How can laminar microelectrodes contribute to human neurophysiology?

Mila Halgren

Abstract Human laminar microelectrodes (linear arrays implanted acutely or semi-chronically in surgical patients) present an exciting new frontier of intracranial electrophysiology. Though most iEEG is limited to imaging networks, laminars can resolve the cortical microcircuits underlying cognition. Normally implanted in animal models, laminar probes can record the current-source-density, which reflects transmembrane currents, as well as single and multi-unit activity (MUA) throughout the cortical depth. These measures of neural activity allow the mapping of laminar physiology underlying diverse neural phenomena in humans. For instance, several studies have shown laminar activity sensitive to language and perception. They've also discovered motifs of different rhythms during sleep (slow waves, spindles) and wakefulness (delta/theta, alpha). Intriguingly, these studies suggest an outsize role for superficial layers in cortical oscillations which may be human specific. Human laminar recordings have also shed light on cortical physiology in general, such as the spatiotemporal dissociation of high-gamma-power (HGP) and MUA. In disease, laminars have elucidated the structure of epileptiform discharges. However, key conceptual and methodological issues like proper referencing, clinical constraints and comparisons with animal models remain. These difficulties notwithstanding, new innovations in recording density, simultaneous surface-laminar recordings and extracranial source-inference will enable laminars to answer fundamental questions in human neurophysiology.

1 Introduction

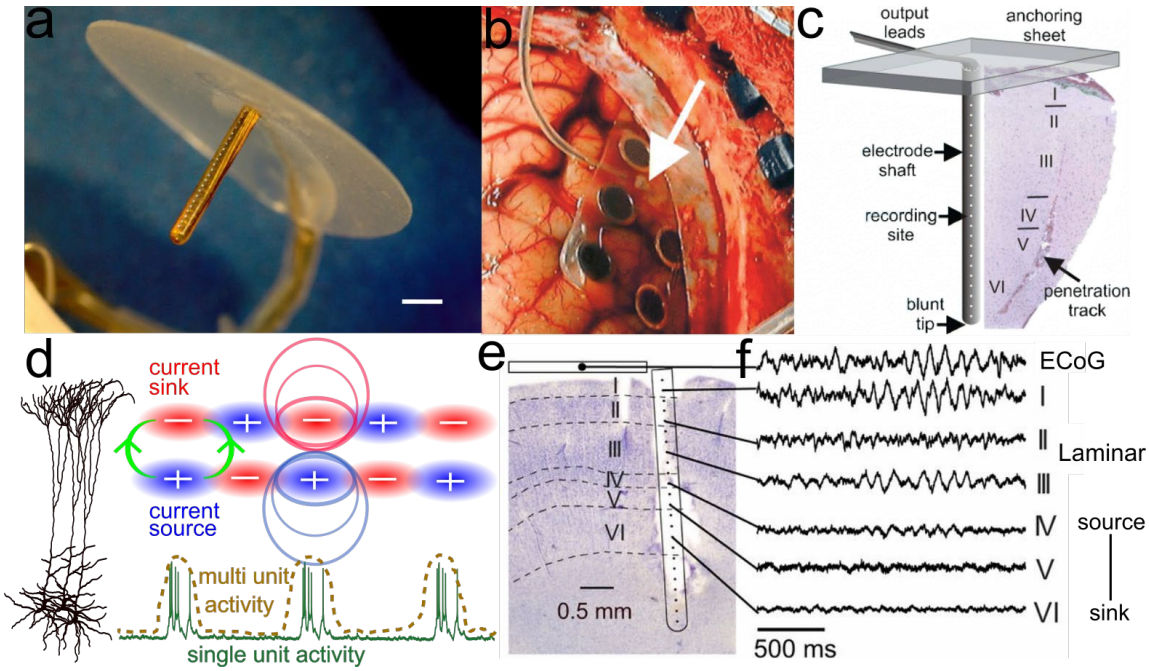

Fig. 1 a) Photomicrograph of a laminar array with anchoring silicone sheet, provided by László Papp of Neuronelektrod Ltd., Budapest, Hungary (scale bar: 1 mm). b) picture of ECoG with simultaneously implanted laminar array (arrow). c) schematic of implanted laminar array, with co-histology from the implantation in b. b and c reproduced with permission from [97] d) schematic of the two principal forms of data measured with a laminar probe: the CSD (reflecting transmembrane currents) and single/multi-unit activity. e) co-histology of laminar track. f) representative traces of CSD recorded from the probe, in addition to overlying ECoG. e and f reproduced with permission from [61].

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As reviewed in other chapters, intracranial human electrophysiology (iEEG) has provided vital insights into human cognition. The exquisite spatiotemporal precision of these recordings allows for the direct study of human cortex. However, a limitation of typical iEEG is the lack of layer specific recordings. Neocortex is characterized by its layered structure, composed of six laminae with distinct cell types, connectivity and physiology. This architecture is highly consistent across cortical areas, leading to the hypothesis that there is a canonical laminar microcircuit [1, 2].

Though laminar physiology has been fruitfully studied in rodents and non-human-primates, humans have considerably different cortical architecture. For instance, human cortex has novel neurons and glia not found in rodents [3–5]. Even homologous cells have strikingly different electrophysiological and transcriptomic properties across species [4, 6–11]. For example, layer V pyramidal cells are 7x more likely to be bursty in mice than humans *in vitro* [6]. On the network level, human cortex is much more recurrent than rodent cortex [12–15]. These interspecies differences are particularly pronounced in supragranular layers, which disproportionately expanded in humans [16, 17], are more cellularly heterogeneous than in rodents [5], and may be critical for human specific cognitive abilities [18–20]. Therefore, the use of animal models for laminar physiology must be validated directly in humans. This is made possible by human laminar microelectrodes, or linear arrays which span the cortical depth perpendicularly.

The only laminar arrays used in humans (save Neuropixels) were designed & developed by Mr. László Papp, Prof. György Karmos, Prof. Eric Halgren, Prof. István Ulbert and Neuronelektród Ltd. in the late 1990s [21], and are manufactured with platinum-iridium for increased biocompatibility (especially in potentially irritable epileptogenic cortex). Harboring 24 contacts with 150μm spacing, they are long enough to span the cortical depth while sampling each cortical layer with multiple channels (Fig. 1a-c). This fine spatial sampling enables the collection of action potentials (AP) as well as their proxies, multi-unit-activity (MUA) and high-gamma-power (HGP). Additionally, transmembrane currents due to synaptic activity and active channels can be estimated by the current-source-density (CSD) within individual laminae (Fig. 1d). The CSD measures current sinks and sources, reflecting net transmembrane current flow in and out of neurons (respectively). Pairs of sinks and sources, or current dipoles, generate the electrical and magnetic signals measured with iEEG, EEG and MEG (see section 3.1). Though diverse cells such as glia and interneurons contribute to transmembrane current flow, the cortical CSD is likely dominated by pyramidal cells due to their numerosity, laminar orientation and large dipole moments [22]. Being able to derive the CSD is a critical advantage of laminar recordings, as the closely related monopolar (distantly referenced) local field potential (LFP) and its first derivative, the local field potential gradient (LFPg) are contaminated by distant sources via volume-conduction (see section 3.1).

These platinum-iridium laminars come in surface and depth varieties. The former anchor to the cortical surface via a thin silicone sheet which sits on the pia (Fig. 1a). This holds the probe in place and keeps it normal to the cortical surface / perpendicular to cortical layers. Conversely, depth laminars protrude from the end of macroelectrode stereo-EEG probes and allow recordings from medial areas such as the hippocampus and cingulate. Recordings can be made acutely (within the operating room, ~1 hour) and/or semi-chronically (within the epilepsy-monitoring-unit, ~1 week). In the semi-chronic case, investigators can record multiple tasks and behavioral states (wakefulness, sleep, anesthesia) from the same patient, yielding large amounts of data from a single implantation. Though previous experiments have used only platinum-iridium laminars, two groups recently recorded with Neuropixels [23, 24]. Neuropixels can record from 384 channels with 20 μm spacing simultaneously, a drastic advance on platinum-iridium probes [25]. Though human laminar recordings are in their infancy, with only 27 papers which analyze this data, numerous insights into cortical physiology have been made. Previous findings from human

laminar recordings are briefly reviewed, before discussing methodological challenges and future directions.

2 Insights

2.1 Oscillations

Oscillations, or rhythmic fluctuations in neural activity, dominate human cortex and are critical for cognition and behavior [26, 27]. Despite a long tradition of study with extracranial EEG and MEG, little is known of the basic physiology underlying these oscillations. Though many seminal studies have been made in animals or *in vitro*, it is unknown how these translate to *in vivo* human cortex.

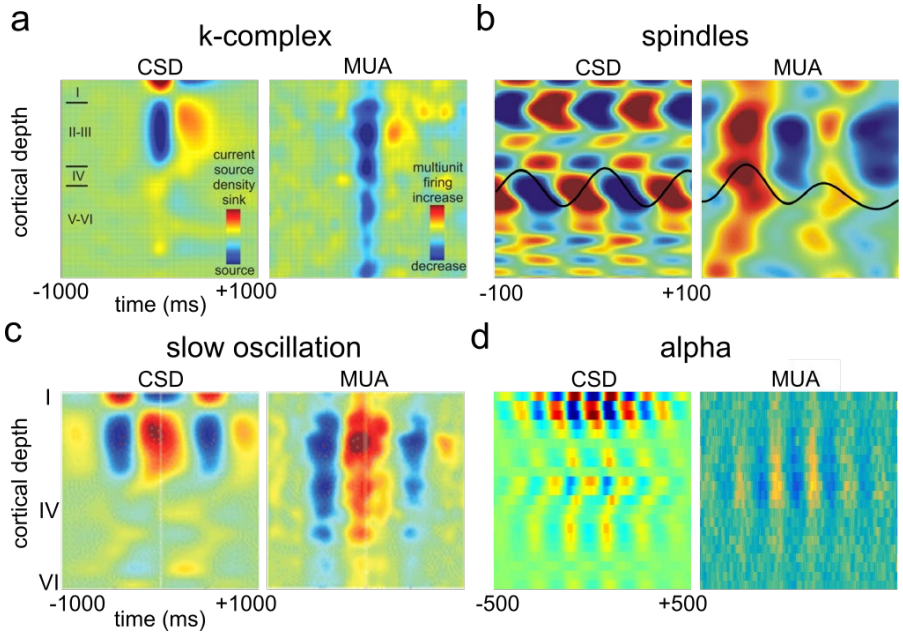

Fig. 2 a) The laminar profile of k-complexes, with the averaged CSD on left and averaged MUA right. b-d) same as a), but for spindles, slow waves and alpha. a, b, c and d are reproduced with permission from [35, 36, 42, 61], respectively.

The key questions human laminar recordings can resolve, over and above macroelectrode iEEG, are: 1. Which laminae do the transmembrane currents which generate these rhythms stem from? 2. Which layers have cell bodies which fire phasically with these rhythms? And 3, how might this laminar profile in humans differ from animal models? Question 1 can be answered by measuring the power of a given oscillation's CSD across the cortical depth; 2 by measuring the synchrony of this oscillation with a simultaneous metric of unit activity; and 3, by recording in areas and behavioral states comparable to an animal model. Most studies have found that low frequency rhythms in humans are dominated by *currents and firing in superficial laminae*; whether this generalizes to other animals is unclear.

2.2 Sleep rhythms

Slow waves & K-complexes (.5-2 Hz) are the largest graphoelements in the human EEG, and coordinate memory consolidation [28] and metabolic maintenance [29]. In rodents, the slow oscillation primarily reflects sinks and sources in deep cortical layers driven by layer V pyramidal cells [30–34]. Surprisingly, Cash et al. found that human K-complexes reflect layer I/II sinks and sources which primarily modulate supragranular firing (Fig 2a) [35]. Human slow waves have a highly similar laminar profile to K-complexes, comprised mostly by layer I/II currents and supragranular firing (Fig 2c) [36].

Spindles, like slow waves, are oscillations critical for learning and memory [37–40]. Two studies on their laminar profile in humans [41, 42] found that spindles were dominated by currents and firing in superficial and middle layers, the latter reporting that superficial currents were stronger (Fig 2b).

Controversy remains over whether these spindles can be separated into hypothesized “matrix” and “core” types, respectively driven by focal or non-specific thalamic input [43].

2.3 Wake rhythms

Delta and theta oscillations are found throughout human cortex [44], and play a crucial role in memory and cognition [45]. Two reports found that delta/theta rhythms were particularly pronounced in superficial cortex throughout a wide variety (19 in the former) of cortical association areas [46, 47]. These rhythms were phase-reset by oddball stimuli, and likely contribute to the novelty-induced P300 and N400 (see section 2.4). An important caveat is that slow delta is sometimes caused by drowsiness or epileptic pathology [48], and does not necessarily reflect healthy or alert cortical activity.

Alpha oscillations (7 to 13 Hz) [26] dominate the waking EEG, and are linked to attention [49], perception [50, 51] and functional inhibition [52]. Within cortex, *in vitro* recordings and animal models suggest that alpha originates from infragranular layers driven by layer V pyramidal cells [53–58] (but see [59, 60]). In contrast, human alpha-band currents are strongest in very superficial (~ I/II) laminae and primarily modulate layer III firing (Fig 2d) [61]. Therefore, the human alpha rhythm likely reflects currents on the apical dendrites of layer III pyramidal cells (see section 3.1). Further experiments should determine if this is a general laminar motif, or if alpha modulates supragranular cells in some cortical regions and infragranular cells in others [60].

In sum, human laminar studies have converged on superficial layers as a primary locus for cortical oscillations. In contrast, animal literature on low-frequency oscillations has emphasized the role of deep layers [30, 53, 57, 58, 62]. A possible explanation is that oscillatory networks shifted from infragranular to supragranular cortex between rodents and primates. This may be due to the enlargement of supragranular layers in humans, occupying ~60% of the cortical depth vs. ~40% in rodents [16]. Human supragranular cells are also more recurrently connected [15] and have stronger h-currents than rodents [11], both of which are critical for rhythmicity. Interestingly,human supragranular pyramidal cells are more transcriptomally and electrophysiologically diverse than in mice, suggesting that laminar changes in gene expression and physiology may account for supragranular rhythms in humans [5]. A critical caveat: even if the currents and firing related to low-frequency oscillations are supragranular, a sparse infragranular population may be causally necessary to generate the rhythm [30]; therefore, stating a rhythm is “generated” in superficial layers simply means that current dipole measured extracranially and the cells which fire phasically with the rhythm are supragranular, not that superficial layers alone are causally sufficient to drive an oscillation.

2.4 Cortical Physiology

Besides oscillatory dynamics, human laminar recordings have yielded insights into cortical physiology. These include the laminar structure of event-related potentials (ERPs) and the differential origins of HGP and MUA.

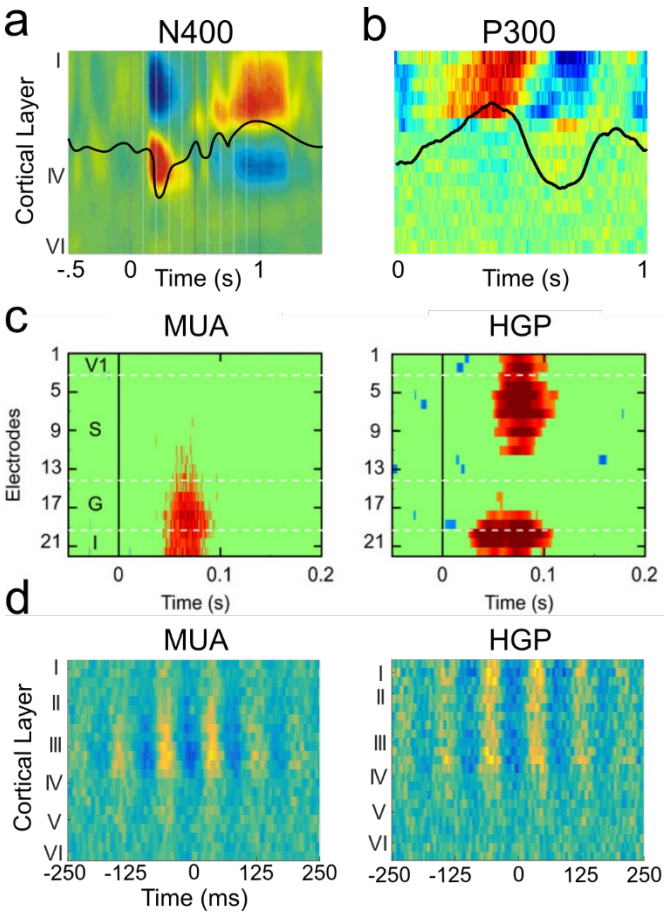

Fig. 3 a) CSD profile of the N400, reproduced with permission from [67]. b) LFPg profile of the P300, reproduced with permission from [46]. c) MUA and HGP in macaque V1 evoked by flashes. Note that MUA is strictly in deep cortex, whereas HGP is evoked in superficial and deep laminae. d) MUA and HGP locked to ongoing alpha in human parietal cortex; MUA is modulated within deep layer III, whereas HGP extends throughout supragranular cortex.

The N400 (scalp-negative, ~400 ms post stimulus) is an ERP elicited by semantically meaningful (particularly anomalous) stimuli [63]. Hypothesized to underly lexico-semantic integration [64] and/or predictive processing [65], it has long been used to probe language and semantic cognition. Despite this, little is known of its underlying physiology as it cannot be studied in (non-linguistic) animal models. Therefore, Halgren et al. made laminar recordings in the anteroventral temporal lobe, a known N400 generator [66], during a semantic priming task [67]. Word presentation induced a prominent excitatory current sink in layer IV & passive return source in layers II/III, with a prominent peak ~400 ms post stimulus (Fig. 3a). This sink was longest in response to semantically anomalous words, much like the scalp N400. Because layer IV receives feedforward input, this suggests that the N400 reflects first-pass lexico-semantic encoding of words within the cortical language network. A further study found that, rather than reflecting a novel potential per-se, the laminar N400 arises from the phase-reset of ongoing theta rhythms [47]. A study in cingulate and temporal areas of the closely related P300 (evoked by anomalous stimuli regardless of semantic content) found it was dominated by superficial currents due to a phase-reset of ongoing slow rhythms (in this case delta) [46] (Fig. 3b), suggesting a similar circuit for processing stimulus deviance via the phase-reset of pre-stimulus oscillations. These results suggest that human theta might have a somewhat deeper (involving layer IV) and distinct laminar distribution than cortical delta; this should be addressed in future experiments.

A further contribution of human laminars is differentiating the origins of MUA (~300-3000 Hz) and HGP (~70-190 Hz). Though HGP is lower frequency than traditional MUA, it's strongly correlated with single-unit firing [68–70] and is therefore the standard proxy for unit activity in macroelectrode iEEG [71]. To determine possible physiological differences in unit firing and HGP, Leszczyński et al. measured HGP and MUA simultaneously in macaque and human laminar recordings [72]. Surprisingly, they found that HGP and MUA had distinct laminar origins; while MUA was driven by middle/deep layers, HGP was found within both middle/deep and superficial layers (Fig. 3c). Intriguingly, this superficial HGP could occur without concurrent deep MUA. A parallel finding was observed in a human laminar study of HGP and MUA modulation by the alpha rhythm [61]. Though HGP was modulated by alpha throughout superficial layers (~layers I-III), MUA was only modulated within layer III (Fig. 3d). MUA stemming from deeper layers than HGP, as well as being dissociable from it, is consistent with HGP reflecting

(superficial) dendritic processes such as calcium spikes dissociable from (deeper) somatic firing. Further evidence to this effect is that the NMDA antagonist phencyclidine attenuated HGP without affecting MUA [72]. Relating discrete calcium spikes (in principle recordable extracellularly [73]) to ongoing HGP, and quenching both via pharmacological manipulation, would provide further evidence that HGP reflects dendritic calcium spikes rather than unit firing *per se*.**3 Challenges**

3.1 Referencing

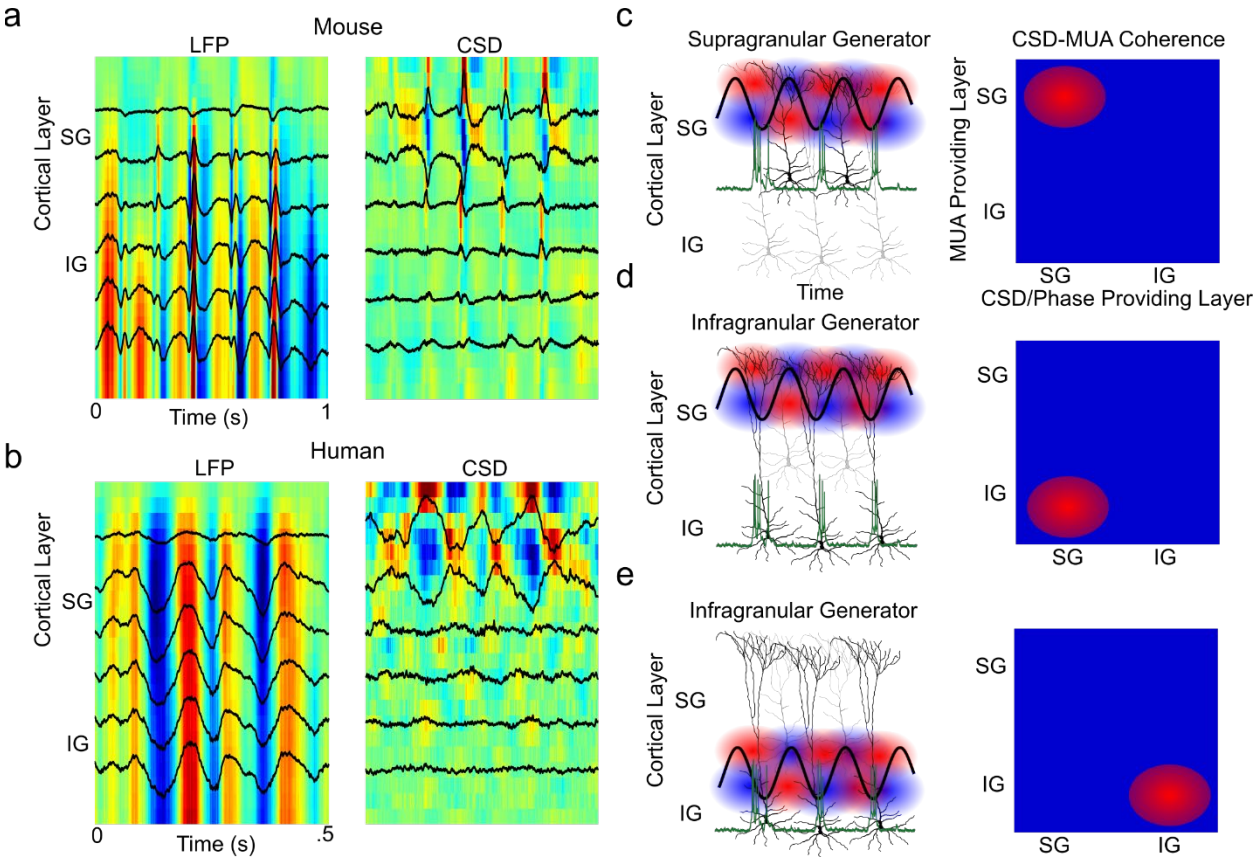

Fig. 4 a) LFP and CSD derivations of the same activity from a mouse laminar recording [114]. b) LFP and CSD from a human laminar recording. In a-b, supragranular currents volume conduct to deeper layers. c) Example of a rhythm generated by supragranular pyramidal cells. This can be represented in the CSD-MUA coherence plot on the right, which shows that supragranular currents are synchronous with supragranular firing. d) Same as c, but for a rhythm generated by supragranular currents onto the apical dendrites of infragranular pyramidal cells. Supragranular currents are now synchronous with infragranular spiking. e) as c and d, but for currents and firing in infragranular layers.

How do we interpret the field potentials recorded by laminar arrays? Electric potentials in cortex are primarily generated by transmembrane currents. These currents arise from synaptic activity and voltage-dependent active channels such as calcium spikes, h and t currents, etc. [22]. Maxwell's equations necessitate that the sum of potential differences in a volume is zero [74]; therefore, these currents form balanced current dipoles of sinks (into cells) and sources (out of cells). Due to cortex's laminar architecture, these dipoles are arranged vertically (Fig. 1d). Therefore, cortical field potentials are due to vertically arranged transmembrane current dipoles generated by synaptic and active channels. It can be shown that given some assumptions such as radially symmetric currents and isotropic & homogeneous tissue conductance, the second spatial derivative of the field potential vertically (i.e. along a laminar

probe) yields the net transmembrane current at a channel [75, 76], also called the current-source-density (CSD).

Consequently, monopolar (distantly referenced) LFPs do not themselves reflect underlying transmembrane currents, but instead the summed fields generated by dipoles volume conducted throughout surrounding tissue. This means that laminar LFPs are not a faithful proxy for local currents. Indeed, the strong influence of volume conduction make the distantly-referenced field potential misleading to analyze. Firstly, this is because potentials evoked by distant cortical or subcortical areas can lead to large field potentials in the absence of local activity [77–79]. Secondly, even within an area, potentials will volume conduct across cortical layers. Alarmingly, infragranular LFPs are often susceptible to volume conduction from supragranular sources [80] (Fig. 4a-b). A common objection to the use of local (bipolar, CSD) referencing is that they can artificially silence synchronous, shared activity between electrodes (see Chapters 25 and 27). However, this is emphatically not the case for laminar recordings. This is because these electrodes lie within, not outside of, the cortex (unlike ECoG or scalp EEG). If a current dipole lies between a series of contacts, field potentials will exhibit changes in amplitude which (when the second derivative is taken) yield a dipole. If the monopolar field potential amplitude does not change, or changes linearly between contacts, the signal must be due to volume-conduction from a dipole in a different cortical layer and/or area. Concerningly, these volume-conducted potentials are often orders of magnitude larger than those produced by local currents [77]. As such, volume conduction can lead to high amplitude, coherent potentials at locations without any local synaptic activity. Therefore, the finding of a perfectly synchronous monopolar potential across some contacts implies that its generator does not lie between these contacts (as the second derivative, or CSD, of a constant is zero). This makes the analysis of monopolar field potentials very difficult to interpret.

The importance of proper referencing is illustrated in the controversy surrounding the cortical alpha rhythm. Several primate laminar studies have emphasized infragranular layers, primarily due to high alpha power in the monopolar field potential in deep cortex [53, 56, 58]. However, laminar studies in humans and macaques which used local referencing found greater alpha power in superficial layers [59, 61]. This is most consistent with a supragranular alpha source which volume conducts to deep layers; because contacts in superficial layers lie within the generating dipole, the monopolar field potential is silent.

Volume conduction makes the use of local referencing, such as CSD, necessary to localize transmembrane currents to specific cortical layers. However, there are several challenges to accurate CSD estimation; firstly, because the second spatial derivative is ill-defined at the edge of an array, the top and bottom channels must be discarded. This can be ameliorated by the Vaknin Correction, which takes the edge monopolar channels (i.e. most superficial and deep), and then pads the referential recording with these signals before computing the CSD [81]. This is justified by the minimal decay of the monopolar field potential above and below the array. A more serious concern is the magnification of spatial noise by the second derivative; small deviations in amplitude across channels, due to differing impedances, spacing, noise, etc. will be exaggerated by CSD. Solutions for this include spatial (Gaussian) smoothing prior to CSD calculation, or kernel-CSD methods [82]. Alternatively, the local-field-potential-gradient (LFPg), or first derivative of the monopolar LFP, can be used instead. This measure has similar spatial localization to CSD by attenuating volume conduction [59], but is less interpretable than the CSD (as it represents the integral of local sinks and sources, not transmembrane currents *per se*). Lastly, a critical assumption of CSD analysis is that electrodes are situated normal to the cortical surface [75]. This can be difficult to ensure, particularly with poor control of implantation in a clinical environment, and with a

lack of co-histology. One solution is to anchor the probe to a silicone sheet which adheres to the cortical surface (Fig. 1a-b).

How do we interpret the relationship of cortical firing (as measured by MUA or single units) and the local transmembrane currents yielded by the CSD? Critically, the CSD indicates which layer a given current lies in, but not the layer of the somas being excited or inhibited by these currents. Because of the rapid spatial decay of the fields generated by action potentials, unit activity is usually only observable near the soma [22]. Therefore, by measuring the synchrony or coherence of currents and unit firing, one can infer the likely layers of both the dendrites and the somas involved in a graphoelement (Fig. 4c-e). For example, the fact that human alpha-band currents are in layers I/II does not (in itself) indicate that alpha-modulated cells reside in superficial layers. These currents could be onto the apical dendrites of either layer II/III or layer V/VI pyramidal cells. The only way of distinguishing these possibilities is to record unit activity simultaneously, which presumably reflects somatic spiking, and measure the coherence between this somatic firing and (usually dendritic) currents (Fig. 4c-e). For alpha oscillations in human association cortex, this CSD-MUA coherence was highest between layer I/II CSD and layer III MUA, suggesting a supragranular pyramidal source for alpha.

How do we determine if a CSD sink/source is excitatory or inhibitory? Though it may seem, trivially, that inward currents are excitatory and outward currents reflect inhibition, this is not necessarily the case. Because current must be conserved within a volume, every excitatory ("active") current sink must be balanced by a return ("passive") current source, and vice-versa. Therefore, current sinks may reflect active excitation or passive return from inhibitory current, and current sources may reflect active inhibition or the passive return from an excitatory sink. We can determine if a current sink/source is excitatory/inhibitory by seeing if it coincides with increased or decreased firing. If a current sink co-occurs with increased firing, it likely represents an active excitatory current, with its paired source reflecting passive return currents to extracellular space. Conversely, a current source accompanied by decreased firing indicates an active inhibitory current, with a paired passive current sink. Because currents can always be active or passive, unit activity must be recorded simultaneously with CSD to infer whether a sink or source is active (excitatory or inhibitory), or merely a passive return current. For example, in recordings of human alpha oscillations, current sinks/sources in layer I were matched to increased/decreased firing (respectively), with matched return currents in layer II/III (Fig. 2d). This indicates that layer I sinks/sources are "active" (reflecting excitation/inhibition) and layer II/III sinks/sources are passive return currents. However, because all extracellular CSD signals represent an unknown mixture of cells, definitive evidence for these excitatory & inhibitory circuits must come from single-cell electrophysiology.

3.2 Recording conditions

As discussed (section 2.3), human laminar recordings have strong currents in layers I-III not found in animal studies [35, 36, 46, 61]. This might indicate a critical interspecies distinction in LFP generation due to differences in cortical physiology. Human pyramidal cells have extremely elaborate layer I/II arborization not paralleled in other species [83, 84], as well as other anatomical specializations not seen in rodents (see sections 1, 2.3). However, the risk remains that these currents are illusory due to poor CSD estimation at the edge of the laminar array. Fine sampling of the gray matter / CSF boundary, possible with human Neuropixels [23, 24], could resolve whether this is artifactual or a real interspecies difference.

Relatedly, it's usually unclear which cortical layers are recorded by each contact on a laminar probe. In rodents, this is resolved by explanting the tissue surrounding the probe and finding the track caused by the

electrode (often with the assistance of electrolytic lesions and/or dye). However, neither electrolytic lesions nor probe dyeing are approved for use in human surgical cases. Some reports have performed histology on the explanted tissue, and find the probe track from tissue damage [23, 36, 42, 85]. When co-histology is not available (as is often the case), there are several strategies for assigning contacts to layers. First, layers may be estimated by current-source-density analysis of stimulus-evoked activity. Within sensory & neighboring cortex, stimuli should evoke a feedforward sink in layer IV, allowing the identification of supragranular and infragranular layers. Unfortunately, it's not clear whether this generalizes to human association areas. Alternatively, laminae might be estimated from anatomical measurements of laminar depth in human staining studies (Hutsler et al. 2005). On average, layers I-III occupy the first 60% of the cortical depth, layer IV 6%, and layers V/VI the bottom 33%. In this case, it is important to determine if the laminar probe spans the cortical depth. This can be done by examining MUA and CSD, both of which should sharply attenuate in white matter. In cases where laminar depth cannot be confidently estimated, it's best to restrict conclusions about cortical dynamics to superficial versus deep layers. Though which layer channels in the middle third of the array lie in will be ambiguous, it's highly likely that the top and bottom third of channels will correspond to supragranular and infragranular laminae, respectively.

A last challenge of human laminar recordings is the lower unit yield than comparable rodent studies. This is due to a few factors; first, clinical equipment in the OR and EMU create significant amounts of electrical noise. Though animal studies can reduce noise by changing grounds/references, turning off other electronic devices & using Faraday cages, this troubleshooting is difficult in a clinical environment. A related issue is that (unlike in animals) one cannot make multiple penetrations of cortex until an area with high spike rates is found. A further difficulty is the trauma suffered by cortex upon the insertion of a microelectrode array. Though animal experimentalists can wait for a long period of time post electrode insertion to allow cortex to adapt, within acute OR experiments, time is of the essence and recordings must usually be started immediately. Lastly, as most platinum-iridium human laminars have intercontact separations on the order of ~150um, units cannot be detected across multiple contacts, which makes spike sorting more challenging than for dense microelectrode arrays. Human Neuropixel recordings don't have this drawback due to their high spatial sampling (20 μm), and have isolated up to 202 single units in an acute recording [23, 24]; future human laminars might also improve their yield via similarly dense electrodes. A useful alternative to single-units is MUA, or the envelope of the signal filtered from ~300-3000 Hz. Analyzing MUA sidesteps the difficulties of single-unit isolation to make general conclusions about firing rates in different laminae, instead of the properties of individual cells. HGP may also provide complementary information about firing to MUA; however, as discussed in section 2.4, HGP does not reflect spiking as tightly as MUA (particularly spatially) [61, 72, 86].

4 Promises

4.1 Macroelectrode-Laminar Correspondence

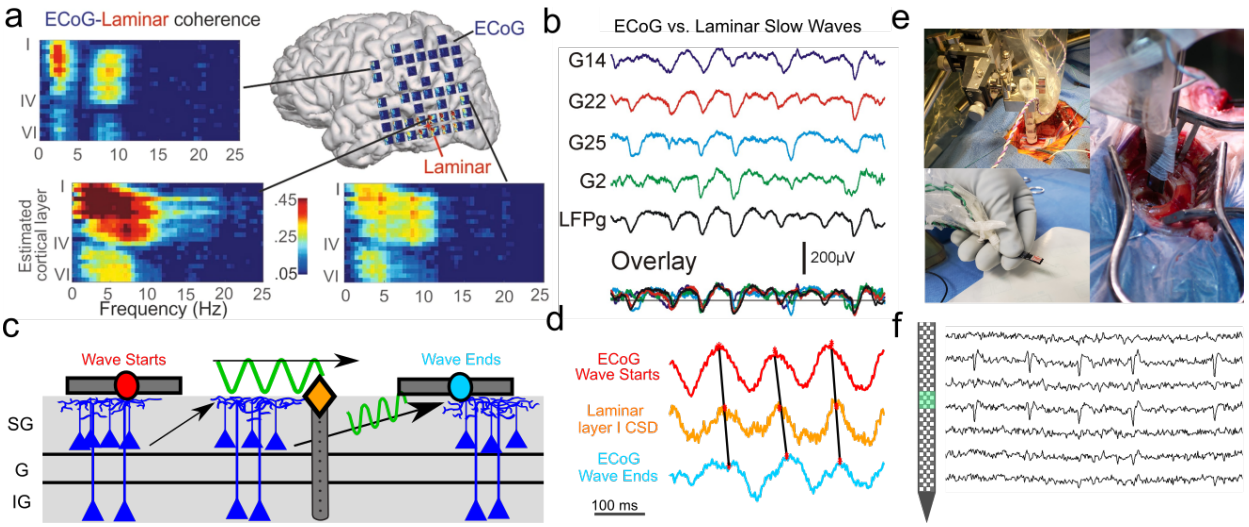

Fig. 5 a) Coherence between individual ECoG contacts and a laminar array during spontaneous wakefulness, as a function of frequency and depth. Reproduced with permission from [46]. b) LFPg from layer II and simultaneous ECoG during SWS in three patients. Reproduced with permission from [36]. c) Simultaneous ECoG and CSD of the alpha rhythm during spontaneous wakefulness. Reproduced with permission from [61]. d) schema of recording travelling waves between two ECoG contacts and a laminar array simultaneously. e) Implantation of a Neuropixel in a human surgical patient. f) action potential traces from a human Neuropixel recording. From Dr. Angelique Paulk, with permission.

Because of the technical and clinical challenges involved in laminar recordings, most iEEG research will continue to rely on macroelectrode recordings such as ECoG. These recordings do not, by themselves, allow for conclusions to be drawn about individual laminae. However, laminar-specific patterns can be inferred from ECoG alone if the correspondence of laminar to ECoG activity is known. This is done by recording events with ECoG and laminar electrodes simultaneously, and then determining how different layers contribute to the ECoG signal. The results of this analysis for a given oscillation or potential can then be used to interpret previous and future ECoG experiments. For instance, Fabo et al. used laminars in temporal cortex and subiculum to study the physiology of inter-ictal discharges (IIDs) and found distinct IIDs corresponding to apical or somatic depolarization [87]. These IIDs were simultaneously recorded with ECoG, allowing future research conducted solely with macroelectrodes to infer the laminar structure of subicular IIDs without a laminar probe.

In general, recent work suggests ECoG primarily reflects supragranular activity. For instance, Ujma et al. recorded sleep spindles simultaneously with ECoG and laminar electrodes. Contrary to the hypothesized split of spindles into “matrix” and “core” types with different laminar profiles, they found that ECoG-recorded spindles consistently co-occurred with laminar spindles with maximal power in superficial layers [42]. Likewise, Halgren et al. found that ECoG recordings were most synchronous with superficial laminae during spontaneous wakefulness and sleep (Fig. 5a). Similar analysis of simultaneous ECoG and laminar recordings of slow-waves and alpha found high correlations between ECoG and superficial (but not deep) contacts [36, 61] (Fig. 5b); the former study found a Pearson correlation of $r > 0.9$ between LFPg recorded in layer II and neighboring ECoG in 5 different patients [36]. HGP recorded by ECoG also reflects superficial layers, as the primary HGP generators are in supragranular cortex [72].

An important factor in the correlation between ECoG and superficial layers is the proximity of superficial laminae to ECoG contacts; a layer I dipole will a field significantly stronger than a layer VI dipole of equal current strength at the cortical surface [88]. However, even ECoG contacts several centimeters away from a laminar probe (for which the distance between superficial and deep layers becomes irrelevant), are coherent with superficial LFPg [46] (Fig. 5a). This may be due to the further finding that,

between two laminar arrays, activity is most synchronous between the superficial contacts of the two probes [46]. The higher amplitude within and synchrony between superficial layers, in addition to their proximity to nearby ECoG contacts, likely explain the correspondence between superficial activity and simultaneous ECoG.

4.2 Laminar structure of travelling waves and propagating IIDs

Oscillations often propagate coherently across the cortical surface. Rhythms which exhibit this wave-like spread are called travelling waves (see Chapter 32). The speed, direction and frequency of these waves are linked to sleep, memory and perception [89–94], and could serve many computational roles [95]. Though their underlying physiology is unknown, propagation speeds and computational modeling point to horizontal fibers within superficial layers as the substrate for these rhythms [96]. ECoG-laminar recordings could allow for the imaging of travelling waves as they "pass through" the laminar array, and reveal which laminae travelling waves propagate "into" and "out of". For instance, if travelling waves generally propagate via intracortical short-range superficial fibers, we should see superficial current sinks coinciding with travelling waves as they propagate through the cortex in which a laminar is implanted (Fig. 5c). This was seen in an ECoG-laminar study of alpha travelling waves, which found that currents in superficial layers had a phase in between that of neighboring ECoG electrodes, suggesting a propagation within superficial laminae [61] (Fig. 5d).

Like cortical rhythms, IIDs also exhibit wave-like propagation through cortex. Ulbert et al. used simultaneous laminar-ECoG to study IIDs which were generated local to the laminar probe, versus IIDs which propagated towards the laminar array from a distant location. When IIDs were generated locally, they initiated within layer V. Conversely, IIDs propagating from a distal location were first seen in granular or supragranular layers [97]. The laminar structure and speed of this propagation ($\geq$ 1 m/s) is consistent with polysynaptic intracortical propagation. Fine-grained analysis of these events should yield further insights into the laminar physiology of propagating rhythms and IIDs.

4.3 Exotic (non somatic action potential) waveform physiology

Though most studies of extracellular activity focus on stereotyped action potential waveforms, other microscale events elude identification. These include W-shaped deflections, large positive spikes and waveforms too slow to reflect somatic spikes [98]. A tantalizing prospect is mapping these events to cellular phenomena studied *in vitro*, such as dendritic (NMDA & AMPA) spikes, plateau potentials, postsynaptic potentials, axonal spikes, etc. This would allow for the study of these sub-cellular events in behaving humans. A compelling example is the measurement of backpropagating action potentials with laminar recordings in mice, rats and rabbits [99–102]. Identifying backpropagating action potentials in human laminar recordings would allow experimentalists to see how these events are related to complex cognitive tasks involving feedback or top-down input.

An important step in this direction was performed by Paulk et al., who searched laminar recordings for these non-action potential exotic waveforms [103]. They found two distinct waveforms, dubbed Type 2 and Type 3 events. Type 2 events had a timescale of ~15 ms, and might correspond to backpropagating action potentials [100]. Type 3 events were significantly slower (~200 ms) and concentrated within superficial layers. This suggests that they may reflect dendritic calcium spikes, which were found to be supragranular & have a similar timescale in extracellular rodent recordings [73]. Critically, Paulk et al. also discovered these events in other recording modalities (PEDOT:PSS surface grids, Utah Arrays, Neuropixels) and species (macaques & mice), and could modulate them with behavioral tasks and pharmacological manipulation. In a further study using Neuropixels in humans, Paulk et al. found many positive-going waveforms, which likely correspond to axonal spikes [24]. Future human Neuropixel

recordings have the fine spatial sampling to characterize these and other exotic events (Fig. 5e-f) [23, 24]. Fortuitously, this may be easier in humans than animal models due to the large size of human neurons. This approach could be validated by simultaneous patch-clamp and extracellular recordings performed in animal models and *in vitro* [98, 102, 104].

4.4 Validation of extracranial laminar inference

Human laminar recordings can also validate and calibrate non-invasive alternatives to imaging laminar-specific activity in humans, such as high resolution fMRI and MEG [105–109]. Being able to make laminar recordings via fMRI and MEG, without the constraints of iEEG, would allow for ambitious future experiments. However, both methods make critical assumptions regarding how MEG/BOLD signals are related to neural activity which drastically impact estimated laminar sources. Though laminar fMRI has exquisite spatial resolution, BOLD activity does not reflect neural firing *per se*, but instead the underlying vascular architecture and cerebral blood oxygenation & volume, as well as MRI imaging parameters [110]. For instance, differences in baseline cerebral blood volume across the cortical depth can lead to differences in the BOLD response across laminae which do not reflect differences in neural activity. Because the vasculature structure and CBV varies across cortical regions, these confounds must be addressed on an area-specific basis [110]. This might be done with human laminar arrays that simultaneously record electrophysiological and hemodynamic data [111]. High-precision MEG has also made inroads into laminar imaging, largely via individualized headcasts and complex source-reconstruction techniques [107–109, 112]. Experiments using these advances have localized low and high frequency oscillations to different layers [108] and furthered a biophysical model of beta generation [112]. Despite this technique's promises, laminar source-reconstruction depends on assumed parameters such as source sparseness and SNR. Different assumptions concerning relative supragranular/infragranular source strength and spatial spread profoundly impact MEG estimates of laminar activity [107]. These assumptions may explain why MEG localizes alpha to deep layers, while human laminar recordings find supragranular alpha [61]. Measuring these parameters with ground truth laminar recordings can calibrate and refine the assumptions made by laminar MEG and fMRI [113].

Conclusion

Laminar recordings promise deep insights into human cortical physiology. Understanding how different layers interact to produce cognition and behavior allows iEEG to move beyond network-level characterizations to mapping cortical microcircuitry. By comparison with analogous animal experiments, we can also gain insights into how human neocortex diverges from other mammals. Despite being only two decades old, human laminar recordings have already yielded important insights into cortical physiology. Striking findings include the dominance of currents and firing within superficial layers during low-frequency oscillations, the laminar origins of ERPs and IIDs, and the dissociation of HGP and MUA. Further innovations in high-density probes and simultaneous macro-microelectrode recordings will allow for a deeper understanding of how different sub-laminae and cell types contribute to high-level cognition.

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