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Mapping human brain networks with cortico-cortical evoked potentials

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The cerebral cortex forms a sheet of neurons organized into a network of interconnected modules that is highly expanded in humans and presumably enables our most refined sensory and cognitive abilities. The links of this network form a fundamental aspect of its organization, and a great deal of research is focusing on understanding how information flows within and between different regions. However, an often-overlooked element of this connectivity regards a causal, hierarchical structure of regions, whereby certain nodes of the cortical network may exert greater influence over the others. While this is difficult to ascertain non-invasively, patients undergoing invasive electrode monitoring for epilepsy provide a unique window into this aspect of cortical organization. In this review, we highlight the potential for cortico-cortical evoked potential (CCEP) mapping to directly measure neuronal propagation across large-scale brain networks with spatio-temporal resolution that is superior to traditional neuroimaging methods. We first introduce effective connectivity and discuss the mechanisms underlying CCEP generation. Next, we highlight how CCEP mapping has begun to provide insight into the neural basis of non-invasive imaging signals. Finally, we present a novel approach to perturbing and measuring brain network function during cognitive processing. The direct measurement of CCEPs in response to electrical stimulation represents a potentially powerful clinical and basic science tool for probing the large-scale networks of the human cerebral cortex.

1. Introduction

There has been a shift in understanding of the cerebral cortex in recent years. The older concept of a highly localized hierarchical structure that forms the intervening steps between stimulus and response has recently given way to the notion of a distributed network of modules with intrinsic properties that integrate in the presence of external stimuli [1,2]. Accordingly, the intrinsic architecture of connections forms a key component of cortical organization. This concept has motivated analyses that enable us to delineate the large-scale connectivity *in vivo* and to assess how neural activity dynamically evolves along these structural links. The present article reviews the unique contribution of cortico-cortical evoked potential (CCEP) research to our knowledge of human cerebral connectivity. We begin by introducing the topic of cerebral connectivity and the range of approaches available to measure it.

(a) Structural connectivity

Structural connectivity refers to the set of anatomical connections between neurons in different regions [3]. Establishing a complete map of brain connections, the

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structural connectome, at a microscopic scale requires determining the anatomy of every neuron in the brain, down to every dendrite, axon and synapse. While such a feat might be within our reach in animal models using electron microscopy and other invasive techniques [4,5], mapping the human structural connectome with such high resolution would be technically and computationally challenging. At a more macroscopic scale, the cerebral cortex may be thought of as a set of hierarchically organized modules, or areas, that perform different sensory, cognitive or motor functions, each of which are formed by large groups (approx. 10^8) of neurons [6]. Non-invasive techniques based on magnetic resonance imaging (MRI) have now made it possible to image and quantify white matter tracts in the living human brain that interconnect these modules. Specifically, diffusion tensor imaging (DTI) takes advantage of the fact that the random microscopic motion of water molecules is biased in the direction of connective fibre pathways. Probabilistic maps of large-scale inter-regional tracts can thus be generated by combining the pattern of diffusion biases across voxels in space [7,8].

The ensemble of white matter connections—the *structural connectome*—is a necessary component of a complete theory of cortical function, as the anatomical substrate both enables and constrains information flow and the dynamic grouping of local neuronal populations into larger assemblies [9,10]. While synaptic terminals represent the fundamental unit of cortico-cortical interactions, estimating these connections via white matter origin and termination is more non-invasively feasible, for example with DTI. Additionally, white matter connectivity should closely mirror inter-regional synaptic connectivity, as the majority of axonal communication occurs across synaptic terminals. A fundamental limitation of MRI-based tractography is that it cannot resolve the functionality and directionality of anatomical links. Even if two areas are connected with an anatomical link, it does not necessarily follow that those links are being used—a road perhaps not travelled. Furthermore, interareal axonal projections have a fundamental directionality with the wave of depolarization travelling from the cell body to the axonal terminal that cannot be assessed by DTI. We propose that the human connectome may be a directed network, with information not necessarily flowing reciprocally between sites. Therefore, it is necessary to use tools for inferring the direction of information flow.

(b) Functional connectivity

Functional connectivity is not an anatomical measure but rather a property of neural dynamics. Two neurons (or two brain regions) are said to be functionally connected if their dynamics are statistically dependent on one another (e.g. if their mean activity levels are correlated over time) [11]. Again, while it is impractical to simultaneously record from large ensembles of identified neurons in multiple cortical areas of the human brain, non-invasive neurophysiological (electroencephalography (EEG) and magnetoencephalography (MEG)) and functional neuroimaging (positron emission tomography (PET) and functional MRI (fMRI)) approaches allow the delineation of human functional connectivity at a modular level with a resolution of a few millimetres [12,13].

(c) Effective connectivity

Effective connectivity refers to the causal influence between brain regions [14]. In contrast to functional connectivity, effective connectivity is a directed measure, where the influence that area A exerts upon area B is not necessarily identical to the influence of B over A. Effective connectivity has been described in detail, beginning with Aertsen's work on evoked connectivity in cat neocortex [15,16], Friston's work on effective connectivity in human neuroimaging [11,14,17] recently has been applied to encompass dynamic causal modelling, Granger causality and other model-free approaches [18–20]. Horwitz has noted that that the term 'effective connectivity' is applied broadly to different computational algorithms across multiple neurophysiology and neuroimaging modalities (PET, fMRI and EEG) with widely variable spatial and temporal resolution, and he suggests that the term should be used cautiously and clearly [21].

There are two distinct approaches to probe effective connectivity: non-interventional and interventional. The non-interventional approaches are observational and attempt to infer causality via the analysis of simultaneous recordings of neurons or areas, in order to quantify the directionality of the functional connections using measures such as Granger causality and dynamic causal modelling [18–20].

By contrast, interventional approaches involve an empiric perturbation of activity in one set of neurons as the independent measure and then quantify its impact, or evoked response, at other sites as the dependent measure. Although non-interventional approaches are promising, and more widely applicable in non-invasive experimental settings, they do not directly measure directed influence. Furthermore, their interpretation is dependent on the validity of modelling assumptions and is considered controversial, especially in the context of neuroimaging [22–24]. In this review, we will focus on the interventional approach to measuring effective connectivity, which we will refer to as *evoked effective connectivity*.

(d) Importance of information flow in the brain

In the past decade, quantitative analysis, based mostly on graph theoretical measures [25], has revolutionized the examination of brain networks. This work is based largely on non-directional interactions between sites—that is, lacking information regarding the causal influence between sites. The brain is composed of hundreds of subregions whose functional specialization is largely determined by their incoming and outgoing connections with other cortical areas. For this reason, *directional interactions* captured with measures of effective connectivity can provide an important additional insight into brain networks. If it is the case, as we suggest here, that connections are not necessarily reciprocal, then it would follow that certain areas may be in a position of great influence, behaving as *projectors*, while other areas may be in a position of receiving influence, behaving as *integrators*.

Effective connectivity measurements have traditionally relied on animal work, but the recent interest in stimulation-based techniques in humans [26–28] now provides new data to investigate the influence of directional connectivity on network topology and behaviour. Non-invasive, interventional approaches that make use of transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) use *distant* (scalp EEG) or *indirect* (resting fMRI) measures of neural activity [13,29–31]. By contrast, CCEP mapping directly measures local neural activity from the surface of the brain. In this review, we focus on the use of CCEP mapping in

answering three fundamental questions regarding complex brain networks:

(1) What cortical physiology underlies CCEPs? (§3)
(2) To what extent do anatomical and functional connections predict CCEP connections? (§4) and
(3) How can the directionality of brain interactions further our understanding of complex brain networks? (§§5–7).

2. Cortico-cortical evoked potential mapping: a directional and causal measure of connectivity

(a) A history of brain electrical stimulation

Fritsch and Hitzig, in the late nineteenth century, were the first to establish a functional link between distant parts of the nervous system. In the early twentieth century, Vogt & Vogt [32] used cerebral stimulation to relate the function of the brain to its architectonic structure. During the same period, Krause [33] and Cushing [34] were among the first to perform electrical stimulation of the human brain to elicit motor responses. Foerster went on to not only stimulate other parts of the human brain, but also combined it with electrocorticography (ECoG), to record electrophysiological responses to brain stimulation [35]. His one-time student Penfield famously went on to perform extensive studies on the sensory, motor and cognitive effects of intraoperative brain stimulation in humans [36,37]. Purpura *et al*. [38] used microstimulation of the human cortex to investigate its neurophysiological properties. In experimental animals, Newsome and co-workers [39] were among the first to demonstrate how microstimulation of a specific cortical area could influence perceptual judgement. Recently, optogenetics have allowed the selective stimulation of neuronal subtypes in localized regions of animal brains [40] and assessing the effects of that stimulation on functional neural networks [41]. With the increasing use of research protocols to study effects of cortical stimulation in patients implanted with invasive electrodes for epilepsy monitoring, there has been recent resurgence of interest into the effects of cortical stimulation upon behaviour and perception [26,42–44].

While most of the aforementioned work focused on the link between stimulation and changes in perception or behaviour (e.g. stimulating the post-central gyrus to establish that it participates in somatic sensation), other techniques including TMS, tDCS and CCEP mapping have been used to measure the inter-regional influence of local stimulation (i.e. effective connectivity). The major advantage of mapping human brain connectivity via stimulation is the ability to assess directedness of cerebral connections *in vivo*, which is not possible using MRI-based tract tracing nor functional MRI-based covariation methods. TMS uses a time-varying magnetic field that propagates through the skull to non-invasively induce changes in suprathreshold neuronal spiking in the cerebral cortex [31,45]. On the other hand, tDCS applies an electrical current between two electrodes placed on the scalp to introduce subthreshold changes in neural activity [46–48]. Combined with scalp EEG or functional MRI, TMS and tDCS have the ability to sample distributed networks with high spatio-temporal resolution in humans. However, the spatial extent of neuronal modulation from the external magnetic field (for TMS) and electric field (for tDCS) is unclear, and experimental control of the precise location of the stimulus is more limited than when electrodes are lying directly on the brain's surface [49].

Table 1. Comparison of different stimulation techniques. The number of plus marks represents the author's expert opinion and is not derived from quantitative measurement.

	microstimulation	CCEPs	TMS/ tDCS
localization of perturbation	+++	++	+
intracolumnar resolution	+++		
sampling of distributed networks		++	++
temporal resolution	+++	+++	+++

Matsumoto *et al*. [50] introduced the 'CCEP' terminology when they measured, using invasive subdural electrodes, the electrophysiological responses of cortical areas to direct electrical stimulation at another site. The electrodes in CCEP studies are implanted for clinical reasons, when patients with intractable epilepsy undergo evaluation for potential resection of seizure focus regions. CCEP mapping has excellent spatio-temporal resolution, accurate localization of the stimulated region and can sample activity across distributed networks. A disadvantage to this approach is the lack of ability to examine effective connectivity in individuals without cortical pathology. Additionally, spatial sampling is restricted by the limited number of intracranial electrodes placed in any single patient. Table 1 and figure 1 summarize the characteristics of each of these interventional techniques.

(b) Overview of cortico-cortical evoked potentials

In order to gain direct access to the awake human brain, patients with medically intractable epilepsy undergoing surgical evaluation for seizure localization are recruited for research purposes. Prior to implantation, the hemisphere and lobe generating seizures are determined by an EEG recording from the scalp; however, electrodes placed inside the skull are necessary for more precise localization of epileptic activity. Two different techniques are performed for intracranial electrode monitoring. The *grid and strip* approach involves a craniotomy and durotomy followed by the placement of two-dimensional strips or sheets (grids) of electrodes (typically 3 mm diameter, 1 cm inter-electrode spacing), where neural activity can be recorded from the surface of the cortex (termed electrocorticography, or ECoG [53–57]). On the other hand, *stereoelectroencephalography* (*SEEG*) involves the placement of multi-contact electrode leads penetrating the brain [58–60]. While in this review we focus on the *grids and strips* approach, the principles discussed may be applied to both techniques.

Following the implantation of subdural surface electrodes, neural activity is recorded until enough seizures are observed for clinical purposes and electrical stimulation mapping can subsequently be performed to define functional areas. CCEP mapping is performed typically after seizures have been captured and antiepileptic medications have been resumed. CCEP mapping begins with the injection of current (1–10 mA

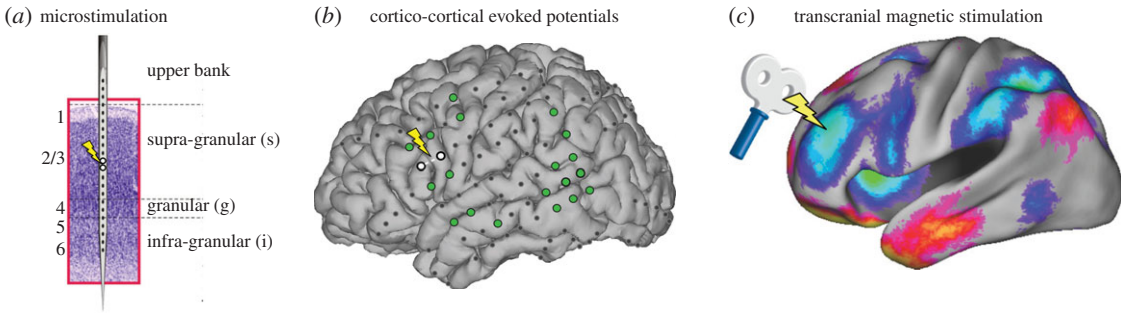

Figure 1. Interventional techniques for measuring effective connectivity. (*a*) Microstimulation: stimulation and measurement of neural activity can be performed within the same cortical microcolumn. (*b*) Cortico-cortical evoked potentials: current is injected across electrodes placed on the cortical surface, and the strength and latency of propagating electrical activity is measured at distant sites. (*c*) Transcranial magnetic stimulation: generation of a large magnetic field outside the skull induces an electrical current inside the skull. Neural activity can be monitored with scalp EEG or functional MRI. Adapted with permission from [30,51,52].

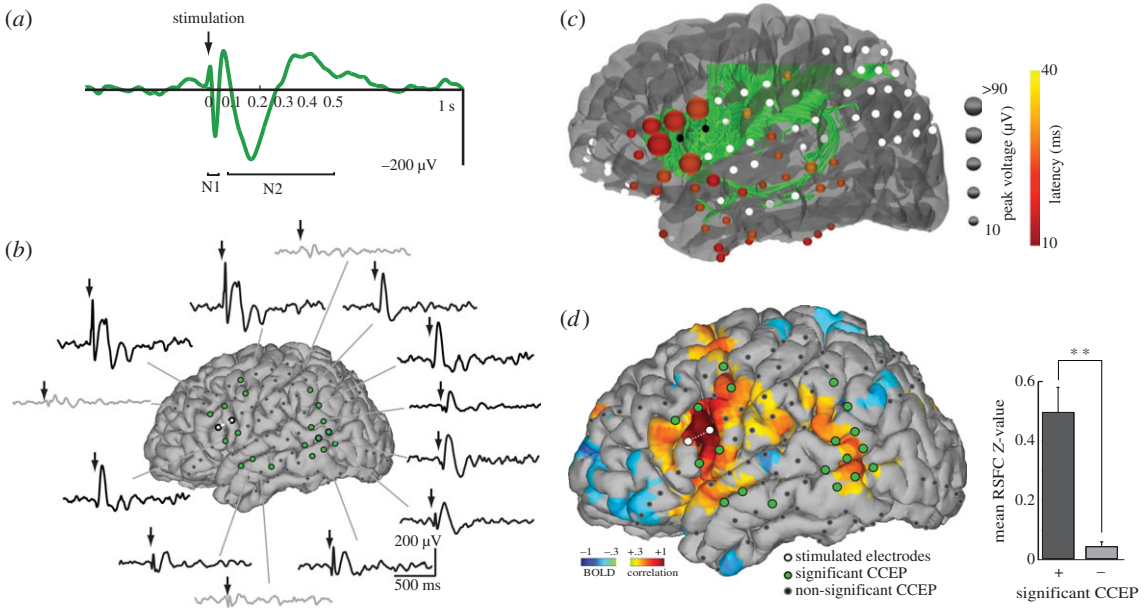

Figure 2. CCEP mapping and the comparison to anatomical and functional connectivity. (*a*) Components of the CCEP include the early N1 and late N2. (*b*) Spatial and temporal distribution of CCEPs. Green and grey coloured electrodes represent significant and non-significant CCEPs, respectively. Bipolar stimulation is applied between the adjacent electrodes (dotted white lines). Examples of CCEP waveforms are shown at several significant (black) and non-significant (grey) regions. (*c*) Comparison of structural and effective connectivity. The number of white matter tracts measured with DTI are positively correlated with the strength of the CCEP's N1 component and negatively correlated with its latency. Black circles denote the stimulating electrodes. The N1 response is represented by latency (colour of electrode) and amplitude (size of electrode). Electrodes without notable N1 responses are shown in white. All DTI pathways passing through the stimulation site are shown in green. Adapted with permission from [61]. (*d*) Comparison of functional and effective connectivity. Regions exhibiting strong N1 and N2 CCEP responses demonstrate correlations as measured by fMRI at rest. CCEP responses to stimulation of the white electrodes are depicted as significant (green) and non-significant (grey) circles. The BOLD correlation map with reference to the seed region at the stimulation site is represented by a heat map plotted on the pial surface. Results are from one representative patient. RSFC, resting-state functional connectivity. Adapted with permission from [52].

for 100–500 µs) between a pair of adjacent electrodes. The extraparenchymal location and wider surface area of the stimulating electrodes using grids and strips results in greater resistance and lower charge density than SEEG. Consequently, brief stimulation of up to 10 mA is commonly tolerated without resulting in unwanted epileptiform afterdischarges using grids and strips. The stimulation triggers a local electrical response at the area of stimulation as well as at adjacent or remote locations in proportion to the strength of the effective connection between the two locations. This procedure is repeated 10–50 times for signal averaging of the evoked response. CCEPs typically consist of an early (10–30 ms) negative surface deflection termed the N1 and a later (80–250 ms) slow wave termed the N2 (figure 2*a*) [50,52,61–63]. Considerable waveform heterogeneity of the N1 and N2 components of the CCEP exists across spatially diverse recording sites following stimulation (figure 2*b*). In this manner, the stimulation-evoked response (i.e. the CCEP) provides a measure of directional connectivity that is sampled directly from the cortical surface.

(c) Cortico-cortical evoked potential mapping of brain networks

Lüders and colleagues were one of the first groups to employ CCEP mapping to investigate the connectivity within functional networks, specifically motor and language regions [50,63]. One advantage of CCEP mapping is the examination of the *reciprocity* between regions—that is, how often stimulation of site A evokes a CCEP at site B, when stimulation of site B evokes a CCEP at site A. Within the motor cortex, CCEPs were observed frequently, with 75% of site pairs exhibiting reciprocal

CCEPs [63]. In another study, CCEP mapping of the language system demonstrated that stimulation of Broca's area but not adjacent regions coding for face movement elicited strong CCEPs in posterior temporal language regions. Moreover, the majority of CCEP responses within the language system were bidirectional [50]. The authors concluded that bidirectional connections observed between anterior and posterior temporal regions argue against the commonly accepted Wernicke–Geschwind model of language, in which word comprehension in Wernicke's area is transmitted to Broca's area to produce speech in a unidirectional fashion [64]. In a CCEP study characterizing the connections between frontal and temporal lobes, a high incidence of *intralobar* connections was observed. By contrast, an asymmetry between *interlobar* connections was observed with frequent frontal-to-temporal and rare temporal-to-frontal connections [65]. CCEP mapping studies have since examined the fronto-parietal network [66], hippocampus [67] and language [60] networks. In summary, CCEP mapping has begun to reveal directional connectivity both within and between human functional networks, which is difficult with non-invasive studies.

3. Electro-mechanistic basis of cortico-cortical evoked potentials

CCEP mapping can reliably localize functionally related brain regions using direct electrophysiological stimulation and recordings. However, uncertainty concerning the neural mechanisms underlying the response to stimulation reduces the neurobiological insight provided by CCEP mapping [68]. Here, we consider the likely mechanisms for the generation of evoked potentials during bipolar, biphasic stimulation, which is our preferred mapping method. Stimulation is biphasic when current injection in each anode–cathode electrode pair is followed by a second current injection of equal strength with the anode and cathode electrodes switched. Biphasic stimulation balances the charge, both at the electrode tip (to avoid deposition of ions) and also in the underlying tissue (which may be more sensitive to one polarity). As opposed to unipolar stimulation where the stimulation is performed between an area of interest and a distant site that may be extracranial or at a site far from the area of interest, bipolar stimulation, where injected current runs between two adjacent electrodes, should deliver a more consistent stimulation configuration by providing a focus of return current. In addition, computational modelling suggests that bipolar stimulation affects a more local region of cortex than monopolar stimulation [69], thereby minimizing the spatial spread of stimulation and increasing the spatial resolution.

(a) Propagation pathways of neural activity during cortico-cortical evoked potential mapping

The CCEP involves two processes: (i) the physiological change induced at the site of stimulation and (ii) the response recorded at the site of projection. Given that pyramidal cells give rise to the major output of the cortex, we focus our discussion on stimulation-induced changes in these neurons. Current injected onto the surface of the neocortex can affect local pyramidal cells through several pathways. First, there is direct depolarization of the superficial dendritic trees of pyramidal cells in cortical layers 2, 3, 5 and 6, which increases the likelihood of raising the membrane potential above the threshold needed to generate an action potential in these neurons. Second, injected current will depolarize layer 2/3 inhibitory interneurons that synapse near the soma on adjacent pyramidal cells [70], leading to an indirect decrease in pyramidal cell firing through the activation of GABAergic synapses. Third, injected current will depolarize long-range axons traversing the region of stimulation, generating action potentials propagating orthodromically (to local and distant pyramidal synapses) as well as antidromically (backpropagating to depolarize the pyramidal cell soma and possibly dendrites [71,72]). These pathways are schematized in figure 3*a*.

Although there are several possible pathways for the propagation of cortical stimulation, animal studies provide some insight into those that are most likely. Specifically, studies in cat neocortex rarely observed antidromic activation following direct cortical stimulation [74]. Moreover, the majority of responses to direct cortical stimulation propagated from superficial lamina to deep lamina [74]. These studies suggest that CCEP generation primarily involves the activation of middle and deep pyramidal cells. Local responses in middle and deep pyramidal cells will then propagate down its axon to mono- and poly-synaptically connected regions via cortico-cortical and cortico-subcortical projections [75]. In summary, it is likely that responses to single pulse stimulation in humans reflect both a major pyramidal cell contribution via orthodromic cortico-cortical and cortico-subcortical-cortical projections as well as a minor antidromic contribution [63].

Next, we focus upon the responses elicited at the sites of projection. Owing to their shape and uniform orientation in cortex, pyramidal cells are also the dominant generators of field potentials at the recording site [76]. Laminar current source density analysis of cortical responses produced by brief, transient (less than 1 ms) sensory stimulation shows the earliest sensory responses as depolarization in the middle laminae (3 and 4) and manifest as a surface negativity that is of short duration (10–30 ms) and 10–40 Hz in frequency [77,78]. This is followed by complex patterns of excitatory and inhibitory post-synaptic potentials across all cortical laminae of longer duration and lower frequency (1–4 Hz). The N1 of the CCEP bears great similarity to the early excitatory cortical response resultant from feed-forward input, whereas the later N2 is reminiscent of the later response [62]. It is likely that both locally driven oscillations with sequences of excitation and inhibition as well as recurrent relay volleys contribute to this prolonged response to even the briefest of stimulation [78–80].

Finally, we consider the termination of the propagation in light of evidence that shows stimulation to be limited in terms of levels of the modular, hierarchical structure of cortex. Combined fMRI/electrophysiology studies in monkeys showed microstimulation in the lateral geniculate nucleus to produce increased blood-oxygen-level-dependent (BOLD) signal that is limited to V1 and not extend to extrastriate cortex [81]. The fact that this effect is abolished by GABAergic antagonists implies that inhibition in the area generating the CCEP, in turn, limits propagation of the effects of cortical stimulation.

4. Relationship between anatomical, functional and effective connectivity

Non-invasive neuroimaging techniques are currently limited by their indirect measurement of neuronal activity. CCEP mapping, on the other hand, measures electrical activity directly from the cortical surface. In this manner, CCEP mapping can

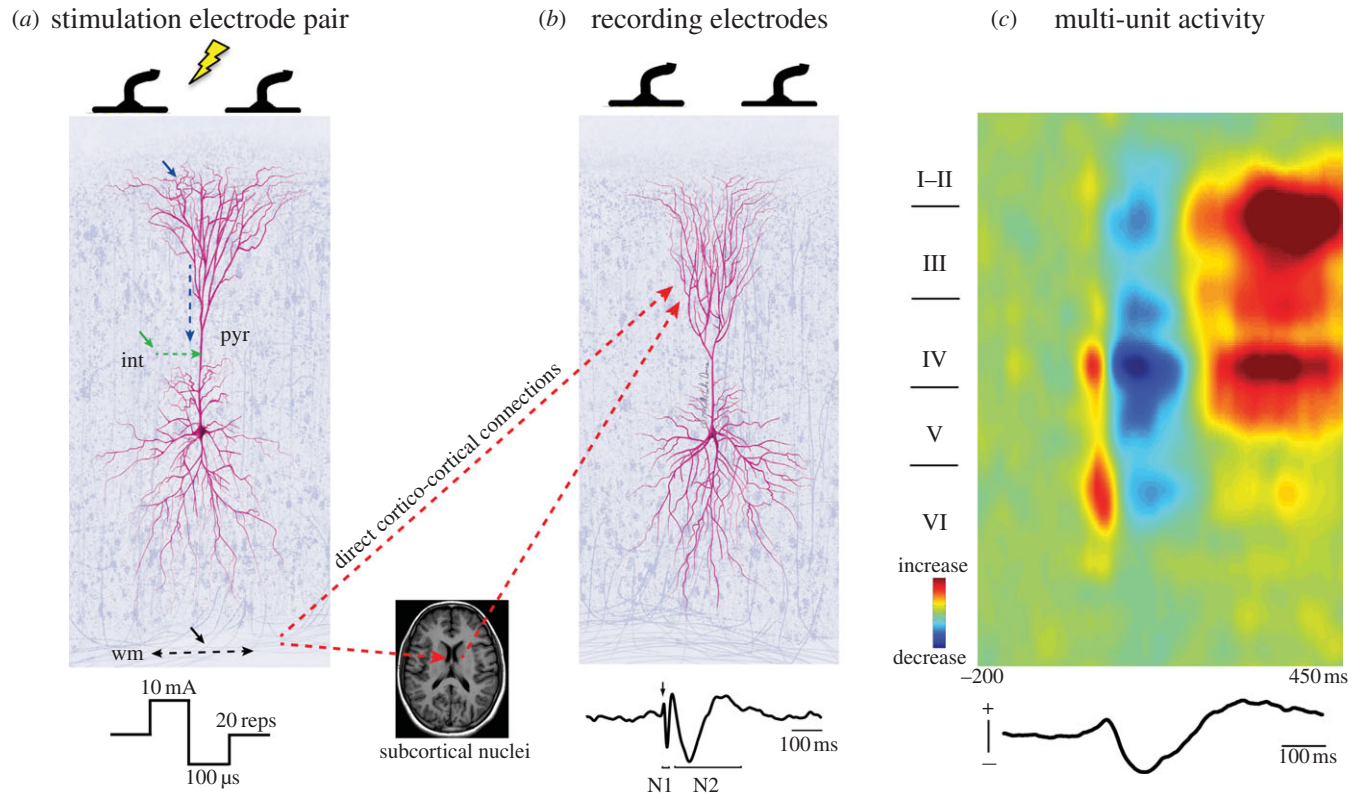

Figure 3. Proposed mechanism of CCEP generation. (*a*) Generation of firing rate changes in pyramidal cells at the stimulation site. The stimulation protocol is shown below. Pyramidal cells are the principal cells of long-range transmission of electrical activity. Electrical current injected at the cortical surface propagates to local pyramidal cells via direct dendritic activity (blue arrows), adjacent interneurons (green arrows) or white matter traversing the stimulated region (black arrows). Solid arrows represent the region of the neuron that is first modulated by stimulation, while dotted arrows denote the direction of propagation within the neuron. (*b*) Electrical activity is transmitted to distant pyramidal neurons through direct and subcortical pathways. An example of the evoked potential at the target site is shown below. (*c*) Multi-unit response to electrical stimulation. Red and blue colours denote increases and decreases in multi-unit activity, respectively. Cortical layers are estimated on the left of the multi-unit colour plot. Curve below depicts a representative recording from the deeper layers. Results are from one representative patient. Adapted from [73]. pyr, pyramidal cell; int, interneuron; wm, white matter.

Box 1. Information. The Neural Basis of CCEP Generation.

While there may be variable degrees of latency to activity after epicortical stimulation [82], it is likely that single pulse stimulation of up to 10 mA results in activation within 2–4 ms [83]. The latency of peaks in the CCEP suggests an oligo- or polysynaptic propagation pathway for both the N1 and N2 components. If a similar conduction velocity is assumed (3–80 m s^{-1} for primate myelinated pyramidal tract neurons [84,85]) while accounting for differences in cortical volume between primates and humans, a 4–8 ms delay from stimulation to the observation of monosynaptic connections at the remote response site is expected. However, for most clinical recording systems, current injection saturates the amplifier for 5–10 ms, causing monosynaptic responses to be missed. Instead, given the temporal delay across synapses (2–3 ms), it is likely that the 10–30 ms N1 response is generated from the electrical propagation across multiple synapses.

Early studies of the effects of epicortical stimulation upon single neuronal firing showed an early excitatory response occurring in the time frame of the N1 followed by a longer lasting, slower inhibition that occurred in the N2 time frame [62]. The early N1 response of the CCEP is accompanied by a burst of action potentials at the remote site [86]. Moreover, data from laminar multi-contact recordings in humans from our group demonstrate that single pulse stimulation elicits an increase in multi-unit activity in deep (layer IV–VI) cortical layers (figure 3*c*), suggesting pyramidal activation during the early N1 response. While the method of propagation to target pyramidal cells is still unknown (as discussed above), accumulating evidence suggests that the N1 represents an excitatory event comprising depolarization of pyramidal cells in deep cortical layers.

By contrast, the N2 slow wave is accompanied by a suppression of action potentials at the remote site [86]. Laminar recordings corroborate the single unit findings by demonstrating a decrease in multi-unit activity (figure 3*c*) in layers III–V. These multi-unit findings are similar to those seen in the laminar profile of slow-wave-sleep and evoked and spontaneous K-complexes [49,50]. The significant decrease in multi-unit activity was associated with current sources in layers III–V and also with significant decreases in spectral power. The decrease in synaptic activity together with current outflow from the neuronal elements (source) suggests the role of non-synaptic regulations, such as disfacilitation (regulated by ion channels) [87]. This profile of decreased deep multi-unit activity and current sources in middle-to-deep layers mimics slow-wave-sleep [88] and K-complexes [89] and suggests that the N2 slow wave of the CCEP represents prolonged inhibition. In summary, single and multi-unit data support the interpretation of the N1 of the CCEP to represent excitation of pyramidal cells, while the N2 represents long-lasting inhibition.

provide a neuronal basis of neuroimaging signals that are used widely to study brain connectivity and function. For example, the N1 of the CCEP partially reflects both structural [61] and functional [52] connections between cortical regions, whereas the N2 partially reflects functional connections [52].

The N1 potential occurs between 10 and 30 ms and is thought to reflect excitation of local cortex ([62]; see Information in Box 1). If the N1 of the CCEP reflects neuronal activity from direct axonal projections, then it should predict the existence of underlying structural connections measured with DTI. The number of tracts between two regions was shown to positively correlate with the strength of the N1 response and negatively with the latency of the N1 response [61], supporting the notion that the N1 at least partially reflects the strength of anatomical connectivity between two regions (figure 2*c*).

CCEP mapping has also been compared to resting fMRI, a measure of functional connectivity that quantifies the temporal coherence of the BOLD signal across cortical regions in the absence of sensory stimuli. Although resting fMRI measures ultraslow (less than 0.1 Hz) fluctuations of the BOLD signal, we hypothesized that fast electrically propagated potentials elicited with CCEP mapping would propagate in a similar manner to slow changes in neural activity that can be indexed by the BOLD signal. Brain regions with temporally correlated BOLD fluctuations also exhibited larger CCEP amplitude during the N1 and N2 time periods (figure 2*d*). These findings, which were replicated across patients and functional networks, suggest that temporal correlations of slow, spontaneous haemodynamics reflect similar functional interactions to those arising from fast electrically propagated activity [52].

Matsui *et al*. [90] examined this question in non-human primates, where electrode placement does not depend on clinical considerations. Consistent with previous work in humans comparing effective and functional connectivity as described above [52], stimulation-induced fMRI (a measure of effective connectivity) in the somatosensory cortex of non-human primates revealed strong intra-hemispheric correspondence with resting fMRI interactions (functional connectivity). By contrast, poor correspondence between effective and functional connectivity was observed for inter-hemispheric connections—that is, regions exhibiting strong inter-hemispheric resting functional connectivity in somatosensory cortex did not exhibit strong effective connectivity [90]. The authors posited that inter-hemispheric interactions may partially result from network-level synchronization not captured with some forms of stimulation-based effective connectivity measures. In support of this notion, while complete resection of the corpus callosum caused a significant reduction in inter-hemispheric functional connectivity in both humans [91] and non-human primates [92], inter-hemispheric functional connectivity persisted if the anterior commissure was left intact. These data suggest that inter-hemispheric functional connectivity reflects indirect processes rather than monosynaptic connections [92].

In summary, CCEP mapping provides a direct measure of local electrical activity to which non-invasive, indirect measurements can be compared and aid in their interpretation. Effective, anatomical and functional connectivity within the same subjects will provide insight into the relationships of these techniques to the underlying neural circuitry. Performing these studies across brain networks will be critical to determine the extent to which inter-modality correspondence depends on (i) the electrode orientation relative to underlying cortex and (ii) local cytoarchitecture and density of white matter tracts.

5. Cortico-cortical evoked potential mapping with network measures

(a) Overview

Mapping the direction of flow of neural activity during specific cognitive processes provides novel insight into the architecture underlying information processing in the brain. As previously noted, CCEP mapping can assess the direction of information flow perturbing electrical activity at one site and measure the cortical response at another site. In the following sections, we summarize recent work in our laboratory combining CCEP mapping with graph theoretical methods to investigate the direction of information flow and the causal influence of brain regions on specific cognitive processes.

(b) Directed graph measures

Several graph theoretical measures describe the directional flow of information in the brain [25]. This terminology includes: *outdegree*—the total number of connections projecting outward from a node, *indegree*—the total number of connections projecting inward to a node, and *net flow*—the direction of information flow at one node calculated as outdegree minus indegree. In the context of CCEP mapping, we refer to *outdegree* of a region representing the number of significant CCEPs elicited following stimulation of the site of interest, while the *indegree* of a region will refer to the total number of significant CCEPs elicited at the site of interest upon stimulation of all other sites. These terms are schematized in figure 4*a*. CCEP mapping results are first transformed into connectivity matrices, such that each row contains the CCEP amplitude at each recording site following the stimulation of one region (figure 4*b*). Next, outdegree, indegree and net flow at each site are computed from the connectivity matrices. In a representative patient, the pre-central and post-central gyrus exhibit strong outdegree, whereas lateral temporal regions demonstrate strong indegree (figure 4*d*). Group analysis suggests that regions in the lateral prefrontal and superior parietal—regions implicated in the default mode network [93,94]—demonstrate strong *indegree* with *net inward* flow, whereas the pre-central, post-central and posterior temporal regions demonstrate strong *outdegree* with *net outward* flow. Moreover, regions involved in motor or language function—defined clinically by behavioural disruption elicited by high-frequency stimulation at specific electrodes—demonstrated strong *outdegree* with *net outward* flow [95,96].

These results provide evidence of consistent directional information flow between regions of the neocortex. Importantly, network measures such as centrality or modularity will be quite different when based on directed and undirected connectivity graphs. In the future, these findings could be compared with non-interventional (fMRI and MEG) and interventional (ECoG) measures of directionality including Granger or Bayesian methods [97,98]. Although the interpretation of these techniques is controversial when applied to functional neuroimaging data with poor temporal resolution such as fMRI [24] millisecond-resolution electrophysiological methods such as EEG, MEG and ECoG may be used with similar analyses. Additionally, it will be important to study the effect of cognitive state (e.g. rest, task) on the properties of these directed CCEP networks.

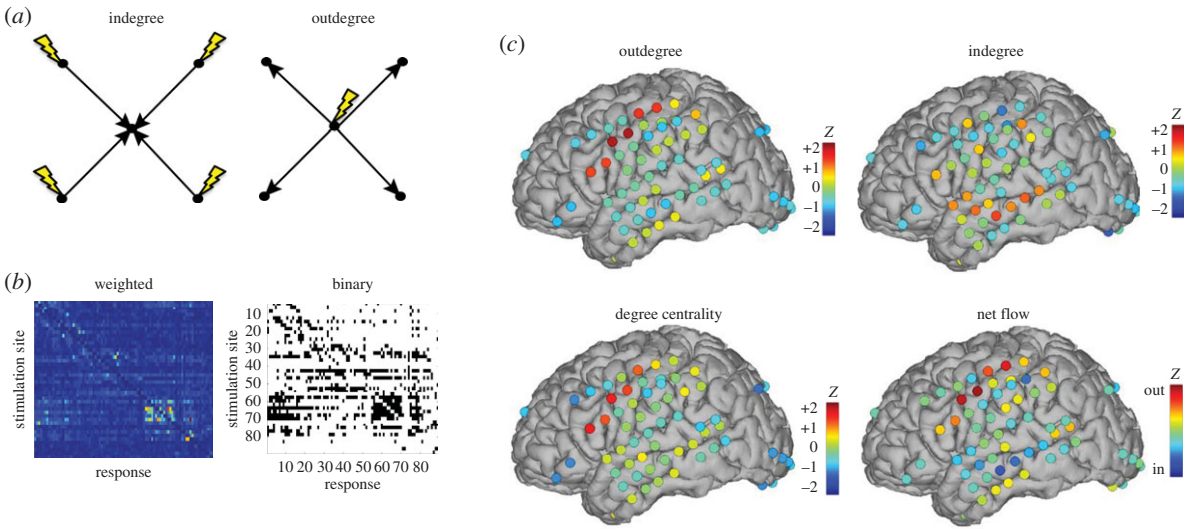

Figure 4. CCEP mapping probes the directionality of complex brain networks. (*a*) Illustration of indegree and outdegree measures derived from CCEP mapping. (*b*) Weighted and binary connectivity matrices for one patient. Each row represents the strength of the CCEP at each electrode following the stimulation of one set of electrodes. Black regions in the binary matrix represent significant CCEPs. (*c*) Measures of network centrality and information flow expressed as *z*-scores and plotted on the cortical surface of one patient. Note the high outdegree, centrality and netflow in sensorimotor cortex with high indegree in the temporal lobe. Adapted with permission from [95].

(c) Reciprocity

The overall extent to which connections are reciprocal suggests whether information flows in a more linear, unidirectional fashion or by bidirectional means. One might hypothesize that specific reciprocal connections are sites of important functional interaction, which may be reflected in stronger functional connectivity (i.e. dynamical correlation) between regions. Furthermore, human brain networks exhibit *small world* properties, defined by abundant local connections and sparse long-range connections [99,100]. These small world networks reflect the opposing demands from local and global processing by minimizing the number of pathways between any two regions [100,101]. Reciprocity for each cortical region can be calculated as the probability that stimulation of site B will elicit a significant response at A when stimulation of site A elicits a significant response at site B. Our analyses quantifying reciprocity across all regions sampled suggest that reciprocity across all networks evaluated is low (approx. 30% for short-range connections and approx. 10% for long-range connections) and the proportion of reciprocal connections in the brain decreases as separation distance increases. By comparing our data against a null model, we determined that the level of reciprocity in experimental data was higher than expected for short-range connections but no different than chance for long-range connections [95].

These results are consistent with the notion of small worldness, with tight interconnected local networks and sparse long-range pathways observed in networks derived from CCEPs. Previous studies reporting higher functional reciprocity (25–50%) [50,63] examined the degree of reciprocal CCEP connections within a single sensory or functional system; thus, it is expected that reciprocity would decrease when examining connectivity across distributed networks. Examination of structural connectivity in the visual system exhibits a similar proportion of reciprocal connections as observed with CCEP mapping [6]. Taken together, these findings suggest that nodes within a network may be reciprocal, but that networks as a whole may not be. Although clear evidence exists for non-reciprocal links in the connectome of non-human primates [102,103], evidence in humans is more scarce. The demonstration that evoked effective connections in the human brain are largely non-reciprocal strengthens the notion that the human connectome is substantially a directed network.

(d) Influence of reciprocal cortico-cortical interactions on functional connectivity

Previous reports demonstrate a spatial correspondence between effective connectivity (measured by CCEP mapping) and functional connectivity (measured by resting fMRI) [52,90]. Recently, we examined the relationship between *reciprocity* of CCEPs connections and the strength of functional connectivity measured with ECoG in the resting state. Here, functional connectivity was quantified by the temporal correlation of low-frequency (0.1–1 Hz) fluctuations of power within the high gamma (70–150 Hz) band, which, in turn, is thought to reflect aggregate spiking activity [104–106]. Regions exhibiting bidirectional CCEPs exhibited 40% stronger resting functional connectivity than those exhibiting unidirectional or no significant CCEP [95]. These data support the notion that the degree of reciprocal cortico-cortical connections predicts underlying functional connectivity.

6. Limitations of cortico-cortical evoked potential mapping

CCEP mapping represents a powerful tool to measure both directionality and causality in cortical networks in the awake human brain. However, several limitations hinder its potential mainstream use in intracranial recordings. First, injecting a large current across a pair of electrodes produces a stimulation artefact that lasts 5–10 ms and can mask potential mono- or disynaptic connections, which would provide important significant insight into brain connectivity. Methods are currently underway to remove the stimulation artefact (via simple subtraction or modelling amplifier ringing) in order to unmask neural processes that may exist during these time periods [107,108]. Lower amplitude, continuous stimulation may provide an alternative means to study effective connectivity by

examining stimulation that is less likely to produce an artefact and be more in line with natural physiological phenomena. Second, the nature of the CCEP is quite complex and the cellular and circuit-level mechanisms generating the evoked potential at each time frame (N1 and N2) are not yet fully characterized. A better understanding of the relationship between the orientation of the cortical column under the surface electrode and the latency, polarity and strength of evoked potentials would be valuable.

Another important caveat to CCEP mapping is the unknown degree to which CCEPs reflect the strength and number of orthodromically propagating action potentials. Cortical responses to distant stimulation are not likely to be due to volume conduction because of the variability in timing and strength of response at regions equidistant from the stimulation site. However, as addressed previously, it is not well known if CCEPs result from (i) excitation of pyramidal cells propagating orthodromically to the recording site or from (ii) orthodromic or antidromic activation of axons underlying the stimulation site. Additionally, the variability of stimulation parameters during CCEP mapping hinders the ability to critically evaluate work across study centres. Specifically, parameters that are not consistent include electrode type (SEEG versus subdural), electrode stimulation configuration (monopolar and bipolar), current amplitude (from 1 to 10 mA), pulse duration (100–500 µs), interstimulation interval (0.5–10 s) and number of stimulation repetitions (10–50). Furthermore, the patient's cognitive state during CCEP mapping is difficult to control. Indeed, we have observed that CCEP amplitude can be modulated by antiepileptic medication, anaesthesia and sleep. Other parameters essential to the interpretation of CCEP results include the relationship of components of the CCEP to cortical orientation, architecture and signal processing.

Finally, a common criticism of this work is the generalization of findings from patients with intractable epilepsy to normal brain networks and cognitive function. Although a valid and significant concern, several reasons argue for the generalization of findings in these patients. First, this patient population is typically highly heterogeneous with respect to age, gender, seizure onset and disease aetiology. Therefore, consistent electrophysiological results across subjects suggest that the patient's disease and subject-to-subject variability inherent in invasive ECoG is not likely to have a significant effect on these findings. Second, electrodes involved in seizure generation and spread are removed prior to all analysis so that the results are based on findings from 'non-pathological' brain regions. Consistent results across patients suggest that findings are not likely to be due to the pathophysiology of the patient's disease and that results may be applied to the general population.

7. The future of cortico-cortical evoked potentials and network mapping

(a) Task-related reorganization of large-scale networks through cortico-cortical evoked potential mapping: a novel method to probe complex brain networks

Modulating neural activity with electrical stimulation during cognitive tasks provides a means to investigate the causal role of specific brain regions in cognitive processes underlying behaviour. To date, studies have examined either the behavioural or electrophysiological consequences of electrical stimulation of intracranial electrodes in the cerebral cortex. There is a rich history of this [35,109], and more recent observations include: (i) high-frequency stimulation of the entorhinal cortex improving spatial memory [27], (ii) experiential phenomena occuring only when electrical stimulation of visual cortex is associated with activity in the temporo-parietal junction [26], (iii) electrical stimulation of the anterior cingulate cortex eliciting the will to persevere [44] and (iv) stimulation to the right inferior frontal cortex inducing more slowing when motor braking was required in a go-no-go task [28,42]. Other studies examined the electrophysiological effects of electrical stimulation during rest, thus without assessing behaviour [52].

The consequences of stimulation can be examined from an electrophysiological standpoint, and ECoG allows us to measure both single site and network-level changes. Specifically, the amplitude and latency of CCEPs can be quantified at each site with and without the presentation of sensory stimuli. In the example shown in figure 5*a*, single current pulses were delivered to the fusiform face area (FFA, which responds selectively to faces [110]) together with the presentation of a face image. A strong decrease in CCEP amplitude was observed during the N2 but not the N1 time period. This finding suggests that the N2 component of the CCEP may be more sensitive to high-level cognitive processes compared with the N1, which may be more automatic. Furthermore, stimulation of the FFA during face presentation resulted in an increased reaction time, whereas stimulation of the adjacent parahippocampal place area (PPA, which is selective for visual scenes rather than faces or objects [111]) during the presentation of face images did not change the CCEP amplitude or reaction time (figure 5*b*).

At a network level, graph theory applied to CCEP mapping allows the quantification of brain network topology during different cognitive conditions. To characterize these network changes, the CCEP response, similar to that in figure 5*a*, is computed for all cortical regions sampled. While graph theory measures are not necessary to analyse the CCEP response at one region or small subnetworks, large-scale network analysis (more than 100 electrodes) would require graph theoretic metrics to quantify network changes. For example, network topology (indegree, outdegree, centrality and net flow) can be quantified at rest, during sensory stimuli and during electrical stimulation of specific subnetworks. Comparing the large-scale network structure of the brain during these conditions can yield important information regarding local and global network reorganization following the activation and disruption of specific cortical regions. In summary, task-based CCEPs are able to quantify the behavioural and electrophysiological effect of specific sensory stimuli on multiple cortical circuits in the awake human brain and represent a complex yet intriguing dimension to CCEP mapping.

(b) Cortico-cortical evoked potentials to study seizure networks

It has become increasingly apparent that epilepsy does not arise from a disturbance in one brain region but rather involves a network of regions [112]. As a result, the use of traditional methods to analyse seizure activity is now complemented by techniques that provide a more quantitative view of brain networks. CCEP mapping could contribute to the care of

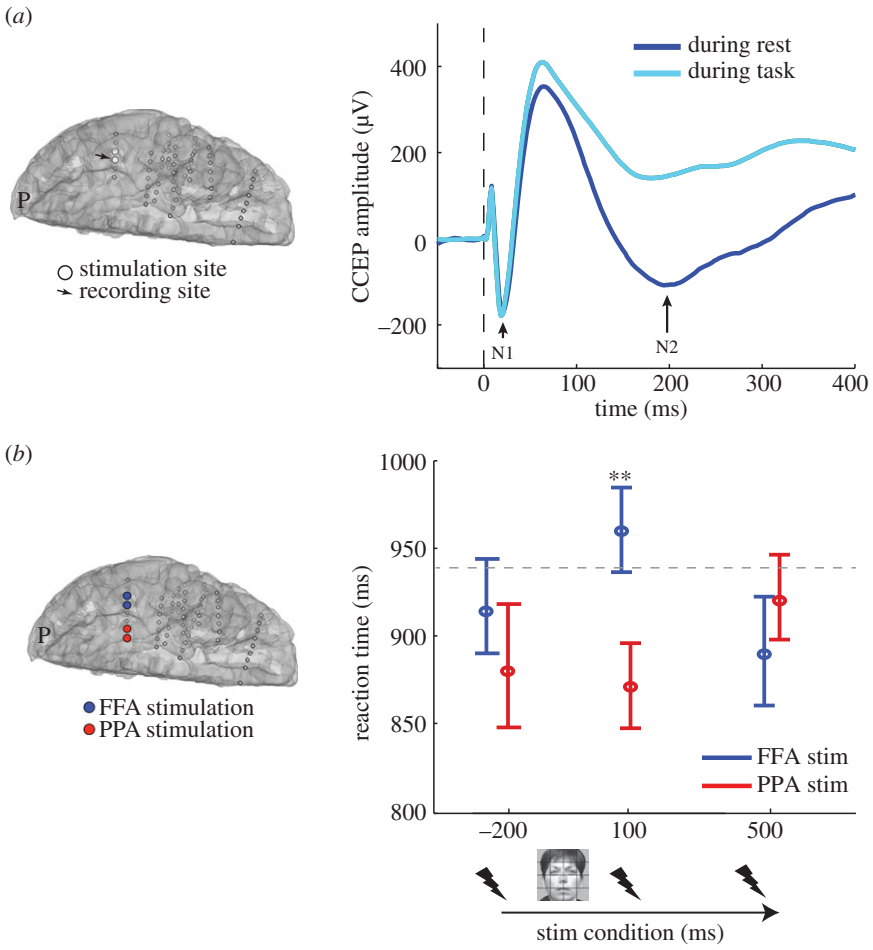

Figure 5. Task-based CCEPs can examine network reorganization during cognitive processing. (*a*) Electrical stimulation is applied to the FFA at baseline (during rest) and 100 ms following the presentation of visual stimuli (during task). Visual stimuli decrease the amplitude of the N2 but not the N1 of the CCEP. (*b*) A face discrimination task was performed while either the FFA or PPA was electrically stimulated. Electrical stimulation was applied 200 ms prior to or 100 or 500 ms following the visual stimuli. Stimulation of the FFA 100 ms after visual stimuli onset increased the reaction time during a face discrimination task when compared with PPA stimulation. Results are from one representative patient.

patients with epilepsy to provide a better resolution of both functional and pathological networks. Understanding the spatial propagation and temporal dynamics of seizure activity can improve the localization of pathological activity and provide insight into the mechanism underlying seizure propagation. Additionally, because seizures occur infrequently, clinicians welcome novel methods such as CCEP mapping to examine pathological activity in the interictal period. Cortical regions involved in seizure initiation are thought to exhibit an abnormal balance between inhibition and excitation [113]. As a result, the latency, strength and directionality of CCEPs may reflect the balance of excitation–inhibition in the source and target sites, potentially localizing regions of epileptic activity. CCEPs elicited in non-pathological regions consist of complex waveforms (N1 and N2) within the first 200 ms. On the other hand, later voltage deflections (200–1000 ms post-stimulation) consisting of 'spikes' or 'sharp waves' appear to localize to seizure-generating regions of the brain [114]. Moreover, a poorer surgical outcome was observed when late afterdischarges (abnormal electrical activity persisting beyond the duration of the electrical stimulation) were observed in tissue that was not resected [114]. In another study involving eight patients with intractable epilepsy, CCEP amplitudes were larger upon stimulation of the seizure onset zone than when control regions were stimulated [115]. However, this relationship was dependent on the type of epilepsy (generalized or focal) and the degree of anatomical continuity between the seizure onset zone and early seizure spread. Supporting these findings, preliminary data from our laboratory suggest that afterdischarges following electrical stimulation, when present, localize to the seizure onset zone (see also [116]). In summary, afterdischarges elicited during CCEP mapping are indicative of pathological brain regions and therefore may provide complementary information regarding the localization of the seizure onset zone.

The aforementioned considerations bear great impact upon the moral ethics regarding informed consent when performing these studies in clinical populations. Typically, patients are told that there is limited risk of producing a seizure or discomfort secondary to dural stimulation. Our experience has been that less than 1% of sites stimulated under CCEP protocols result in any experiential phenomena and that in no case has CCEP stimulation of a grid or strip electrode resulted in a seizure. Patients are also typically told that the benefits of participating in this type of research are limited to contributing to the understanding of brain function for society as a whole. However, in our experience of over 50 patients undergoing CCEP mapping, we have seen more direct benefits afforded to the patient by: (i) increased vigilance and error checking from the research team that communicates with the clinical team; (ii) improved localization and identification of implanted electrodes with

respect to individual cortical and functional anatomy; and (iii) using the rare circumstance of discomfort or phenomenology during CCEP mapping to tailor the clinically indicated higher frequency mapping protocols to avoid sites of discomfort and attend to sites where either afterdischarges or phenomenology is elicited. The possibility for CCEP mapping to define functional and epileptogenic zones adds one more potential benefit to patients to outweigh the minimal risks of participating within these research protocols.

(c) Towards an effective connectome database

CCEP mapping is limited by the relatively low number of centres performing this technique routinely and the relatively few patient studies performed at each individual centre. This limitation supports a call for the development of a cross-centre database—an *effective connectome*—similar to those implemented with non-directed functional and structural connectivity techniques [117]. As described in the preceding section, CCEP mapping may provide clinical benefit.

This multicentre database would require a joint effort by groups to choose a set of stimulation parameters optimal for CCEP mapping in order to include patients across centres within the same study. Additionally, seizure-generating regions in each patient can be compared to similar anatomical but non-seizure-generating regions in a large population to serve as a control. Finally, CCEP databases based on the grids and strips approach [50,52,60,61,63,66] can supplement those based on the SEEG approach [67,118], and both can be compared to other effective connectivity measures including microstimulation and TMS.

8. Conclusion

In summary, CCEP mapping represents a feasible technique requiring little additional supplementation to standard invasive electrode implantation protocols. This would provide greater detail as to the organization of cortical networks with excellent spatial and temporal resolution. In this review, we addressed three central questions to further the development and understanding of brain networks and connectivity. In examining the neural basis underlying generation of the CCEP, evidence suggests that the N1 component of the CCEP represents early excitation of pyramidal cells at the remote site, whereas the N2 represents a long-lasting net inhibition. Regarding the comparison of CCEP mapping to established structural and functional connectivity techniques, we conclude that the N1 of the CCEP at least partially reflects the structural connectivity strength between regions, whereas the N2 may be influenced by factors such as brain state and cognitive demands. Finally, we present data regarding the influence of the reciprocity of connections on functional connectivity and outline a method of using task-based CCEPs to modulate brain networks during specific cognitive processes. This underused tool in basic and clinical neuroscience represents a powerful method to provide insight into non-invasive measures and investigates the causal involvement of brain regions during cortical information processing.

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