Gauging and controlling excitability in cortical disorders

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Purpose of review
Cortical excitability, defined as the cortex's responsiveness to incoming stimuli, is a fundamental concept in neuroscience and a targetable mechanism for controlling brain dysfunctions such as epilepsy, as well as other neurological and psychiatric disorders. In this review, we delineate the boundaries between physiological and pathological excitability, highlighting recent theoretical, experimental, and translational advances relevant to human brain disorders. Specifically, we describe the dynamic regulation of cortical excitability and propose practical means to monitor its known fluctuations as to guide therapeutic interventions.

Recent findings
From a conceptual standpoint, the last decade of research on cortical excitability has benefited from dynamical systems theory, which studies the behavior of nonlinear systems (here, the cortex) and their resilience to perturbations in different conditions (here, variable excitability). We review how fundamental relationships between excitability and resilience were verified in the brain in a series of recent studies. We also review natural fluctuations in cortical excitability, and how these may open windows of vulnerability for the expression of cortical dysfunctions. We then turn to the practicalities of measuring and monitoring cortical excitability, a latent variable that must be actively probed.

Summary
Practical means for gauging cortical excitability likely have broad applicability. To enable new developments in clinical practice, a principled design of pharmacological and neurostimulation therapies must leverage current understanding of cortical dynamics.

Keywords
cortical dynamics, epilepsy, excitability, resilience, seizure

INTRODUCTION

The cerebral cortex is the essential information processing system of the brain, which underlies the multifaceted mammalian cognitive abilities. To fulfill these functions, the cortex must be excitable to respond to environmental stimuli and propagate the information, but also resilient to avoid that excess stimulation disrupts its dynamical equilibrium. Many cortical disorders are believed to result from different flavors of imbalance in this fine equilibrium leading to seizures in epilepsy [1], sensory hypersensitivity in migraine [2], hallucinations in schizophrenia [3] or affective disturbances in bipolar disorder [4,5]. As a matter of facts, many drugs widely used to treat symptoms of these disorders, such as antiseizure medication, neuroleptics and mood stabilizers, act on the cortex by modulating its excitability [6].

Despite its relevance, a strict definition of cortical excitability, based on a sound understanding of its dynamics is often lacking in current research and finding ways for its reliable measurement and control remains an acute issue for translation to clinical practice. Although, the theme has been discussed for three decades in the context of transcranial magnetic stimulation (TMS, [4,7,8], renewed interest comes from the availability of neurostimulation devices and intracranial EEG in epilepsy capable of probing excitability more frequently and at finer spatio-temporal scales.

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KEY POINTS

- Incorporating dynamical system theory into research on cortical excitability has recently added mathematical exactness to historical terminology (seizure thresholds, (hyper-)excitability, etc.).
- Natural fluctuations in cortical excitability can be monitored passively with chronic EEG recordings, but actively probing the brain may prove more accurate.
- Translational research has incorporated quantitative methods to measure cortical excitability in both animal models and patients.
- Currently available antiseizure medication can act by dampening natural fluctuations in cortical excitability and lead to measurable decreases in an excitability index proposed here.
- Neurostimulation devices can likely modulate cortical excitability to influence seizure risk, but the lack of monitoring hampers the personalization of neurostimulation protocols.

We propose that epileptology can provide a fundamental definition of cortical excitability over its entire spectrum, delineating boundaries between its physiological and pathological counterparts. In the past two years, progress has been made in the theory [9], experimental models [10▪▪,11▪▪] and measurements of cortical excitability with intracortical [10▪▪] or transcranial [12▪▪,13▪▪,14] stimulation forming the focus of this review. Drawing on fundamental advances, we highlight the upcoming translational importance of probing brain circuits to understand their excitability and discuss the relevance of such measurements to cortical disorders. For future research, we propose the calculation of an 'excitability index', a unit-free metric that can be intuitively interpreted and derived from electrical or magnetic stimulation of the cortex.

Cortical excitability

Excitability is the essence of neurons in the cortex, which respond to incoming stimulation by mounting and propagating an electrical pulse - the action potential – to excite or inhibit other neurons. Cortical excitability results from thousands such cascade reactions and putatively reflects the excitability of individual neurons [15], the efficacy of their synaptic coupling [16] and the balance between excitatory and inhibitory neurotransmission (E–I balance) [17,18] as well as neuromodulatory and plastic changes (Fig. 1a). In the absence of a detailed mechanistic understanding, cortical excitability is simply conceptualized as a latent variable, which also integrates modulation by many endogenous and exogenous factors (e.g. ionic concentrations, neuromodulators, illicit or therapeutic drugs, etc., Fig. 1a) and is difficult to measure directly. Yet, cortical

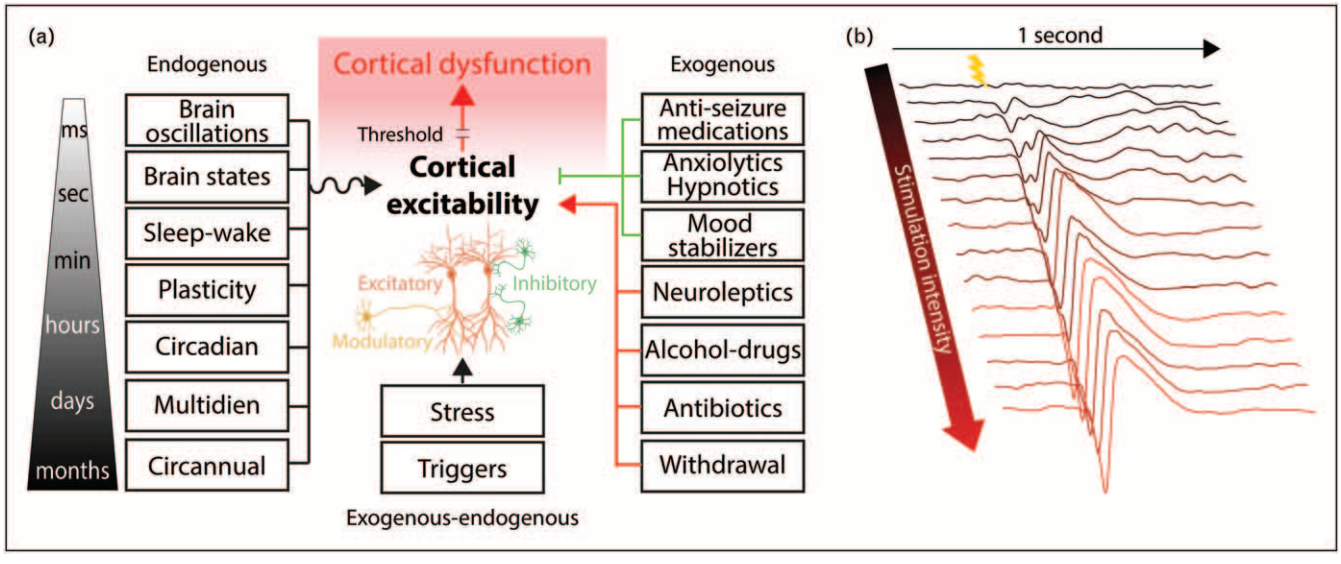

FIGURE 1. Cortical excitability. (a) Constituent neurons and factors modulating cortical excitability. Left: endogenous factors that cyclically modulate (oscillation-arrow) cortical excitability at different timescales. Right: medical and illicit drugs or their withdrawal may increase (red) or decrease (green) cortical excitability. Bottom: stress and other triggers in the environment may also modulate cortical excitability. Heightened cortical excitability (red gradient) in turn determines the occurrence of cortical dysfunctions upon crossing a threshold. (b) Cortical excitability probed in the EEG as the varying cortical responses elicited by a range of stimulations (bolt) at increasing intensity.

excitability dictates the possible dynamics of brain circuits, including cortical responses and recovery upon stimulation, as well as their resilience, that is the amount of sustainable perturbation beyond which abnormal cortical dynamics arise [9,19]. Epilepsy has often been said to be a disorder of 'hyperexcitability' of the cortex, even though seizures can be triggered in healthy brains too [10▪▪]. In fact, vulnerability and excitability are two indissociable facets of any cortex (see chapter 'critical cortical dynamics').

Further, the excitability of cortical circuits fluctuates naturally, opening windows of peak cognitive performance [20] and vulnerability (low resilience). Fluctuating excitability is difficult to apprehend as its regulation simultaneously occurs at multiple timescales: within milliseconds with brain oscillations [21▪], within seconds with neuromodulation (or 'brain states', [21▪,22], within minutes with vigilance states [23–25] and within hours and days with circadian [26,27] and multidien (multiday) rhythms [26,27] (Fig. 1a). Thus, innumerable physiological factors influence cortical excitability at multiple temporal and spatial scales. Cortical disorders are believed to result from specific imbalances in the excitability of specific cortical circuits at specific times. In particular, the symptoms of epilepsy [27], mania [28] and migraine [29] occur in windows of vulnerability, during which excitability is presumably heightened.

Operationally, cortical excitability can be measured as the varying response elicited by a range of stimulations at increasing intensities [30], a methodological approach asking 'how sensitive is the cortex to input stimulations' shared by many researchers working with noninvasive and invasive stimulation techniques in animals and humans (Fig. 1b, see chapter 'gauging cortical excitability' [30,31]. This approach affords a dynamic view on cortical excitability.

Critical cortical dynamics

Dynamical systems theory delves with the mathematical description of nonlinear phenomena such as *tipping points* and has broad applicability in science and the forecast of catastrophes [32,33], in our case cortical dysfunctions. The dynamics of a complex system (here, the brain) can be distilled into a bifurcation diagram that maps its current (Fig. 2a, b, ball) as well as possible states (Fig. 2a, b, landscape) and trajectories (Fig. 2b, arrows). Therein, slow increases in a control parameter (here, excitability, Fig. 2b, *x*-axis) can lead to sudden regime shifts (mutually exclusive regimes on *y*-axis in Fig. 2b) at a critical or *tipping* point (Fig. 2b, red dot), often with catastrophic consequences (e.g. a seizure, Fig. 2b, ictal regime). Conceptually, any brain entails a so-called fold bifurcation (Fig. 2a, b), a threshold beyond which its dynamical regime changes dramatically. The healthy brain operates in a dynamic regime characterized by high resilience to internal or external perturbations: ictal transitions can only be forced by applying a sudden strong perturbation (e.g. an electroconvulsive stimulation, path *over* the threshold in Fig. 2b) or through slower but significant increases in excitability (e.g. psychotropic drugs, electrolyte disturbances, path *around* the threshold in Fig. 2b). In contrast, the epileptic brain is characterized by an enduring predisposition to seizures, reflecting a state of low resilience to perturbations, where even minor perturbation can trigger ictal transitions (Fig. 2b, pink to red ball). Thus, brain disorders bring circuits dynamics closer to a preexisting critical point.

In this framework, recent research has sought practical means to capture warning signs in complex systems [32,33] for example to forecast upcoming seizures. Changes in the system's excitability (*x*-axis) are difficult to capture as they correspond to very slight changes in the system state (*y*-axis) until a critical point of sudden change is reached. Still, predictions from the fold bifurcation model entail that critical transitions are preceded by *warnings* or *precursor* signatures [32,34,35]. As the system approaches the critical point, it displays a slower recovery rate from small perturbations (Fig. 2a, curved double-arrow). Actively probing the brain dynamics with magnetic or electrical pulse stimulation helps reveal the magnitude of the response, and its recovery time (Fig. 2a, b, curved arrows). Translated into EEG signals, this means that a given probing pulse stimulation will lead to a stronger (weaker) cortical response and a slower (faster) recovery in conditions of higher (lower) excitability (Fig. 2c-e). Thus, 'critical slowing' – the slowed recovery at the approach of a critical point - can be revealed without the risk of provoking a seizure, using merely *probing* perturbations, or indirectly and less reliably through passive signatures found in the statistics of EEG recordings (see below).

Gauging cortical excitability

Given the key importance of cortical excitability in healthy and disordered cortical dynamics, a quest for measurement methods to assess this latent variable has taken place in different fields, from neuroscience [10▪▪,11▪▪] to neurology [8,36–40] and psychiatry [6,41]. Passive signatures are easiest to collect but of ambiguous significance, whereas active probing requires a stimulation apparatus, but appears more robust.

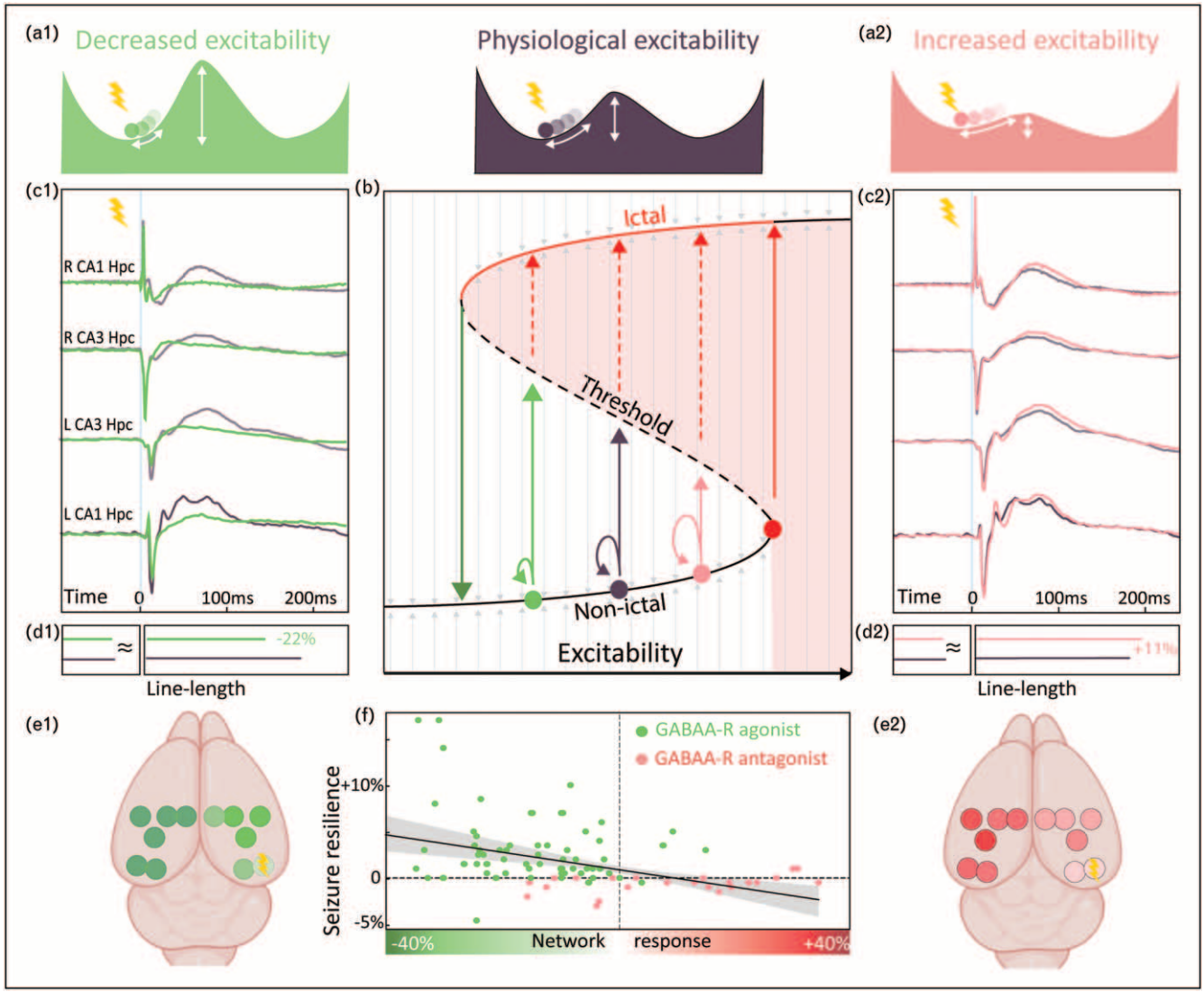

FIGURE 2. Critical cortical dynamics. a. Schematic showing variable seizure thresholds at different heights, the resulting increase and decrease in resilience (vertical double-arrow), as well as the corresponding change in the response magnitude and recovery (curved double-arrow) to a perturbation (bolt) in conditions of decreased (a1) or increased excitability (a2). (b) Model of a fold bifurcation that captures landscapes from (a), as well as possible trajectories from the nonictal to the ictal state over the threshold (dashed red upward arrows) or across the critical point (full red upward arrow) and back to a postictal state (downward arrow). Large and small perturbations at different levels of excitability (green, black, pink and red balls) result in an inverse relationship between response magnitude (curved arrows) and seizure resilience (vertical colored arrow). (c) Measured average decrease ($n = 40$ sessions) and increase ($n = 23$ sessions) in the EEG response magnitude in the mouse hippocampal circuits upon stimulation in the entorhinal cortex (bolt). (d) Corresponding EEG line-length before (left, ≈ no change) and after stimulation (right, %change indicated) emphasizing how probing at a fixed stimulation intensity can reveal subtle changes in recovery rates. (e) Average line-length decreases and increases across hippocampal circuits. (f) Inverse correlation between the measured changes in seizure resilience (*y*-axis) and response magnitude (*x*-axis) for decreased excitability with GABA-A receptor agonists (green, diazepam) or increased excitability with GABA-A receptor antagonists (red, pentylenetetrazole) compared to baseline. See Lepeu G. *et al.*, Nature Communications, 2024 [10].

Passive signatures of intrinsic excitability

Traditionally, passive signatures found in the EEG of people with epilepsy have been described as signs of 'irritability' or 'hyper-excitability' since the 1930s [42,43]. They include interictal spikes, sharp-waves, high-frequency oscillations (HFOs) [44▪] and electrographic seizures. Recent advances have captured the cyclical organization in their temporal expression [26,45,46], putatively reflecting fluctuations in underlying cortical excitability at a range of timescales. While the description of 'seizure cycles' in epilepsy is historical [47,48], the fine

characterization of interictal-ictal cycles has only been possible with the advent of chronic EEG devices that can monitor epileptic brain activity over months to years [26,45]. In nearly all patients with focal epilepsy, interictal and ictal discharges tend to occur at preferential time of the day, a circadian modulation [27]. Further, in most patients, single or clusters of seizures recur with a multidien periodicity, from about a week to about a month, or even longer [27]. These advances have led to the search for cyclical markers of 'intrinsic excitability', from signals in the 'background EEG' that may help explain the emergence of epileptiform discharges [49▪,50].

Critical slowing

The statistics of a complex system are expected to change in relationship to its proximity to a critical point in a fold bifurcation (Fig. 2b). Several studies have sought passive signatures of critical slowing to help predict upcoming seizure (i.e. preictal increases in signal line length, variance, skewness, autocorrelation and spatial correlation). Enthusiasm mostly stemmed from recordings of in-vitro 'ictal ramps' in brain slices kept in an artificial milieu [9,19] but could not be systematically found in the *preictal* (minutes) EEG signals of human patients in the hospital [19,51,52], nor in their everyday environment [19]. Rather, statistics of critical slowing seem to accompany the previously described circadian and multidien cycles of interictal-ictal discharges [46], likely highlighting hour-long and days-long periods of heightened excitability, called *pro-ictal* periods [53]. Recently, we confirmed in controlled experiments in mice and humans that the passive signatures of critical slowing can be modulated subtly by bi-directional pharmacological control of cortical excitability, although their individual predictive value remained ambiguous [10▪▪].

Functional connectivity

Critical slowing could also be reflected in reverberations of signals within cortical networks [32,54] which bi-variate statistics (across two recorded signals) may better capture. There are numerous ways of measuring functional connectivity in the EEG, including the spatial correlation [10▪▪], phase-locking values [54,55▪▪,56] or the coherence with which two regions oscillate. Using such methodology, Khambhati *et al.* showed that in patients with mesiotemporal-lobe epilepsy implanted with hippocampal electrodes, functional connectivity between and within the two hippocampi followed predictable multidien periodicity and correlated with the occurrence of seizures [55▪▪]. This suggests that inter-regional connectivity and cortical excitability are linked, putatively via the dynamical impact of increasing sensitivity of nodes in a communicating network. Such an increase in signal transmission must result from shifts in the balance of neuronal excitation and inhibition.

Excitation-inhibition balance

In neurons, the excitation–inhibition (E–I) balance is well defined at the level of dendrites and dictates whether received signals trigger an action potential (microscale). Putatively, this neuronal mechanism is reflected at the level of an ensemble of cortical neurons (mesoscale) [57], and results in variations in the EEG (macroscale). Practical means to directly measure the E–I balance in the human cortex are currently lacking, although this may be achievable with micro-electrodes in research settings [57].

Aperiodic EEG power

One computational prediction of major impact in the recent years concerns the prevalence of fast aperiodic signals in the EEG as a potential macroscale indicator of the E–I balance [58,59]. In practice, this is simply measured as the slope of the high-frequency power decay in the EEG power spectrum (i.e. a power-law $1/f$ exponent) now typically calculated using the FOOOF algorithm. However, evidence to support this approach is ambiguous. A computational study using biophysically credible models suggests that factors other than the E–I balance also contribute to the $1/f$ exponent [60▪]. A range of pharmaco- and chemogenetic-interventions in mice also indicate that the 1/f exponent does not consistently reflect the manipulated E–I balance [61▪▪], nor does TMS-probed excitability [14].

Actively probing cortical excitability

Given the ambiguity of passive signatures, there remains the need to identify a practical method that can unambiguously assess cortical excitability. The idea of probing complex systems with perturbations to understand their dynamics is rooted in dynamical systems theory ([27], see above), used routinely in neuroscience experiments, and may emerge as a clinical modality. Unlike passive measurements that are correlational by nature, probing the cortex affords causal inferences, arguably representing the most promising advance for human applications.

Probing devices

Practically in humans, two electrophysiological methods can probe cortical excitability by triggering neuronal firing, either noninvasively, with Transcranial Magnetic Stimulation (TMS), or invasively, with direct (intra)cortical stimulations. Others have

proposed the use of parametrized photic stimuli [62] to assess cortical excitability, and some of the considerations below may also apply in this case. In patients undergoing invasive workups for the localization of their epilepsy, penetrating electrodes can be used to record but also to stimulate the cortex, triggering so-called cortico-cortical evoked potentials (CCEPs). Beyond the invasiveness of implanting intracranial hardware, unnoticed probing stimulations can be seamlessly and serially applied over long periods of time, unlike TMS.

Probing excitability invasively

In 2024, we published a large study on cortical excitability that encompassed simulations *in silico*, optogenetic experiments in healthy mice and intracortical electrical stimulations in human patients with epilepsy [10▪▪]. Aiming at experimentally verifying predictions from dynamical system theory, we controlled cortical excitability pharmacologically and systematically measured the recovery from pulse-stimulations and the resilience to train-stimulation of human and mouse hippocampal circuits. As suggested in computational studies [63] and brain slices experiments [9,11▪▪,19], we showed that active probing *in vivo* could improve the detection of latent shifts in cortical excitability. Specifically, we found unambiguous evidence for critical slowing in the recovery from probing stimulations (Fig. 2). Measuring the dynamics of cortical responses is appealing because it captures core system behaviors that are independent of specific biophysical details [9], and these responses can be assessed at scales ranging from individual dendrites [11▪▪,64] to entire circuits [10▪▪].

Probing excitability noninvasively

TMS has been largely employed since the 1990s to measure changes in cortical excitability in different brain disorders [4–6,8,37–41] and with a range of medications [65,66]. Applied to the motor or nonmotor cortex, TMS triggers neuronal firing which reflects excitability along the corticospinal [7] or cortico-cortical tracts, measured with an EMG (motor-evoked potentials, MEPs) or an EEG (TMS-evoked potentials, TEPs), respectively. TEPs are traditionally summarized as positive (P) or negative (N) peak-amplitudes at preset latencies (in ms). Early components, such as N15-P30 are believed to reflect local cortical excitability [67], but their measurement is complicated by pulse and muscle artifacts (see [68] for a methodological review). Later components, like N45 and N100, are associated with GABAergic inhibition [69] and reverberations within the broadly connected cortex [12▪▪] as elegantly shown using intracranial EEG (iEEG) [13▪▪]. Serial measurements with TMS are demanding but achievable and have helped confirm the circadian [24] and/or homeostatic [23,25] regulation of cortical excitability in humans. Such longitudinal TMS-EEG designs are statistically more powerful than cross-sectional studies seeking to establish abnormalities in excitability across cohorts of patients with brain disorders such as epilepsy [37,38], migraine [40], pain [39], or schizophrenia [41] to cite a few. For example, seizures, migraine attacks and mood phases are all strongly modulated by multidien cycles, but we did not find any longitudinal study assessing the temporal variations in underlying cortical excitability.

The excitability index

To assess the dynamic range of cortical excitability, many researchers have converged to measuring growing cortical responses over a range of increasing stimulation intensities [30,31,36,70,71] from zero to maximal safe level. The resulting stimulation-response curve (Fig. 3) dynamically quantifies cortical excitability in corticospinal tracts [30] or cortico-cortical connections upon transcranial [70] or intracortical stimulation [10▪▪,36,71], similarly to measuring gain in neuronal firing [72]. We adopt this approach and propose two additional refinements.

First, we found that the line-length is a robust and simple measurement of the response magnitude in the time domain [10▪▪] that does not require the sometimes-difficult detection of peaks in evoked potentials and is unaffected by EEG offsets, unlike the area under the EEG curve. In addition, line-length is theoretically grounded as it reflects 'how long' the system takes to recover from a perturbation (Fig. 2, 10).

Second, to compute a single unitless value – the excitability index (ExI) – that captures the dynamical range, we propose to simply measure the area under the normalized stimulation-response curve (Fig. 3). Linking with dynamical systems theory, the ExI inversely relates to the slope of the basin of attraction (Fig. 2). Intuitively, ExI $\rightarrow$ 1 for maximal response with minimal stimulation (i.e. maximally excitable, flat basin in Fig. 2), ExI $\rightarrow$ 0 for no response at maximal stimulation (i.e. nonexcitable, vertical pit), and ExI $\sim$0.5 for linear response increases (e.g. a constant slope). In practice, the ExI is often $>$0.5, capturing the nonlinearities of cortical excitability with floor (i.e. threshold minimal intensity) and ceiling effects (i.e. saturation of the response) in a characteristic sigmoid stimulation-response curve (Fig. 3). We believe that the proposed calculation of the ExI will allow for robust comparisons across different experimental conditions and measurement methods.

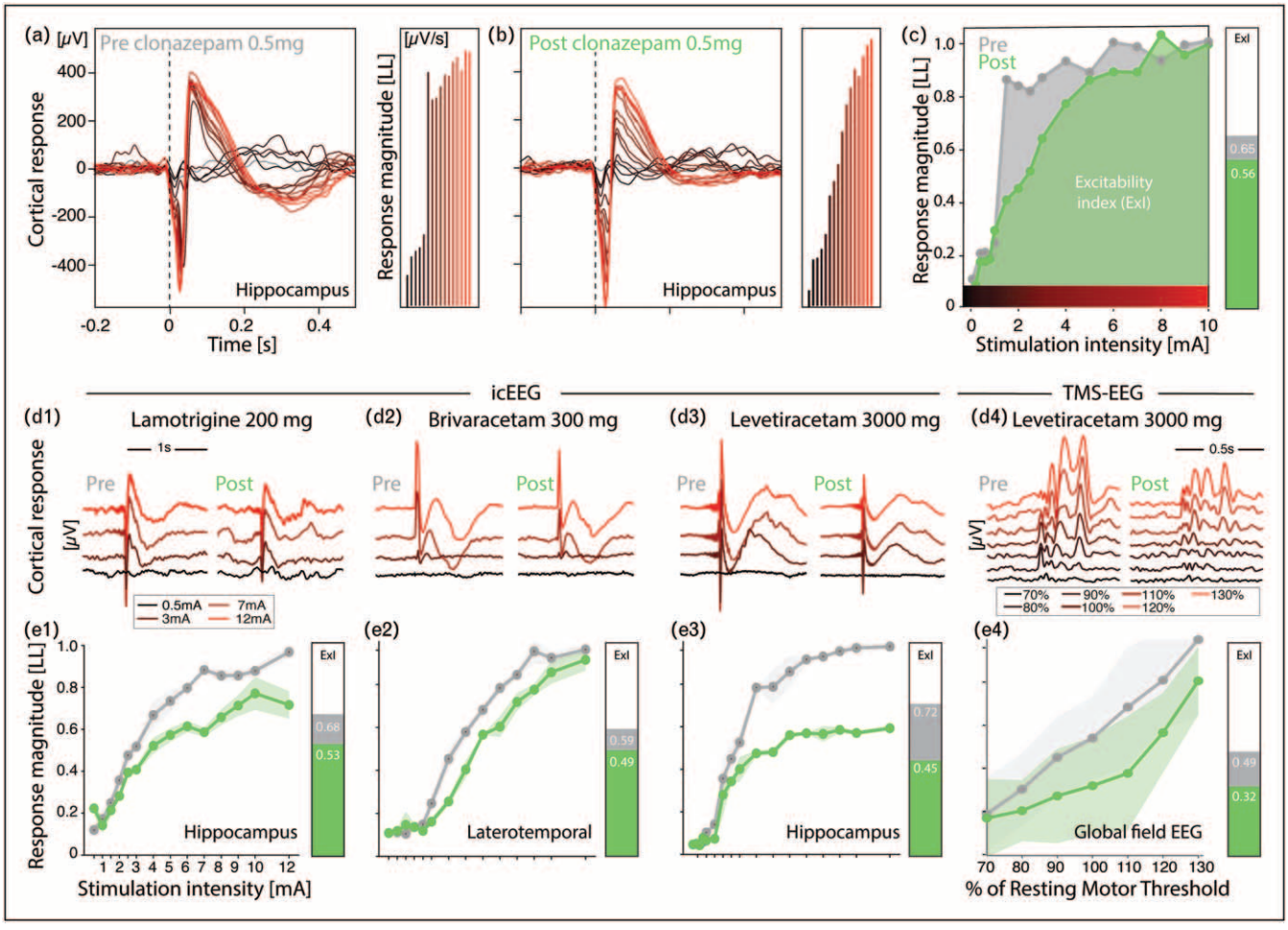

FIGURE 3. Probing cortical excitability. Methodology and examples of pharmacological modulation of cortical excitability. (a, b) Measured cortico-cortical evoked potentials (CCEPs, here 'cortical response') in the hippocampus upon single-pulse stimulations at a range of intensities 0.2–12 mA applied to the entorhinal cortex in one human participant, before (a) and after administration of i.v. clonazepam. Right panel: corresponding response magnitude quantified as the line-length over a window of 250 ms (LL) and color-coded by stimulation intensity. (c) Corresponding stimulation-response curves pre and postmedication, wherein the area-under-the-curve is the excitability index (ExI, right panel), which varies between 0 (nonexcitable) and 1 (maximal excitability), showing how stimulation at increasing intensities can evaluate excitability over a dynamic range. (d) Cortical responses measured as iEEG CCEP (d1–3, location of measurement electrode indicated in e) or EEG global mean field amplitude (GMFA) upon single-pulse electrical (d1–3, average of three trials per intensity and condition) or magnetic (d4, average of 50 trials per intensity and condition) stimulations at a range of intensities pre and postmedication, all i.v. except lamotrigine p.o. (e) Average (SD shaded) 0–250 ms line length of single-trial CCEPs (1–3) or 0–250 ms line-length of average TEPs across channels (SD shaded) pre (grey) and postmedication (green). Right panel as in (c). For better interpretability, the stimulation intensity on the *x*-axis is normalized between zero (or sham) and maximal safe or tolerable stimulation, and the response magnitude is normalized between the minimal and maximal response observed across conditions for each recording electrode. Modulation of the ExI can be inferred within tested connection by simple subtraction across conditions. However, ExI cannot differentiate whether changes in excitability are additive/subtractive (change in plateau, e.g. e1 or e3) or multiplicative/divisive (change in slope, e.g. e2 or e4), and sigmoid fits could capture these nuances.

Controlling cortical excitability in practice

It is arduous to control what is not measured. Thus, quantifying, monitoring and mapping cortical excitability may enable an unprecedented level of control on cortical dysfunctions.

Measure-based pharmacotherapy

Many neuroactive drugs modulate cortical excitability as their target- or side-effect. By design antiseizure medications (ASMs) decrease cortical excitability and some can be used as mood-stabilizers,

whereas beta-lactams antibiotics or psychoactive medication (e.g. antidepressant, neuroleptics, psychostimulants) may increase it, raising the risk of seizures even in those without epilepsy.

Despite an avid search for rapid and reliable biomarkers, no point-of-care method is currently established to routinely assess the actual cortical impregnation with neuroactive drugs. A recent scoping review of 93 studies [73] found insufficient evidence that any of the extensively researched passive EEG signatures of intrinsic excitability (e.g. power spectrum or connectivity analyses) could be broadly used to guide treatment. A major limitation of most EEG studies therein is their short duration, which under-samples fluctuations in IEA [74]. Recently, we published a study in 88 patients with epilepsy [75▪▪] that uniquely took advantage of chronic iEEG recordings for up to 10 years to identify ASM-related changes in multidien IEA fluctuations (Fig. 4). As a promising marker for ASM effectiveness, observing a reduction in the strength of IEA fluctuations following the introduction of a new ASM could prognosticate improved seizure control for up to 12 months [75▪▪]. Similarly, for patients with genetic generalized epilepsies, control of the duration of epileptiform discharges by ASMs evidenced by conventional EEG may suffice to gauge treatment efficacy [76–79].

For a more direct assessment of the effect of neuroactive drugs on cortical excitability, a number of experimental studies in healthy volunteer and neurological or psychiatric patients have used TMS following acute medication administration and observed informative modulation of TEPs [69,80,81]. Using intracranial EEG, we found that benzodiazepines [10▪▪] and other ASMs with different modes of action could decrease cortical excitability, as measured by the ExI (Fig. 3).

Importantly, since cortical excitability fluctuates physiologically at multiple timescales, serially or continuously monitoring the efficacy of neuroactive drugs may be advantageous. From the evidence above, it appears that ASMs mainly control seizures by reducing cortical excitability overall, and not only by changing the seizure threshold (Fig. 4a1 vs. 2). Indeed, in pharmacoresistant epilepsy, it appears that medication become insufficient in periods of heightened cortical excitability, suggesting that a chronotherapy of seizures could help target medications when they are most needed (Fig. 4c). Thus, the possibility of gauging and controlling cortical excitability with neuroactive drugs is forming, but future clinical trials will be needed to confirm the relevance of such an approach in clinical practice.

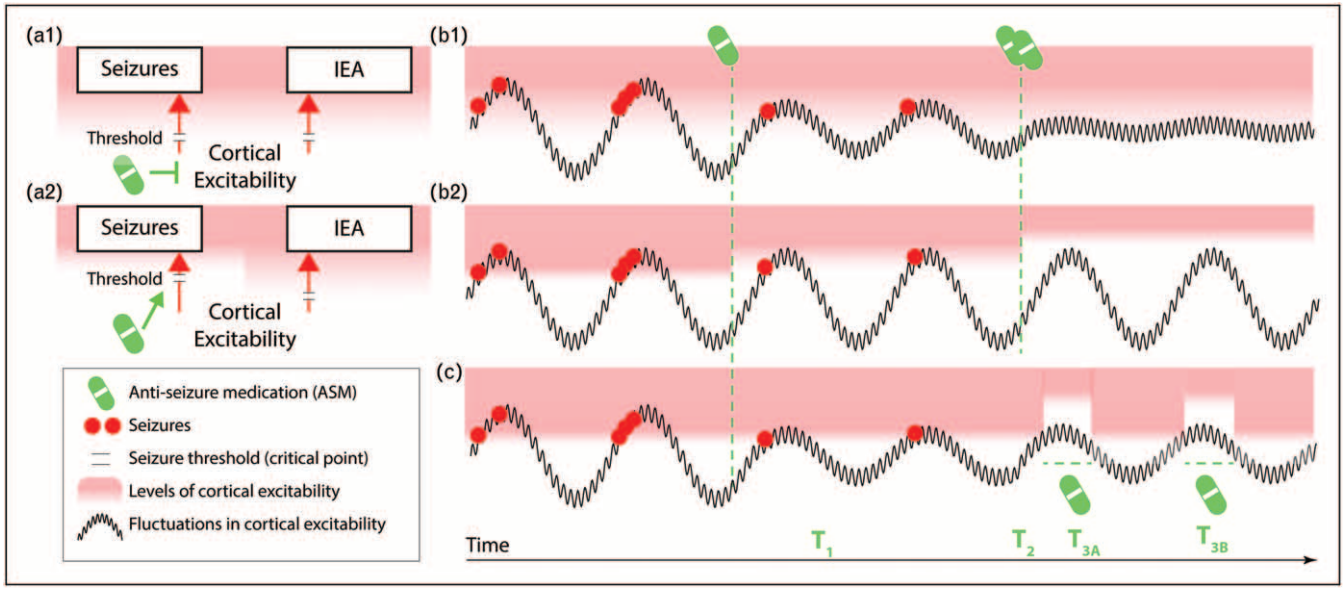

FIGURE 4. Measure-based pharmacotherapy. (a) hypothetical mechanisms by which antiseizure medications (ASMs) may control seizures by decreasing cortical excitability overall (1) or increasing the seizure threshold (2). (b) Fluctuations in cortical excitability underlying the occurrence of seizures at times of vulnerability. In scenario 1, ASM introduction decreases cortical excitability overall (a1) and dose increase (green vertical line at T1 and T2) result in lower peak excitability (b1) and increases the distance to the seizure threshold (red gradient), thereby decreasing the number of seizures per cycle (b1). In scenario 2, ASMs raise the seizure threshold (a2) with resulting decreased seizure risk, but without changing the underlying excitability, (b2). (c) Illustration of chronotherapy with targeted reinforcement of the ASM treatment scheduled during high-risk periods (green horizontal line at T3A and T3B). IEA, interictal epileptiform activity.

Rationale neuromodulation

Therapeutic cortical stimulations are being used in chronic pain [82,83], depression [84,85] and epilepsy [86,87] and have all shown some empirical improvement on patient-reported outcomes, but a mechanistic understanding is lacking, hampering further improvements [88]. For example, in epilepsy, overall efficacy remains moderate, with approximately half of patients achieving a partial reduction in seizure frequency, whether stimulations are triggered by epileptiform activity [89] or not [90,91▪], or consisting in high- or low-frequency [92▪] applied directly to the cortex or extracranially [92▪]. Whether and how seizures can be curtailed after their onset remains an important research question [93].

Presumably, the goal of these invasive and noninvasive neurostimulation treatment modalities is rather to elicit durable changes in cortical circuits that will correct their dysfunctional dynamics [91▪,94,95▪]. Remarkably, recent evidence suggests that cortical stimulations should be delivered at times of low-risk for seizures rather than seeking to curtail seizures after their onset [91▪]. However, a fundamental understanding of how this stimulation-induced neuroplasticity may correct circuit dysfunctions is lacking, and the combinatorial parameter space to design stimulations (duration, frequency, intensity, etc.) is very large and must also account for when and where stimulations are delivered [95▪]. Thus, there is a need to monitor the effect of each stimulation on cortical dynamics and excitability, such as to guide the choice of subsequent stimulation parameters. Such a closed-loop device needs to embark intelligence that can decode momentary degrees of cortical excitability.

Network surgery

The goal of epilepsy surgery is to remove the epileptogenic tissue, after delineating the 'hyperexcitable' cortex. An early encouraging trial on stimulation-triggered epileptiform discharges [96,97] has not translated into a routine use of probing to guide surgical resection. Currently, research continues to seek changes in waveform [98–100], or their resonance properties [101]. In the future, mapping excitability in specific connections within and around the epileptogenic network could allow for more targeted 'network surgery', including with virtual brains, as currently trialed in France [102]. To our knowledge though, direct probing of cortical excitability is not included in these models [102].

CONCLUSION

Publications reviewed here highlight recent advances in our understanding of cortical excitability and practical means to measure this crucial latent variable. Incorporating tight cortical monitoring may enable the personalization of treatment in cortical disorders. Translational efforts should be aimed at developing techniques that can monitor long-term fluctuations in cortical excitability and better guide personalized interventions, with medication or neurostimulation. Due to its noninvasiveness TMS appears as a promising tool for hospital-based punctual assessments. However, continuously monitoring excitability will require the development of implantable devices. By engineering such systems, we are confident that control of cortical disorders can only improve.

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Conflicts of interest

C.F.M., G.L. report no conflict of interest. M.O.B. is a shareholder of Epios SA, a medical device company based in Geneva.

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- ▪ of special interest
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