellectual content; final approval of the submitted version; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. LEH participated in drafting the work or revising it critically for important intellectual content; final approval of the submitted version; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AM participated in drafting the work or revising it critically for important intellectual content; final approval of the submitted version; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CLE participated in drafting the work or revising it critically for important intellectual content; final approval of the submitted version; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AIA participated in drafting the work or revising it critically for important intellectual content; final approval of the submitted version; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. TT participated in drafting the work or revising it critically for important intellectual content; final approval of the submitted version; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. PL participated in drafting the work or revising it critically for important intellectual content; final approval of the submitted version; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. TW participated in drafting the work or revising it critically for important intellectual content; final approval of the submitted version; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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