INTERPRETING ELECTRICAL SIGNALS FROM THE BRAIN*

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One of the holy grails of brain research is to understand how the brain functions in a way that would allow us to alter it in positive and productive ways. In this respect, one of the most promising tools is the measurable electrical signal that is produced by brain tissue. However, as there are many ways to approach experimentation and analysis of the signal, it is of value to have a framework in which to do so. This series of lectures attempts to provide this in three distinct parts. The first part lays out a framework for asking and answering questions about what is universal *versus* unique across species and individuals in the context of specific motifs *versus* statistical features. It includes thinking on how to interpret an aggregate field signal, how to understand the signal from the perspective of field potentials at different resolutions (LFP, ECoG, EEG) and the choice of systems and preparations of study (*in vivo*, *in vitro*, species choice). The second part describes the phenomenology of avalanches and coherence potentials in LFP and ECoG and the way they fit into the framework described in part I. Accordingly, it describes the insights that arise about species universality *versus* uniqueness, as well as behavior on instantaneous *versus* integrated timescales. The third part explores the unique opportunities afforded by the noninvasive nature of EEG to combine dynamical views with behavioral inputs and outputs. I provide a schema that considers the design of studies that relate acute and integrated inputs or life experiences to dynamics, and, in turn, to cognitive and emotional outcomes and behaviors. I also suggest that insights from LFP and ECoG can drive new waveform-based analytical approaches and insights with EEG and provide an example to demonstrate this.

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1. Introduction

There are many ways to study the inner workings of the brain. Often, we approach neuroscientific research from the perspective of the tools and equipment that we have available. These could include working with a preparation from a particular species, using a specific measuring device or apparatus, or a unique set of analytical tools. The costs of setting up a laboratory and the skill needed to use the tools and equipment effectively necessitates such choices and specialization. However, such specialization constrains our ability to think beyond the tools available and often creates silos and overreaching interpretations. For example, given the ease of working with rodent brain tissue and, in contrast, the extreme constraints of working with human brain tissue, the bulk of neuroscientific research is built around rats and mice and overlaps little with research groups working on humans. Furthermore, there is a tendency in the literature to interpret and discuss findings from the mouse brain as essentially equivalent to the human brain, with limited qualification of the potential differences across species. Further, as fields become siloed, analytical methods and measurement tools rarely cross over. How then do we create an integrated view across species, measurements, analytical tools and approaches that can help us understand what is universal across species *versus* unique to humans, as well as what is universal to all humans *versus* unique to individuals? This series of lectures in three parts provides a framework for doing this along with examples.

2. Part I: Frameworks and approaches to electrical brain signals

Electrical signals can be recorded from brain activity at multiple levels of resolution. This ranges from small electrodes that can resolve single cell activity to field electrodes of different sizes placed within brain tissue, on the surface of the brain, and on the scalp. How does one begin to devise an approach for analyzing and interpreting the signal? We have little understanding of how these field potentials aggregate from the underlying electrical activity and even less insight into the underlying coding mechanisms that allow semantic representation in the brain.

Consequently, this poses an enormous challenge with many possible methodological approaches. In this section, I outline a general framework, strategy and considerations for the investigation of electrical signals in the brain.

2.1. Frameworks of investigation

Signals can be investigated from two points of view: searching for universal or generalized statistical principles of brain activity that relate to the overall modes of functioning of the brain, or seeking specific motifs or

features that relate to specific inputs or outputs of the system. The first approach answers questions about the nature of the system, while the latter provides a view into specific interpretations of its instantaneous behavior. Further, these statistical principles can be compared across species to determine which aspects are universal signatures of the brain *versus* unique to a species, or unique to an individual within a species (Fig. 1). In this framework, cross-species statistical principles provide a view of the universal construct of intelligent life, while statistical characteristics and specific features unique to humans provide a view into the question of what it means to be human. Finally, specific features that are unique to an individual allow insight into the question 'who am I as an individual?' as well as the potential to interpret the activity of that individual at any given moment, essentially interpreting a stimulus-response or thought. Thus, knowing where, within this framework, a specific research question falls, provides the direction and contours for structuring one's efforts.

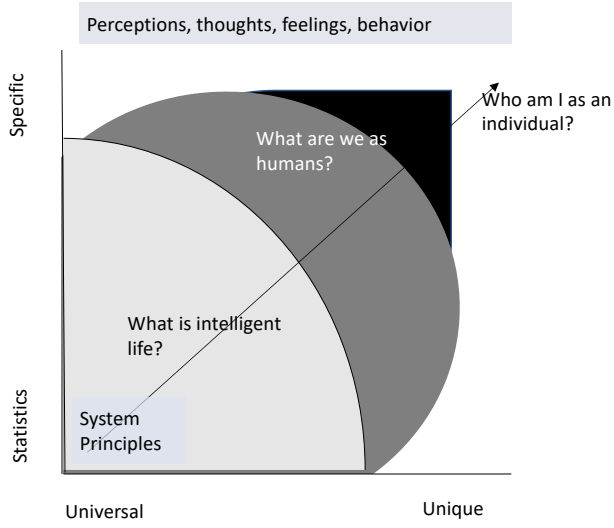

Fig. 1. A framework for approaching brain signals; Universal statistical principles across species may inform us about the nature of sentient or intelligent life. However, to understand what we are as humans, we must look at both statistical characteristics and more specific features that are unique in humans. To understand ourselves as individuals, we must look to find specific unique features that define us relative to others.

2.2. Individual neurons versus field recordings

In studying electrical activity in the brain, there are two distinct approaches. The first focuses purely on studying spiking activity of individual neurons [1–8], while the second focuses on a complex aggregation of the activity of fields of cells including neurons and glial cells and the various electrical components from spiking activity to synaptic, dendritic and glial currents [9–11].

The choice of one approach over the other has multiple considerations. The first approach of measuring neuronal spiking activity makes a fundamental assumption about the relative importance of neuronal spikes over other aspects of electrical activity. The latter assumes that the aggregate electrical activity may be more meaningful and gives up the ability to distinguish its elements. Arguments may be made for both approaches. A great deal of the literature has been dedicated to identifying correlates between stimuli and behavior and neuronal spiking, particularly in rodents and monkeys [1–8]. However, there is increasing evidence that glial cells play a significant and fundamental role in modulating and shaping the signal, particularly in humans, where glia also give rise to much faster calcium waves [12, 13]. Therefore, neurons in isolation may contribute only one part of the story. Furthermore, there are practical considerations of measurement as well.

Consider the analogy of the simpler system of atoms and molecules that make up any particular type of conductor. While it may be the case that the nature and state of the system could be perfectly measured by assessing the changes in the energy and spin states of the electrons in each atom, this is extraordinarily difficult from a technical perspective. Furthermore, it is not clear if a macrofeature, such as conductivity, could actually be inferred by measurement of the electron states in individual atoms. On the other hand, simply measuring conductivity with a simple conductivity meter does a pretty good job of estimating what is going on in the conductor and can ultimately be put more easily to use. Similarly, measuring the activity of individual neurons is technically more difficult. Besides requiring invasive implantation, microelectrode arrays today can typically only handle up to 100 electrodes [14], while new generation technologies can measure a few thousand [15, 16]. However, these are still only a tiny fraction of the brain's billions of neurons. Therefore, analogous to the conductivity meter, field potentials might similarly be more easily exploited to gain insights into the brain's behavior.

However, even field potentials can be measured at different scales and have different technical considerations (Fig. 2). Currently, there are three distinct levels at which measurements are made. These are called Local Field Potentials (LFPs), Electrocorticographs (ECoG) and Electroencephalograms (EEG) [11]. LFPs are measured with microelectrode arrays

that are typically 30 microns in diameter and about 1 mm apart [14]. Each electrode covers a field consisting of 10 to 100 neurons and several hundred glial cells (in humans; there are far fewer glia in rodents). These arrays can be both surface or deep electrodes, either parallel or transverse to the cortical surface, and must be implanted with surgery. They can also be used to

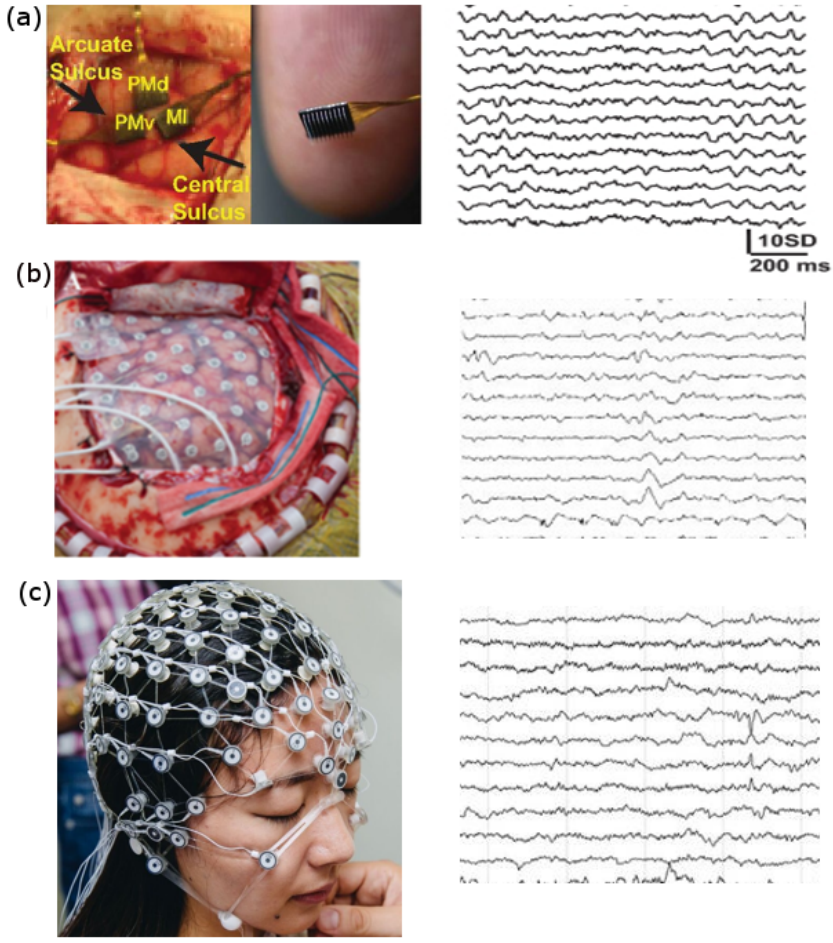

Fig. 2. Different levels of electrical brain signal measurement; (a) Microelectrode arrays of 30 micron diameter placed in or on the surface of the brain measure Local Field Potentials (LFPs) (from [17]). Example of LFP recording from a monkey shown on the right. (b) Flexible strips of 2–4 mm diameter electrodes placed on the surface of the brain measure Electrocorticographs (ECoG) (from [18]). Example of human ECoG recording shown on the right. (c) 7–10 mm diameter electrodes placed on the surface of the brain measure Electroencephalograms (EEG). Example of human EEG recording shown on the right.

measure the activity of brain tissue in a dish. ECoG (Fig. 2 (b)) is measured with electrodes placed directly on the surface of the living brain that are typically 2 to 4 mm in diameter and placed 1 cm apart [18, 19]. This again is invasive and requires opening up the skull and dura for placement of the electrode array and is, therefore, restricted to neurosurgery candidates. Finally, EEG is measured on the scalp surface and involves electrodes that are 7–10 mm in diameter covering a field of 100k+ neurons and several hundred thousand glial cells. Unlike all other methods, EEG has the advantage of being noninvasive. On the other hand, it is not a direct measure of brain activity as it is subject to a distortion of signal due to the conductivity of the skull, other intervening tissue such as the skin, dura and pia, and interstitial fluid on the brain surface. Thus, choice of measurement scale depends on the type of question being asked and the practical requirements.

2.3. In vivo versus in vitro systems

Another dimension of consideration is the particular type of system in which to measure electrical activity — *in vitro* (in a dish) or *in vivo* (in the live organism). In the laboratory, there are a number of *in vitro* brain preparations from which electrical signals are measured. These include cultured neurons, which are cell lines grown in a dish [20]; dissociated cultures, which are cells extracted from newborns that are dissociated from one another and grown in a dish [21, 22]; organotypic slice cultures, which are slices of brain from newborns that continue to grow and flatten out in the dish [23] and, finally, acute slices, which are thin slices of brain extracted from the adult animal and measured in a dish [24]. *In vivo* measurements, as described in the earlier section, can be both invasive requiring insertion of electrodes into the tissue or directly onto the surface of the cortex, or noninvasive scalp electrodes.

In vitro preparations are particularly amenable to measuring electrical activity of individual neurons. However, they generally require sacrifice of the animal and, therefore, typically use rats and mice. This limits study to simple species and, therefore, cannot provide insight into the aspects of the signal that are unique to humans. Further, there is the larger question of the value of measuring electrical activity in a distorted system — one that is not in its intact functioning form.

Consider the following example of this much simpler system. Both diamond and graphite are constructed from the carbon atom (Fig. 3). Diamonds and graphite cannot be formed from any atom other than the carbon atom and, therefore, the type of atom sets a constraint on possible outcomes. Yet diamond and graphite are completely different types of material. One is translucent, the other black. One is extraordinarily hard, the other soft.

Indeed, important properties such as hardness and color are not properties of the atom itself but of the system overall and, therefore, one cannot ask if the carbon atom is hard or a particular color. Rather, carbon alone can produce outcomes of completely opposite properties purely by virtue of how the atoms bond with one another. The nature of these bonds influences the way external energy such as light and mechanical forces interacts with it and, therefore, the outcomes. Furthermore, the type of bonding is determined by the conditions of temperature and pressure of the environment in which they were formed. Consequently, studying the carbon atom in isolation or studying a carbon-based material formed under one set of conditions would not provide insight into the nature of an allotrope arising from a different set of conditions.

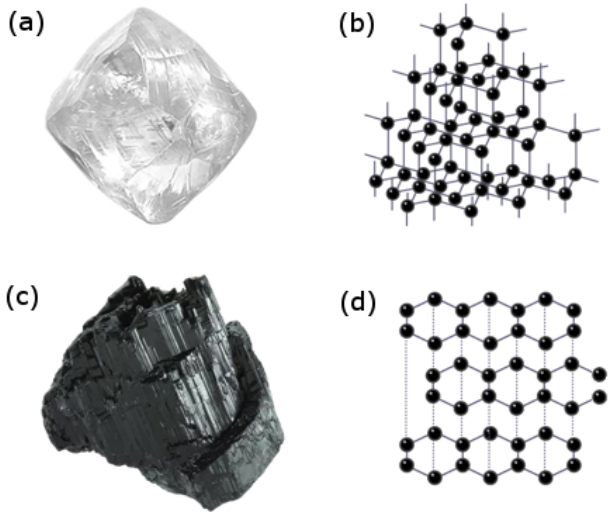

Fig. 3. Impact of link or bond structure on system properties; (a) Image of a diamond with properties of translucence and hardness and made entirely of carbon (from [25]). (b) Bond structure of diamond shows each carbon molecule has four covalent bonds conferring these macroproperties of the material or system (from [26]). (c) Image of graphite, also made entirely of carbon, with properties of softness and black color (from [27]). (d) Bond structure of graphite shows each carbon molecule has a sheet structure with two covalent bonds in one plane and weak forces between the sheets (from [26]).

Similar to how carbon atoms are predisposed to bond with one another and do so based on environmental factors of temperature and pressure, the brain is characterized by the innate nature of neurons to connect with one another in a manner that is based on their experience of the environment. It is, therefore, a reasonable assumption that the unnatural environment of

the dish would alter some aspect of the way neurons wire up. Indeed, there is evidence that neurons have different gene expression patterns [28] as well as behave differently *in vitro* than *in vivo* [29]. A brain system, where the formation of connections between neurons occurs under unnatural circumstances may, therefore, not provide insight into the working of the brain in its natural environment. Furthermore, the way external stimuli or electrical energy interacts with these preparations could also be fundamentally different. One would not want to unwittingly report the properties of diamonds as those of graphite or *vice versa*. By this same logic, studying the electrical signals of brain systems that are not intact in their normal environment may yield misleading results. Thus, the desired insights should be carefully considered when deciding whether to choose an *in vitro* or *in vivo* system of measurement.

2.4. Choice of species

Much of the research in the field of neuroscience today is conducted on species other than humans. These include species like drosophila (fruit flies), zebra fish, *C. elegans* (worms), rodents and monkeys. Species like flies, fish and worms have neurons but not a brain as we think of it. While certain features of the electrical signal generated such as the action potential have conserved mechanisms, there are crucial differences in gene expression in neuronal and non-neuronal cell types across species [30–32]. Furthermore, the gross structural differences would render local field activity fundamentally different compared to mammals.

Across much of the field, the most commonly studied species is the rodent, a mammalian species that can be easily bred and sacrificed for access to their brain tissue. There is a conserved architecture across mammalian species that has led researchers to implicitly assume measures of electrical activity in the rodent brain mirror the activity found in the human brain. Much of the literature on rodents, therefore, draws conclusions about 'the brain' in general rather than the rodent brain in particular. Increasingly, evidence is mounting that this is not the case. Human neurons have significantly higher conduction velocities than other species [33, 34]. More substantially, glial cells, which outnumber neurons by 1.4× in the cerebral cortex of the human brain (but not rodent brain, where the ratio is 0.4) [12] are more dissimilar across species than neurons. The human brain has new types of glia that are 2.6× the diameter of those in mice, have 10× more processes, 3× faster calcium wave propagation, and patterns of gene expression that are more similar to mouse neurons than mouse glia [12, 13, 30]. These glial cells have also been implicated in Alzheimer's and epilepsy, perhaps explaining the poor performance of mouse models of human disease [35, 36].

This points to a differently constructed system suggesting that many properties measured in mice that are considered general or universal properties of the brain are not so. Indeed, such comparisons may be as flawed as studying different forms of matter simply because they were composed of similar elements. Imagine studying amino acids to understand nucleic acids simply because they were both composed largely of carbon and nitrogen? Or even studying one amino acid to draw conclusions about the behavior of another since they were so similar that they differed only by one side chain. It is well-known that even single amino acid differences can completely change the function of the protein. The functional differences arising from cellular and structural distinctions across species, which are essentially systems of molecules, may, therefore, be even further amplified at the level of a network.

Fundamentally, interpretation of electrical activity as universal across species or unique to one species requires measurement across species. It is further obvious that one cannot understand what is unique about the activity of the human brain by studying other species.

2.5. Group versus individual

In the field of human brain research, the dominant approach is to look at differences between groups. For example, a clinical disease group and normal or nonclinical group, or an intervention group and control group. This approach makes an implicit assumption that most measurements of electrical activity are similar across individuals with only some normally distributed variation. However, there is considerable evidence of substantial individual variability.

One stark example of such variability can be found in reports on the outcomes of neurosurgery. In patients with Rasmussen's encephalitis undergoing hemispherectomies (removal of an entire half of the brain) for example, the outcomes vary across the entire spectrum of possibilities. Some become vegetative, some retain ability to dress and feed themselves but no more, some experience various degrees of mental retardation and a lucky few, such as the remarkable case of Cameron Mott which received much media coverage, recover all physical and mental function. In one study of 115 hemi children who were assessed six years after the surgery, 28 were either in a school for the disabled or cared for at home, 9 could not walk, whilst 5 were attending a regular school without assistance [37]. Others show similar heterogeneity of results [38–40]. Thus, which functions are lost and how well the brain can adapt to the loss is highly individual.

These large individual differences in plasticity will also manifest as different outcomes under the normal course of development and life experience. Unlike other organs of the body, the brain does not behave the same way

from birth. Rather, the brain's function develops in an experience-dependent manner over one's lifetime. In fact, experience alters every dimension of its physiology from its gross anatomy to its fine scale architecture and gene expression.

A growing literature has now begun to demonstrate these differences in the EEG. For example, a metric of variability in the EEG has been shown to reduce when an individual is attending to a stimulus. This change in variability during a stimulus-dependent task is highly individual and has consequences for performance [41]. Furthermore, the slope of the $1/f$ spectrum of the EEG changes with age [42]; features such as the alpha oscillation are tied to factors such as technology use and can exhibit many-fold differences across diverse populations [43]; and signal complexity is closely correlated to factors of life experience such as education, income and geofootprint (physical exploration) (see part III for more details) [44].

From these various results, it is clear that group metrics cannot effectively describe each individual. It may be that characterizing the diversity across the group can yield more interesting insights into the dynamical possibilities of human brain signals beyond simply focusing on group averages. Further, this individual characterization is essential when trying to interpret the features and motifs relating to the thoughts and behaviors of any individual.

2.6. Summary

In summary, this section presents a framework for approaching electrical signals that address different levels of questioning from what is common and distinct across all intelligent life to what is unique about the individual. In this context, there are four key points: First, it is important to determine whether one is seeking to uncover dimensions that are universal or unique to species or individuals and depending on the purpose of the study, whether to look at statistical principles or specific motifs. Second, field measurements offer technically easier and potentially integrated views of the functioning of the system although the specific details of the underlying contribution of cells are obscured. Third, choice of species, experimental system and analytical approach to the signal must be conscious decisions based on where, along these dimensions, one is interested in probing. Fourth, using analytical approaches that explore the diversity within a population rather than simply comparing group means can help determine both the state space across populations as well as individual uniqueness.

3. Part II: Examples of statistical and specific features of electrical brain signals

3.1. Understanding universal statistical features versus unique motifs

To better understand the dimensions of universal statistical features *versus* unique motifs, it is useful to consider a more familiar signal — human speech or language. It has been found that the most commonly occurring word occurs twice as often as the next most common word, three times as often as the next most and so on [45, 46]. In English for instance, 'the' is the most common word with 7.5% of word occurrences, followed by 'of' with 3.5%, and then 'and' with $\sim 2.5\%$. What this means is that there is a characteristic inverse relationship between the frequency of occurrence of any word and its rank of occurrence. This statistical structure is called Zipf's law (Fig. 4) and is represented as a near straight line with a characteristic slope of -1 when plotted as the log(occurrence) *versus* log(rank). Mathematically it can be written as $P(\text{occurrence}) \propto 1/\text{rank}$. What is remarkable however, is that this pattern is universal across all languages. Although there are deviations from the strict definition of Zipf's law at higher ranks [47], the structure is a universal statistical signature of human language. Thus, while this statistical signature might serve as a tool to identify whether a book or speech is gibberish or real language, it cannot tell you what language it is.

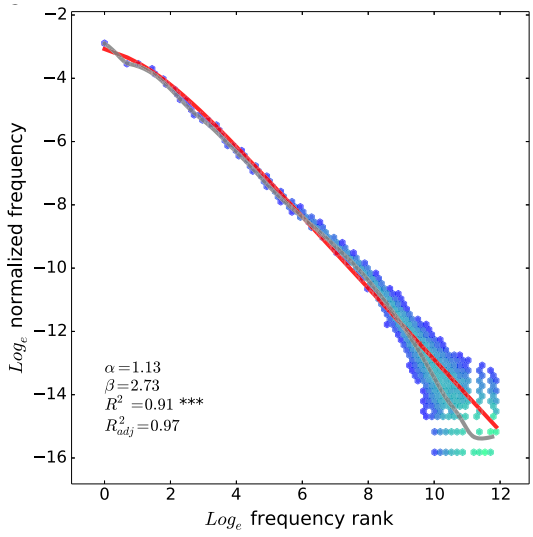

Fig. 4. Zipf's law: an example of a universal statistical principle of language; All languages show a similar structure where the frequency of occurrence of any word is inversely proportional to its rank. This inverse proportionality is referred to as Zipf's law and can be represented as a near straight line with slope -1 on a double logarithmic scale. Figure from [45].

To understand something specific to a particular language you would have to understand its unique vocabulary. What word occurrences characterize and distinguish one language from another? A fallout of Zipf's law is 135 words account for over half of all vocabulary usage in a language. Thus, a particular set of vocabulary form the motifs that could serve as a universal identifier unique to a particular language. Similarly, specific semantic patterns such as conjugations are specific features that can distinguish one language from another. However, neither can tell you anything about a particular speaker. An individual may have unique patterns for usage of vocabulary (favorite words for example) and structures (slang or other atypical usages) or intonations that can be characterized to provide a view of their uniqueness or similarity compared to the spectrum of speakers of that language.

Similarly, one can imagine that signals produced by the brain have certain statistical similarities across species and individuals but perhaps motifs that differ.

3.2. Neuronal Avalanches as a universal statistical feature of cortical tissue

One example of a statistical feature of the brain signal are what are known as *Neuronal Avalanches* (Fig. 5). This phenomenon was first characterized by Beggs and Plenz in an organotypic *in vitro* preparation from mice [48, 49]. In this preparation, 300 micron thin cortical slices from newborn mouse pups were plated below 64 channel microelectrode arrays, where still migrating cells grew out over a two week period to cover the electrodes in a pattern that mimicked intact cortical architecture but in 2D form. Remarkably, after two weeks, during which the cultures were placed in a dark incubator with no electrical stimulation, synchronous events began to occur that could be visually identified as sharp negative deflections in the local field potential (LFP) recordings (Fig. 5 (a)). Beggs and Plenz noted both the timing and amplitude of these negative LFP deflections (nLFPs) in raster plots (Fig. 5 (b)) and characterized how they were grouped in time. All simultaneous and consecutive nLFPs were grouped into an event. The end of an event was marked by an empty time bin with no nLFP peak.

Remarkably, the size of these events organized into a statistical structure where the probability of finding an event of size s, $P(s)$, was inversely proportional to its size s (Fig. 5 (c)). This was the case regardless of whether s was considered to be simply the number of nLFPs or the sum of their amplitudes.

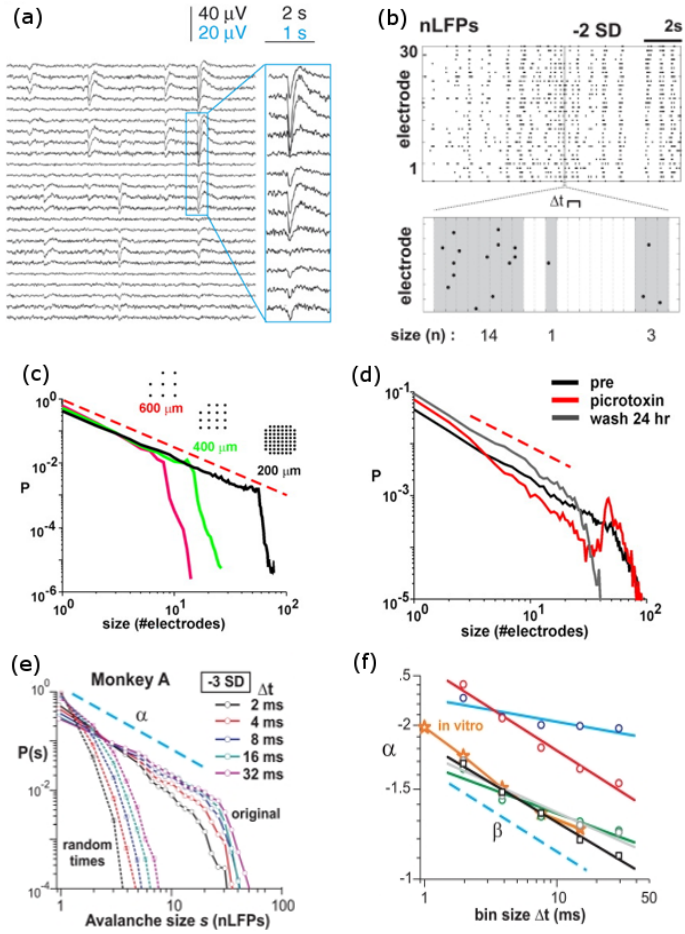

Fig. 5. Neuronal Avalanches: a universal statistical principle of the mammalian brain activity; (a) LFP recordings from mouse cortex grown in a dish (each line is an individual electrode) show distinct negative deflections (nLFPs) that appear to form cascades that spread across electrodes (from [49]). (b) Raster plot of peak positions of nLFPs for each electrode (from [50]). Expanded view shows cascades or avalanches (peaks detected on at least one electrode in each successive time bin) separated by pauses (empty time bins). Number of peaks in each avalanche represents its size n. (c) Power law size distribution of avalanches in mouse cultures (in log–log scale) for different numbers of electrodes (from [48]). (d) Disruption of the power law distribution by the application of picrotoxin which changes the balance of excitation and inhibition (from [48]). (e) Power law distribution in a monkey for different time resolutions compared to distributions after random shuffling of nLFP positions (from [50]). (f) Relationship between temporal resolution (or bin size t) and power law exponent (note log scales) (from [50]).

This statistical structure is called a power law and is similar to Zipf's law but has a different exponent. Where Zipf's law has an exponent α of -1, this power law has an exponent α that was less than -1. This means that an event of size one is more than twice as likely to occur than an event of size 2 or, in other words, the distribution is steeper,

$$P(s) \propto s^{\alpha}.$$

Regardless of how you sliced and diced the measurement by removing every other electrode from the grouping or looking at just one section of the array, this structure still held up (Fig. 5 (c)). Essentially, it was invariant to the spatial scale or resolution. What this meant was that the largest size of an event was constrained only by the size of the system [49]. This statistical pattern of occurrence of periods of synchrony was termed neuronal avalanches for their similarity to the behavior of 'avalanches' of sand in the famous sandpile model demonstrated by Bak, Tang and Weisenfeld [51, 52].

The specific value of the exponent α, however, was dependent on the time scale used to resolve the events. If the recording was carried out at 1000 samples per seconds, the bin size Δt would be 1 ms. However, as bins were collapsed together to create a coarser and coarser time resolution, or larger values of Δt, the exponent decreased systematically [48, 50]. This statistical characteristic was, therefore, not just invariant to the spatial scale, it was also invariant to the temporal scale. Essentially, it was multifractal in nature and had the implication that one could identify this structure regardless of the spatial or temporal scale of measurement. That it occurred across every mouse organotypic culture measured indicated that it was an intrinsic property of the tissue that was not dependent on any external stimulus. It could, however, be disrupted by the application of drugs that changed the balance of excitation and inhibition (Fig. 5 (d)) [48], a key property of the cortical network.

Remarkably, the structure has been found to be conserved in slices of cortex extracted from adult rats, in the cortex of awake monkeys chronically implanted with microelectrode arrays (Fig. 5 (e)) [50] and even in human ECoG recordings [53]. The only differences were in the relationship between how fast the exponent changed with the time resolution, Δt, indicating a distinct spatiotemporal relationship (Fig. 5 (f)) [50]. Thus, all evidence points to neuronal avalanches as an intrinsic and universal statistical feature of the mammalian cortex that is conserved across species but suggests a species-specific spatiotemporal relationship of avalanches.

This statistical structure has some potentially significant implications. For example, certain exponents, in theory, imply a precise branching process or rules governing propagation of activity such that the possible outcomes or patterns in the system are maximal, sometimes referred to as a 'critical state' [54–56].

3.3. Coherence potentials — moving towards identifiable motifs

Just as Zipf's law characterizes the statistical occurrence of words, neuronal avalanches characterize the statistical occurrence of cascades of synchrony. However, to move towards a deeper understanding of specific features, it is essential to understand something further about these cascades of synchrony. In the way that words are meaningful for the understanding of language, are these cascades or periods of synchrony relevant and meaningful features or motifs of the system?

The nLFPs measured on any individual electrode that made up part of the cascades of synchrony were typically waveforms of a duration of 100 to 300 ms (Fig. 6 (a)). Furthermore, the power spectral density of these periods followed a similar $1/f$ pattern that is characteristic of most field potentials (Fig. 6 (c)) [57]. This was the case in both rats and monkeys, *in vivo* and *in vitro*. However, they were not represented by a stereotypical pattern but rather were complex and varied. Using a correlation measure to compare waveforms provides a simple measure of waveform similarity that is relatively independent of amplitude (Fig. 6 (b)). Avalanches or cascades of nLFPs occurring with temporal pauses (Fig. 6 (d)) tend to have similar waveforms within an avalanche or cascade but distinct waveforms between them (Fig. 6 (e), (f)). Furthermore, within any cascade, when amplitudes were above a certain threshold, they maintained their complex shape without any distortion or decay in amplitude either in space (Fig. 7 (a)) or in time (Fig. 7 (b)) and appeared to 'jump' in space, crossing over electrodes in between [57]. In contrast, avalanches with subthreshold nLFP amplitudes tended to progressively distort over time (Fig. 7 (b)). Such behavior runs counter to the expectation that a complex field level signal would result in a progressive distortion or dissipation as it propagated in space and time. This behavior has analogy to the action potential at the level of the neuron where spikes travel down the axon in a directed manner without any distortion to their size. In the absence of this active propagation process, charge would simply dissipate progressively in every direction. This phenomenology suggests an active synchronized network level propagation process. Given the tight coherence of these periods as they propagate, they are termed coherence potentials. Coherence potentials thus represent unique, identifiable motifs that can provide a relatively instantaneous view of cooperating regions of the cortex. This allows understanding on a more instantaneous timescale in contrast to the overall avalanche statistics which are an integrated view of many coherence potentials over time. It is significant that the rate, complexity and diversity of coherence potentials was greater in monkeys than rats.

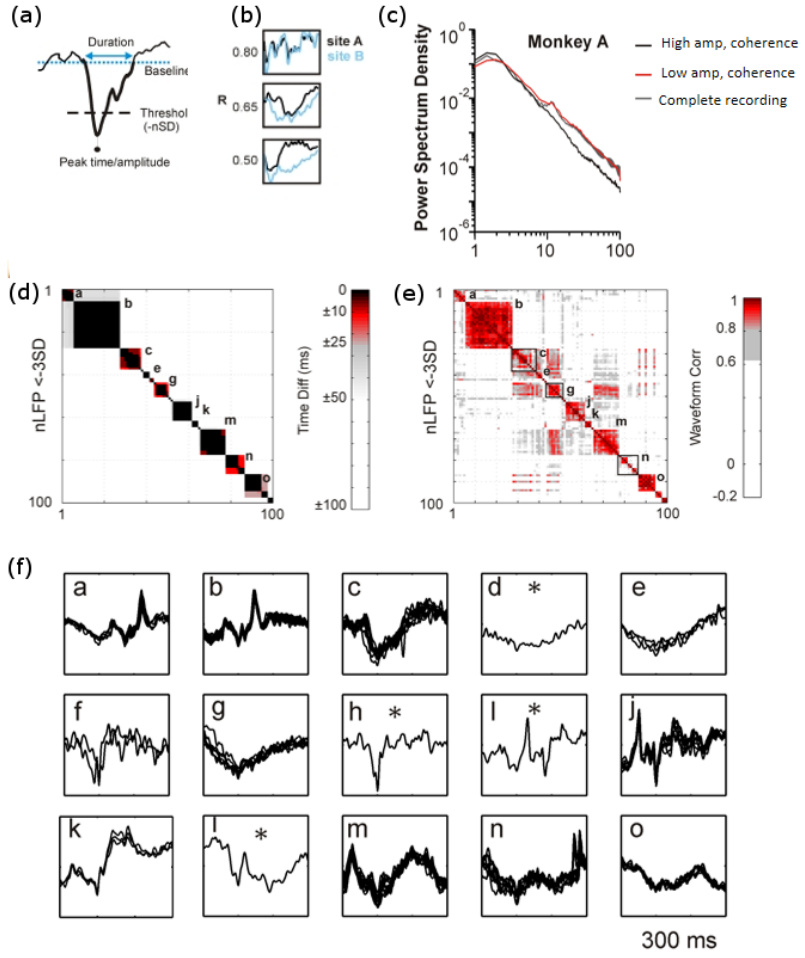

Fig. 6. (Color online) Coherence potentials represent undistorted propagation of high amplitude LFP periods; (a) Negative periods in the LFP (nLFPs) with peak amplitude beyond a certain threshold are extracted to identify coherence potentials (same manner as avalanches). (b) Correlation of nLFPs of different shapes provides a measure of waveform similarity. (c) Average power spectral density (PSD) of suprathreshold nLFPs (black), subthreshold nLFPs (red) compared to the PSD of the entire recording (gray) shows that coherence potentials are spectrally broad. (d) Time difference between successive nLFPs for a short period shows fast cascades or avalanches followed by pauses. (e) nLFPs show generally high correlation or waveform similarity (> 0.8) within each cascade or avalanche but not between successive avalanches. Each individual avalanche is marked in panels (d) and (e) with the letters a–o. (f) Each box shows overlays of the nLFP waveforms within one avalanche or cascade marked a–f in (d) and (e). All panels from [57].

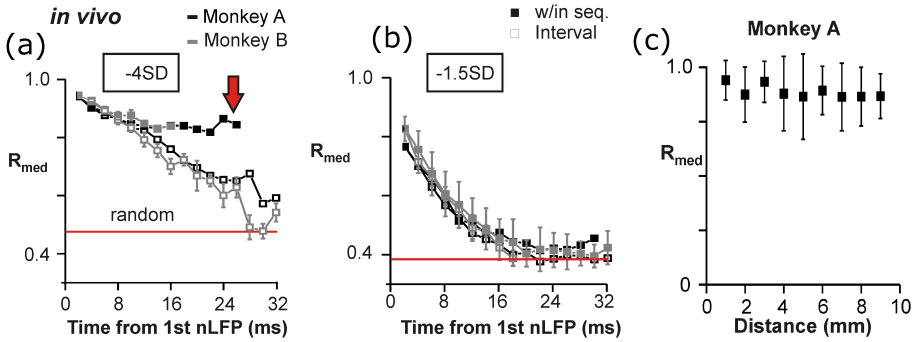

Fig. 7. Coherence potentials do not decay in space or time; (a) Waveform similarity of suprathreshold nLFPs occurring successively in time (within a cluster) does not decay (filled squares), while nLFPs separated by pauses of the same duration show progressive decay. (b) Waveform similarity of subthreshold amplitude nLFPs occurring successively in time (within a cluster) decays progressively in the same way as nLFPs separated by pauses of the same duration. (c) Waveform similarity of suprathreshold nLFPs is not impacted by physical distance of the electrode on the array. All panels from [57].

The next question is whether these potentials are meaningful in the context of behavior. A simple hypothesis might be that a particular waveform may in some way encode information about a particular behavior. While this remains to be fully explored, one experiment using ECoG on a patient undergoing surgical resection for epilepsy suggests that this may indeed be the case, although also raising further questions about how it works [53]. In this experiment, the ECoG array was placed roughly in the left somatosensory cortex region and a map of motor and sensory response was established by stimulation of each electrode (Fig. 8). With this mapping, it was found that the array largely covered the right-hand representation region (but not foot). Subsequently, recordings were obtained while the subject performed a task where he was shown a picture of a particular movement that he had to copy (fist clenching or foot dorsiflexion; Fig. 9 (a)). Unique sets of coherence potentials were found to reliably coincide with each distinct movement and spanned all the trials for that movement (trial spanning coherence potentials). However, interestingly, the particular spatial spread of the coherence potential varied from trial to trial. The frequency of occurrence of the coherence potential on each electrode spanning right hand or fist clenching trials is shown in Fig. 9 (b). Nonetheless, while its presence on most electrodes appeared random, the particular coherence potential for right fist clenching occurred reliably on one of two electrodes involved in right finger movement immediately after presentation of the cue with a timing that predicted the

onset of fist clenching (Fig. 9 (c)). Thus, whilst it is clear that particular waveforms may be meaningful, the relationship between how they propagate in space and the behavior is unclear.

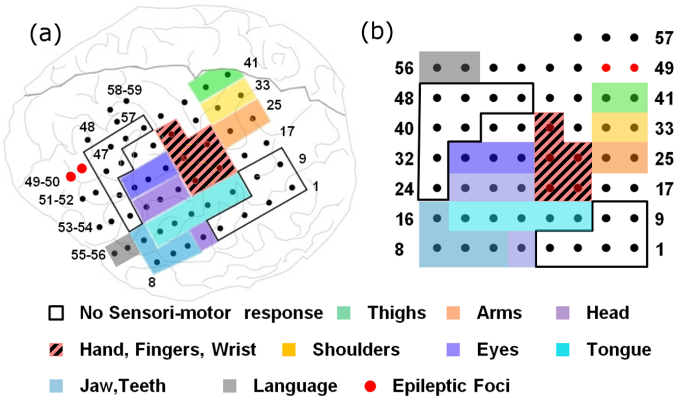

Fig. 8. ECoG array used to assess coherence potentials and behavior; (b) Array placement on the cortex and motor movement mapped onto the array based on response to stimulation. Note coverage of hand movement area (hand, fingers, wrist) in hatched. (b) Array shown separately. All panels from [53].

Unraveling the mysteries of the relationship between the temporal and spatial aspects of the brain signal and their relationship to thought, feeling and behavior is an open and exciting field of questioning. Indeed, neuroscientists have been thinking about this for many decades with unexpected results. In the 1970s, neurosurgeon Wilder Penfield reported on stimulation experiments in the somatosensory cortex in 163 patients showing that these maps of motor movement were not static and shifted over sessions and that no particular localization could be found for sensation [58]. Furthermore, the work of several people beginning with Lashley in the early part of the 1900s [59–61] have shown that while particular functions can be localized, memory is distributed across the cortex and cannot be easily wiped out by lesions or even, sometimes, removal of an entire hemisphere [62].

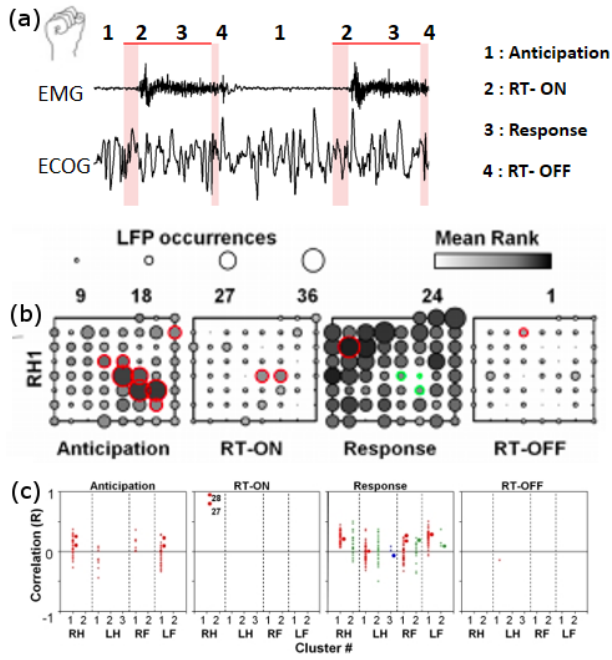

Fig. 9. Coherence potentials corresponding to fist clenching; (a) Hand EMG along with example of a single ECoG channel during a right fist clenching task. Patient had to clench his right or left fist (or flex his right or left leg) for the duration of time when the picture of the action is shown. Task elements were divided into four parts: (1) Anticipation: the period before the cue is presented, (2) RT-on: the reaction time or duration from when the cue is presented until the start of the muscle contraction in the EMG, (3) Response: the duration of the muscle contraction, and (4) RT-off: the duration from when the cue disappears to the end of the muscle contraction. (b) Frequency at each electrode location for a particular coherence potential that occurred during each right fist clenching trial. There was significantly higher participation of several hand electrodes during the anticipation period, and of just the finger electrodes (27,28) during the RT-on phase. The same electrodes had significantly lower participation in the response phase and hardly any participation in the RT-off phase. (c) Correlations between the timing of the trial spanning coherence potentials (CPs) on each electrode and the reaction time or motor onset. Right finger electrodes 27 and 28 are highlighted as larger dots separated from the others. The timing of occurrence of the RH (Right Hand) CP on either electrode 27 or 28 in the RT-on phase was highly correlated with the reaction time. However, while the coherence potentials associated with other tasks (left and right foot (LF, RF), left hand (LH)) were also present during the anticipation and response periods of the right fist clenching trials, no electrode was particularly correlated to onset of the motor behavior. All panels from [53].

3.4. Summary

In summary, the goals of interpreting electrical brain signals might be thought of by analogy to mechanisms of speech or language. Here, a certain statistical structure known as Zipf's law defines language signals, while particular words within this signal represent motifs with a specific meaning. The power law statistics that define neuronal avalanches, for example, represent a universal statistical feature of the mammalian, cortex while the particular relationship between timescale and power law exponent appears to be species specific. Similarly, the presence of coherence potentials, or the propagation of large amplitude field potentials without distortion of their waveform shape, also appears to be a cross-species phenomenon. However, the rate and complexity of these waveform shapes appears to be species specific. Taken further, the particular waveform shape may represent motifs that hold information about behaviors.

4. Part III: Understanding human brain dynamics and their meaning with EEG

4.1. The EEG signal

Unlike field potentials measured directly on or within the brain such as in LFP and ECoG, EEG is separated from the brain surface by various types of tissue from the interstitial fluid to the pia and dura mater, the skull and skin tissue or scalp [63, 64]. This adds a completely different dimension to the signal. Beyond the aggregate signals of the underlying neurons and glial cells, there are various other factors that influence the signal including the conductivity of the intervening tissue and head geometry. To add to this, skull tissue is not uniform in its thickness [64] and its conductivity in a living person is difficult to measure.

Models exist that attempt to parse out the effects of the volume conduction of the intervening tissue and the cortical surface. However, these models make a number of assumptions that ignore many important aspects of the human cortex. For example, these models assume that the cortex behaves as a dipole [65–67]. Such models must necessarily make a number of assumptions and, for simplicity, do so in ways that ignore various aspects of cortical behavior. First, they assume that the signal travels in only one direction although back-propagation of action potentials into the dendrites has been well-established [68–71]. Second, they fail to account for the glial cells which outnumber neurons by 1.4× and heavily modulate neuronal activity [12, 13, 72], propagate fast calcium waves [73–76] and play a role in buffering or mopping up charge from the external space around the

neurons [77, 78]. Third, they do not account for active propagation processes at the network level such as those demonstrated by the phenomenology of coherence potentials [57].

Altogether, there are a great deal of unknowns. Consequently, the EEG can be regarded as an epiphenomenon of the individual, comprising an aggregate of many factors.

Nonetheless, its noninvasive nature, low cost, portability, ease of measurement and high temporal resolution confer several advantages over other views of brain activity. Other methods of peering into the human brain such as fMRI, which measures changes in blood oxygen levels on the slow time scale of a second, are well-suited to delivering insights into *where* activity is occurring under any given circumstance. Invasive approaches such as LFP recordings that can be combined with physiological interventions and pharmacology are better suited to answer *how* the signal comes about. EEG, on the other hand, with its easy integration with human behavioral experiments, is best suited to answer the question of *what* the signal is saying in terms of relationships to inputs and outputs.

4.2. Discovery of the EEG signal

The EEG signal in humans was first reported by Hans Berger in 1929 [79]. This was the pre-computer era when analysis involved essentially 'visual inspection', looking at the signal and using a ruler to measure some aspect of it [80]. The most obvious visual element was durations of periodicity around 10 Hz when the eyes were closed. These were reported in the earliest EEG recordings by Hans Berger and called alpha waves. Everything else in the signal he referred to as beta waves, acknowledging that they were non-periodic complex fluctuations of higher frequencies that could not be readily characterized. The absence of this visible periodicity (the alpha waves) when the eyes were open gave rise to the generalization that what remained, the beta waves, signified alertness [81]. This idea of 'more beta means alertness' continues to prevail in popular dialogue even today.

In the 1930s and several decades beyond, EEG was recorded on film or on the less affordable but more accurate ink-writing oscillograph. The ink-writing oscillograph had better resolution but could not typically write faster than 30 Hz. This capped the range that defined the 'beta waves'. However, in 1936 Jasper and Andrews [82] were able to identify frequencies higher than 30 Hz and called them gamma waves. Similarly, slower frequencies, previously ignored, were reported by Hoagland, Rubin, and Cameron [83] and given the name delta waves. The separation of the spectrum into these broad bands along with its nomenclature continues to persist today despite their origins in the technical constraints of the pre-computer era of the 1930s and 40s.

4.3. Traditional analysis of the EEG signal

One of the most commonly used methods of analyzing statistical features of a continuous EEG signal is to transform the signal into its power spectrum and then collapse the spectrum into single values for each of its historical band definitions. The separation into bands has its origins in the workarounds of the 1930s and 40s, when the challenge of manual analysis led to the use of photomechanical analyzers (Fig. 10 (a)) which parsed the signal by frequency bands before writing it on the oscillograph [84, 85]. Essentially, these were mechanical band pass filters.

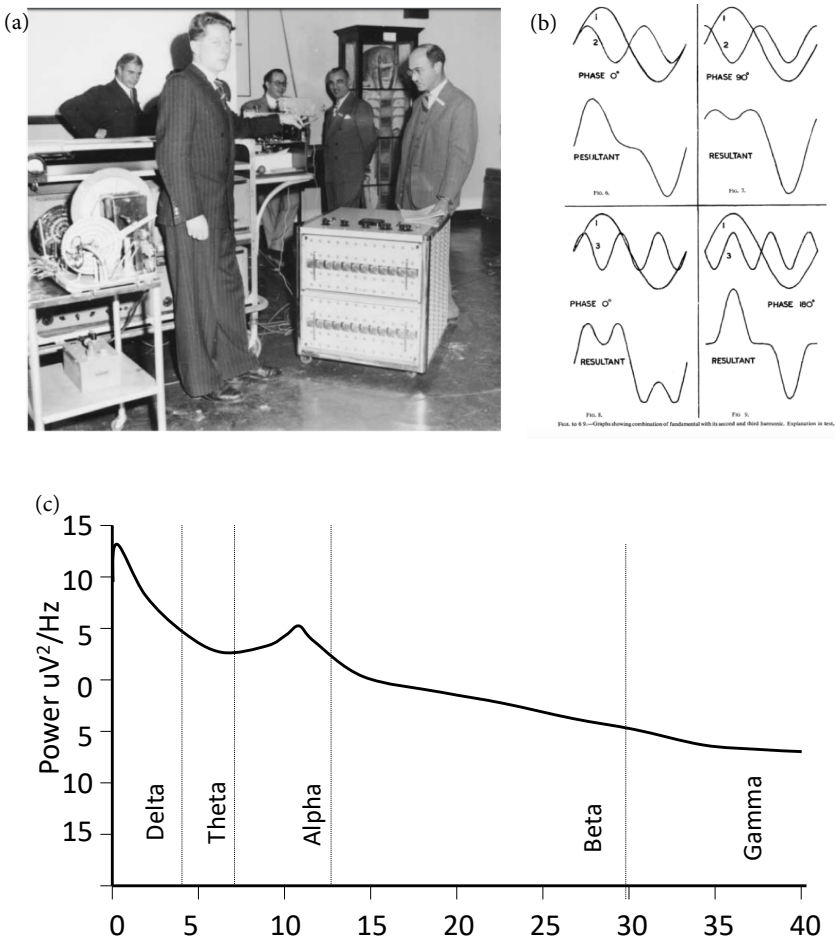

Fig. 10. History of EEG; (a) William Grey Walter with his EEG Analyzer in 1942 (from [86]); (b) Examples of the many possible waveforms arising from different phase relationships of the same underlying sinusoids (from [87]); (c) Example of an EEG power spectrum and its break-up into broad bands.

In the 1960s with the advent of computing, Fast Fourier transform (FFT) algorithms, such as the Cooley and Tukey [88] method came into play providing a computationally efficient view of the entire power spectrum (Fig. 10 (c)). This led to the view that the power spectrum of the EEG signal had a $1/f$ like structure, where the power was roughly inversely proportional to the frequency [42, 89–91]. In addition, the alpha periodicity observed visually by Berger was visible as a peak above this $1/f$ structure [43, 92–95]. Like avalanches, this $1/f$ structure and alpha peak are also visible across species in the LFP [50] and ECoG [96] and represent a universal principle. In addition, the $1/f$ exponent varies individually with factors such as age [42]. Numerous computational tools now exist to assess features of the entire spectrum. Despite these advances, the collapse of the spectrum into bands (Fig. 10 (c)) still persists today.

This traditional EEG analysis method does not typically take into consideration the enormous nonstationarity and waveform variability in the signal. In 1938, William Grey Walter, one of the inventors of the mechanical band pass analyzers himself (Fig. 10 (a), (b)) discussed at length the considerable limitations of this method in this respect [97]. He says:

> The chief limitation of automatic e.e.g. analysis with instruments at present available lies in the fact that whilst they will separate and measure mixed and modulated rhythms in the e.e.g. they give no information about the relative phases of the waves making up these rhythms. When harmonically related higher frequencies are added to a fundamental frequency, the shape of the resulting waves depends entirely on the phase relations of the harmonics to the fundamental. Therefore, two compound waveforms which have components identical in frequency and size, and so will show the same analysis, may yet have entirely different shapes. In the visual examination of an e.e.g. record it is important to know some of the forms a given set of rhythms may produce by phase. A series of harmonically related components may produce an infinite variety of waveforms.

Spectral decomposition of the signal might be considered similar in approach to analyzing an image based on its color spectrum while throwing away information on the relative position of the pixels. While some colors may bear correlation to certain types of pictures (*e.g.* pictures dominated by green and blue may be more likely to be natural landscapes), this approach is not powerful enough to clearly identify the contents of the picture. Similarly, spectral analysis throws away relative phase information of the waveform losing fine scale information on its complex and nonstationary properties.

Another common method employed in EEG is the averaging of the signal during a period following presentation of a stimulus to compute a trial averaged event related potential or ERP. A number of stimulus presentations have been shown to cause an increase in the ERP amplitude and the timing of the peak is often considered a marker of normal stimulus response [98–101]. However, traditional ERP analysis typically does not take into consideration the waveform variability of the underlying signals which might lend a new dimension to identifying stimulus response feature.

4.4. Frameworks for EEG signal analysis

Given the huge variety of waveforms produced within the brain signal, and the avalanche and coherence potential phenomenology outlined above in LFPs and ECoG, new approaches focusing on characterizing the spatial and temporal features of waveforms may yield novel insights into brain function. However, one of the significant challenges of working with brain signals is that we do not have any *a priori* understanding of which aspect of the signal is relevant. It is, therefore, easy to go down irrelevant paths. To understand the perils in such an undertaking, consider the example of language. Imagine if an alien species were to record the sounds produced by human beings but had no *a priori* knowledge of the nature of language or its manner of production.

A first crude approach might be to look at the power spectrum of the signal. Using this approach, one might find different categories of human sound and an ability to roughly distinguish song from speech perhaps. One may even be able to classify different languages based on differences in their spectral characteristics. However, it would be grossly insufficient to understand what these sound structures mean. Let us say, as a next step, the aliens decided to look at the signal with fine resolution identifying the characteristics of different sounds. It would seem logical to assume that the particular sound mattered and, therefore, that similar sounds such as p and b were more similar in meaning. With sophisticated tools, they could then study the occurrence of different sounds and their relative positions and speculate on their meaning. Yet, it would be an irrelevant approach. Even if they were to make the leap and figure out the concept of words, two words could sound the same in different languages but mean something totally different. Conversely, two words with totally different sounds could mean the same thing and be used interchangeably. How would they be able to make sense of this?

In interpreting the EEG signal, we are in the same position as aliens trying to interpret human sounds. However, there are ways by which one can find better paths to useful interpretation. Ultimately, what is relevant

is to understand how to map particular features of the signal to inputs and outputs to the system (Fig. 11). Any individual or acute stimuli or experience would result in a particular response in the EEG dynamics which would lead to a particular thought, feeling, cognitive output or behavior which can be measured and mapped. However, all of these acute stimulii, large and small, integrate over time into a larger context of life experience. Thus, inputs can be thought of as the various life experiences we have, the food we eat and the environment we live in — essentially the nutrient and stimulus environment in which our brain develops and operates. Both of these, individually and cumulatively, could result in adjustments to the macrostatistical characteristics of the system, which could, in turn, inform the nature of response produced by any acute stimuli. Thus, it is also relevant to look at the effects of cumulative life experiences over longer time scales such as education, or even our overall demographic context, and its relationship to macrofeatures of the dynamics. Similarly, it is of interest to evaluate the impact of these macrofeatures on acute stimulus-response profiles.

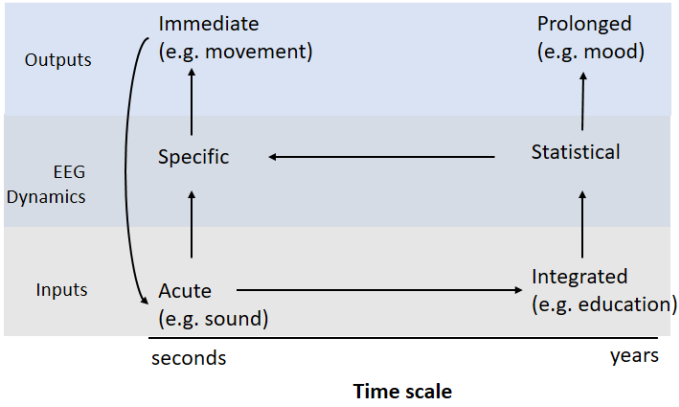

Fig. 11. Of all techniques, EEG allows the most flexibility to study the relationship of brain dynamics to inputs and outputs on various time scales. Studies of acute responses to stimuli are best approached from the perspective of seeking specific instantaneous features. All acute stimuli integrate over time into larger experiential contexts which may impact the overall statistical characteristics of the system. These, in turn, will influence the dynamical responses to acute stimuli.

Ultimately, the goal is that by experimenting with various approaches, one would identify those metrics that can inform a person about themselves in a productive manner. This could allow one to answer questions such as what metrics predict different cognitive or mental health outcomes and, therefore, what changes to inputs could alter this metric.

To arrive at such productive outcomes of EEG investigation, it is important to consider the great deal of individual variability both among individuals and within any one individual. In this context, universal statistical principles of the signal that do not change much are not likely to yield very many useful outcomes, except in identifying extreme disorders such as epilepsy or coma, where the conscious state of the brain is fundamentally changed. For the more subtle deviations in cognitive and mental health aspects, one would rather want to look for aspects of the signal that have large variance across the population.

To arrive at this, it is essential to perform analysis on large samples, goings from study sizes of 10s to 100s to 1000s and even hundreds of thousands, in order to capture as much of the state space and variance of these metrics across populations. It is also essential to capture extensive metadata pertaining to the various input and output states in order to parse out their individual contributions.

From a practical perspective, this may include collecting standard demographic and environment information from subjects across numerous studies as well as standard session information pertaining to stimulants consumed in the 24 hours prior to the recording session and state of mind at the time of experimentation. Given the cost effectiveness and portability of EEG today, such large scale studies are now within the realm of possibility.

4.5. Complexity as an example of an EEG metric that relates to inputs and outputs

Given the wide variety of complex waveform shapes in aggregate brain signals, their possible active propagation, and relationship to behaviors as demonstrated in LFP and ECoG, one approach could be to further explore the complexity of these waveforms. In this respect, I provide here one example of a metric of waveform complexity (C_{W}) that describes the diversity of waveforms within a period of time and its relationship to both inputs and outputs. This metric which is described in detail elsewhere [44] is constructed by comparing periods of 750 ms in duration (a duration where variance across the measured population is maximal) using a correlation measure, r. This describes the similarity of their shape rather than amplitude. A diversity distribution is then constructed by taking the $1-|r|$ values and the waveform complexity for any individual channel is then computed as the median diversity multiplied by 100 ($(1-|r|)\times 100$).

The waveform complexity thus observed in the resting state with eyes closed has been found to reflect changes in various inputs or context variables as well as performance on a cognitive task [44]. For example, mean group complexity scales systematically with aggregate scores of life context that

broadly represents access to modern services and technologies such as education, mobility and communication (Fig. 12 (b)). Statistically, these trends had p-values less than 10^{-6} for various statistical and bootstrapping methods. Similarly, individual waveform complexity measured with eyes closed immediately before the participant took a Raven's pattern recognition test, correlates strongly with their performance or score (Fig. 12 (b)).

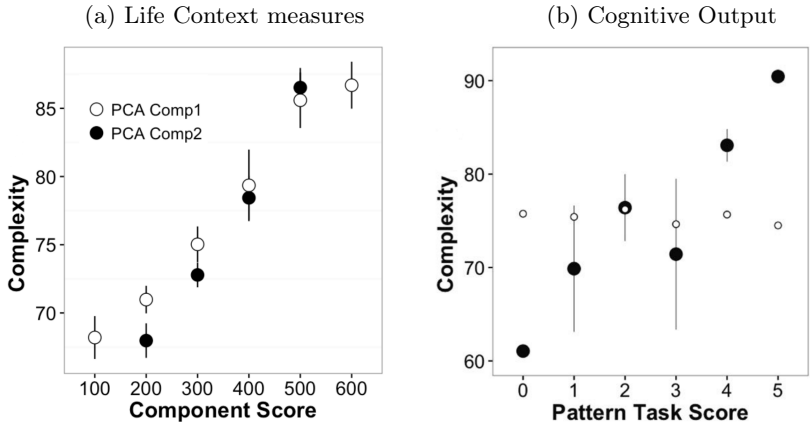

Fig. 12. Resting state EEG waveform complexity correlates to inputs and outputs. (a) Waveform complexity (mean ±SEM) of the EEG during a resting eyes closed condition increases systematically with principal component scores of life context features of income, education, geofootrprint, mobility and communication. (b) Waveform complexity (mean ±SEM) of the EEG during a resting eyes closed condition increases systematically with scores on a Raven's progressive matrix task performed immediately after the recording. Plots from [44].

4.6. Summary

In summary, I provide here an approach to the EEG signal that illustrates its tremendous potential for unlocking new insights into the relationship between features of the signal and inputs and outputs that are both acute and integrated over longer time scales. Further, I suggest that analytical approaches to the signal that focus on the complex waveform features of the EEG rather than traditional spectral and ERP measures may provide new kinds of insights. I also provide, as evidence, an example of this approach using a new measure of complexity.

5. Conclusion

In conclusion, the electrical field potential in the brain is an aggregate signal that, while mechanistically difficult to understand, has enormous potential to provide a view of the working system and its relationship to inputs and outputs. Furthermore, working within a larger integrative framework along the dimensions of species universality to individual uniqueness and statistical characteristics to specific motifs can provide a guide for experimental design and interpretation of results. The phenomenology of the avalanches is an example of a statistical principle that spans across species but with a species specific relationship between exponents and timescales. Its scale free nature also establishes an equivalence across spatial and temporal scales enabling logical comparison of signals measured at different resolutions. Similarly, the phenomenon of coherence potentials is a mechanism for identifying specific motifs that span across species but which also have species and individual specific threshold characteristics. Finally, EEG offers the valuable opportunity for noninvasively establishing relationships between brain dynamics, experience and behavior. Based on the phenomenology found in LFPs and ECoG, I suggest new insights might be gained by probing both specific and statistical features of the waveform in relation to both acute and integrated stimuli and mental states.

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