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Electrocorticographic Sensorimotor Mapping

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Introduction

Localizing eloquent cortex during neurosurgical resection planning is critical to minimizing postoperative neurologic deficits. Despite a host of sensorimotor mapping technologies including somatosensory evoked potentials (SSEP's), functional magnetic resonance imaging (fMRI), and electrocorticography (ECoG), the accepted gold standard is still considered to be electrical stimulation mapping (ESM; Haglund et al., 1994, Keles et al., 2004). ESM can be performed intraoperatively, which requires an awake, cooperative patient for language mapping, or appropriate anesthetic and absence of muscle relaxant for motor mapping. However, ESM can elicit afterdischarges and seizures, both of which can impair subsequent ESM testing. ESM can also generate painful stimuli due to activation of dural and trigeminal nociceptive afferents. In the extra-operative setting, ESM requires some degree of cooperation so that movements can be differentiated as evoked or spontaneous, and sensory responses can be elicited with patient feedback. Unlike ESM, ECoG records spectral changes in various frequency bands due to normal cortical function during overt or imagined motor activity. ECoG not only provides clinical recordings for epilepsy monitoring on an unparalleled spatiotemporal scale (Toole et al., 2007), but also is also able to resolve task-associated spectral changes in high frequency bands that may reflect local cortical activity (Miller et al., 2007 a, b, Szhuraj et al., 2005, Crone et al., 1998 a, b, Leuthardt et al., 2007). Newer approaches also include observations of spectral changes in slow cortical potentials during resting states. A number of ECoG studies (Table 1) attempt to compare ECoG with ESM, with varying results.

Review of current paper

In this issue of Clinical Neurophysiology, Vansteensel and colleagues report their effort to use ECoG signals to map motor cortex in patients with subdural electrodes implanted for epilepsy surgery planning (Vansteensel et al., 2013). The authors confirm the work of a few other centers (Table 1) showing that high frequency (here, 65–95Hz) band power (HFB) has the highest sensitivity and specificity relative to electrical stimulation mapping sites. Their novel contribution is the use of evoked signals during epochs of movement defined from the patient's own spontaneous movement. One can appreciate the advantage of this approach in

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the uncooperative or impaired patient, where cued-based movement might have a variable response delay, or even not be performed. Most methods of behavioral mapping would not work in such a situation, whereas this post-hoc approach does succeed. However, this limitation has not necessarily been an overwhelming obstacle, as even in the pediatric population, band frequency mapping can be applied successfully (Wray et al., 2012). In addition, the method described requires lengthy video reviewing to tag the epochs of movement, and thus is not feasible in an intraoperative environment. Integrating the activity-recorded videos with relevant signal processing also introduces a delay in obtaining the mapping results in a situation where results are usually desired in hours or minutes. However, the fact that this approach utilizes signals generated during patient self-directed, spontaneous and unrestricted movements, rather than as directed by the examiner, is philosophically appealing. It remains to be seen if this is an additional advantage. There is some discrepancy between the frequency mapping and the stimulation results, which tended to manifest as more widespread frequency changes. The authors eloquently discuss the implications of this, questioning the 'gold-standard' status of ESM and adding insight into the discussion on its role in optimizing the balance between neurosurgical treatment and functional outcomes.

Comparing approach with studies using directed motor task paradigms

The authors' comparisons between their ECoG maps and single-electrode ESM sites yielded a maximal sensitivity of 0.82 and specificity of 0.83 at the 65–95 Hz band. This compares favorably with past studies also directly assessing ECoG sensorimotor mapping accuracy versus ESM (Leuthardt et al., 2007, Brunner et al., 2009, Crone et al., 1998 a, b, Sinai et al., 2005; see Table 1), with results varying from sensitivities from 0.43–1.0 and specificities of 0.72- 0.94 for methods utilizing statistically significant task-oriented changes in the 70–100Hz band. Vansteensel's group also demonstrates inferior results for their low frequency bands (LFB) compared to their HFB results, a departure from Leuthardt et al., 2007's findings (Table 1). Generalizing and comparing different ECoG studies' concordance with ESM is difficult, however, in part due to the way ESM positive sites were defined. Many studies performed their ECoG comparisons against ESM electrode pairs; in instances where they were compared against individual ESM electrodes; many studies did not define how they verified single ESM positive sites from pair-wise stimulation trials. Sometimes, isolated positive sensory findings were excluded.

Interestingly, unlike most prior studies which report consistently higher gamma band spatial localization compared to lower frequencies, Vansteensel did not note any gross differences in cortical localization of the higher frequencies' spectral changes compared with the lower frequencies. This may be a reflection of the non-task focused cognitive states of the subjects, or possibly due to spontaneous use of more mixed and varied sets of complex movements and muscle groups as opposed to simple task-oriented hand clench/finger flexion paradigms. The extensive involvement of non-Rolandic areas (Figure 2 in Vansteensel et al., 2013) when looking at 65–95Hz further suggests a complex, perhaps ecologically more valid, set of motor activities. Given the already demanding video screening already required, further distinguishing leg/hand/face topographies would be challenging, as Vansteensel and colleagues acknowledge. For purposes of supplanting ESM, being able to distinguish within functional areas becomes important for intraoperative orientation and localization, especially in the context of abnormal and/or altered cortical surface anatomy. This also becomes clinically relevant in cases where pathologic foci involve non-dominant hemisphere sensorimotor cortex, and the extent of lesion removal affects the likelihood of symptom relief and guides further patient care. In such situations, facial weakness caused by resecting non-dominant face motor area is typically transient and recoverable over several months (LeRoux et al., 1991, Duffau et al., 2003), whereas surgically caused somatic motor weakness is less forgiving. In addition, recent human ESM studies suggest overlap within and between functional areas (e.g. hand and foot motor, hand motor and hand sensory) in as high as 11% of tested subjects (Branco et al., 2003), with regions of overlap extending as much as 1cm (Farrell et al., 2007). As some studies have previously shown (Table 1), it will remain important to continue assessing ECoG's accuracy versus ESM especially with respect to somatotopic specificity.

Other non-directed, "Passive" ECoG methods

A great methodological challenge involved in activity-based ECoG sensorimotor mapping is having the patient awake and reliably cooperating with a cued series of specific body movements repeatedly. While Vansteensel and colleagues' novel approach of spontaneous patient self-directed activity reduces the amount of required behavioral input, other methods of "passive" ECoG are also being investigated. Resting states networks identified in the fMRI literature have recently been demonstrated as potential alternatives to passive non-task oriented ECoG sensorimotor mapping. Slow cortical potentials (SCP) <0.5Hz, thought to represent slow rhythmic depolarization of apical dendrites in superficial layers, have been noted to be strongly correlative within and between functional cortical regions, and persist in anesthetized states (Breshears et al., 2012). Another approach utilizing <0.1Hz fluctuations in the 70–100Hz band during resting state ECoG recordings was used to delineate sensorimotor, and visual networks (Ko et al., 2012, in preparation). It remains to be seen if further optimization of these ECoG mapping methods will improve clinical accessibility.

General Discussion: ECoG versus ESM and comparing mapping methods

Modern ESM consists of traditional 50–60 Hz bipolar pulse trains (Penfield 1937, King 1987, Berger 1990), with some reporting success with shorter trains of 250–500 Hz monopolar stimulation (Taniguchi et al., 1993). The practice of ESM is not standardized and its status as the widely accepted gold standard has not been validated in any randomized controlled fashion. Hence, even after optimizing ECoG frequency sensorimotor mapping, instead of a strict comparison between ECoG and ESM, clinical outcome data involving one of each or both modalities will likely be required in order to truly assess efficacy (Hamberger et al., 2007). Lesion based mapping (ESM) interferes with absolutely critical cortical areas for function, whereas activation based mapping (ECoG) identifies associated and potentially non-critical functional areas (Sergent et al., 1994). Comparing these methods is reminiscent of prior fMRI versus ESM studies that demonstrated high fMRI sensitivity and low specificity in language mapping (sensitivity 81–92%, specificity 53–61%; Fitzgerald et al., 1997, Pouratian et al., 2002, Roux et al., 2003, Rutten et al., 2002). Similar to fMRI, ECoG mapping creates a cortical activation map with a range of values which, when temporally correlated with task movements, is then thresholded (i.e. the magnitude of high gamma power change that constitutes "cortical processing" is not known a priori). In contrast, ESM is an all or none phenomenon, and has no time-dependence. To further compare these types of mapping methods requires collapsing ECoG data across time, which may contribute an under-sampling error (Sinai et al., 2005).

ECoG is inaccurate across cortical regions with varying depth profiles, such as areas with large superficial cortical veins, the Sylvian fissure, cortical sulci, and the insula. This is in contrast to ESM when performed in the operating room, since cortex is directly stimulated under visualization without any obstacles. ECoG likely has a more rapid current density drop-off as well; and the cortical area seen beyond the ECoG electrode is likely quite small compared to the intervening cortical area between two ESM-stimulated electrodes. This would likely be true particularly for high-frequency ECoG changes that are low-amplitude and more likely to reflect local processing than more widespread low frequency changes. At the same time, the area of tissue exposed to an applied current during ESM on the edge of the ECoG grid could potentially involve cortex outside the grid coverage, and the intervening tissue between the individual sites of a bipolar ESM (+) pair is also considered to be functionally active. On the other hand, it is common practice to designate an ESM site as functionally negative if any of its pair-wise stimulations with its neighbors is functionally negative as well; however, it is unclear from previous ECoG studies, how thoroughly investigators verified ESM (+) sites (understandably, to do so will raise the number of stimulation trials for each patient and lengthen each session).

ECoG often requires significant signal processing post-hoc analysis performed offline, which limits its use in the intraoperative setting. Several groups however have demonstrated real-time mapping with ECoG (Miller et al., 2007 a, b, Brunner et al., 2009, Lachaux et al., 2007, Roland et al., 2010), which may continue to help bridge this gap.

Limitations of High Gamma frequency mapping

Given the relative lack of sensitivity in most of the studies presented using high gamma (HG), it is possible that that ESM may affect cortical areas that are too small to register HG changes on a traditional ECoG grid with 2.3mm contacts and a 1cm interelectrode distance. It has been suggested that optimal interelectrode spacing to avoid aliasing is 1.25mm (Freeman et al., 2000). Smaller ECoG grid recordings (Wang et al., 2009) with 1.5mm contact, 4mm inter-electrode distance have demonstrated lower coherence that is more pronounced in the 60–120Hz range, suggesting greater, non-redundant recordings. On an even smaller scale (Leuthardt et al., 2009) with 75 μm contacts and 1mm interelectrode, differences during task-associated evoked potentials are evident between ipsilateral and contralateral hand movements. High-resolution flexible ECoG grids (Viventi et al., 2011) also show promise in providing broad-coverage grids with sub-millimeter electrode spacing while minimizing the number of exiting subdural wires and potentially providing inter-sulcal coverage, which may provide a greater variety of different signals which may be helpful for classifying different upper limb movements (Yanagisawa et al., 2009). The optimal electrode diameter size and inter-electrode distance, however, have yet to be determined, in order to yield maximal spatial resolution while minimizing inter-electrode shunting and signal redundancy in order to achieve reliable, independent cortical control signals for brain computer interfaces.

It is also possible that HG frequency mapping itself does not sufficiently capture cortical activation. High frequency sensorimotor rhythms are thought to reflect local neuronal processing, and low frequency oscillations thought to reflect wider spread subcortical-cortical interactions. Only approximately 22–28% of fMRI BOLD changes have been shown to be accounted for by changes in HFB power (Hermes et al., 2012, Logothetis et al., 2001, Connor et al., 2011), and the degree of local field potential (LFP)-BOLD coupling varied between lobes, as well as between gyri within the same lobe (Connor et al., 2011). Hermes et al., 2012 demonstrated that an additional 13% of the fMRI BOLD change during motor movement was explainable by associated decreases in low frequency band (LFB) (5–30Hz) power. Hence, it is possible that investigators will need to look beyond solely using HG frequency mapping, and also consider different frequency bands based on location, for further ECoG optimization.

Limitations of Electrocortical Stimulation Mapping

Further questioning ESM's status as the gold standard for mapping, multiple investigators have suggested that ESM may overestimate functionally critical areas (Nii et al., 1996, Luders et al., 1991, Krauss et al., 1996), and thus underestimating resectable cortex. ESM might also have effects beyond the direct field of stimulation; despite rapid current density drop-off with distance, ESM-induced afterdischarge can spread to adjacent electrodes. Induced cortico-cortical evoked potentials in distant essential areas with strong functional connectivity to the stimulated nonessential region have also been demonstrated (Lesser et al., 1994, 2010; Blume et al., 2004, Matsumoto et al., 2004), and ESM of basal temporal cortex has been noted to interfere with language tasks but incur no language deficits after resection (Luders et al., 1991, Krauss et al., 1996). In some cases, using ESM for language mapping can affect mouth or face-motor sites, which could potentially over-count the number of sites actually critical for language production.

ESM is usually not performed during anti-epileptic drug weaning due to greater risk for eliciting a seizure, until the medications are resumed. This is not a limitation with ECoG mapping. However, even without replacing ESM for clinical mapping, ECoG can still prove to be of significant utility. Given the reasonably high specificity demonstrated in many studies, ECoG could be used as a preliminary sensorimotor map during surgical planning, with ECoG (−) areas near the resection area reconfirmed with ESM. This would reduce the number of stimulus pulses during a mapping session. ECoG has been shown to be useful in conjunction with fMRI in a small series of pediatric patients otherwise unable to tolerate ESM (Wray et al., 2012).

Future Directions

In order to more effectively compare results from ECoG mapping, investigators will need to consistently define their ESM parameters in order to reduce possible variability resulting from differing ESM clinical practices. This includes defining an ESM (+)/(−) electrode, including whether or not the ESM (+) site was re-confirmed in at least one other pair-wise stimulation trial. With respect to ECoG mapping, investigators should be more consistent in using the same frequency ranges in their studies. As we continue to optimize ECoG high-frequency mapping, further sensitivity may be gained via increased spatial sampling via high-resolution microelectrodes. Combining identified sites of ESM (+) from different frequency bands in addition to high gamma may further improve sensitivity/specificity. Also, combining different methods (e.g. task-oriented gamma changes and resting state slow potentials analyses), in addition to fMRI and SSEP modalities, may prove overall to be an optimal mapping approach.

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Table 1

Studies comparing sensorimotor mapping with ECoG versus ESM. *ECS(+) = Cortical stimulation responsive, ECoG(+) = Significant spectral change identified by ECoG in given frequency band, LFB = Low frequency band, HFB = High frequency band. ERS = event-related synchronization, ERD = event-related desynchronization. Sen = sensitivity, Spe = specificity. FPR= false positive rate, FNR = false negative rate, NPV= negative predictive value, SD = standard deviation.* Multiple studies did not clearly specify how individual ESM (+) electrodes were defined, and several did not consider positive sensory responses as criteria for ESM (+).

Study	Patients	Motor Task	Frequency Band	Methods	Correlation relative to ESM results
Leuthardt et al., 2007	7	Hand/Mouth	LFB: 8–32Hz; HFB: 76–100Hz	r^2 weights	Vs. ESM(+) pairs: LFB sen .89–1.00; spe .79-.82 HFB sen .72-.88; spe .92-.94 LFB OR HFB: sen 1.00 spe .74-.78 Vs single ESM(+) sites: LFB OR HFB: sen .43-.5, spe .89-.91
Miller et al., 2007	8	Hand	76–200Hz	Power 2SD's above baseline rest activity	Direct comparisons with ESM not listed
Miller et al., 2007	22	Hand/Arm/Mouth	LFB 8–32Hz; HFB 76–100Hz	r^2 weights	Of 20 ESM(+) pairs, 19 LFB, 17 HFB, 16 Both LFB+HFB had significant changes (hence FNR .05, .15, .2 respectively)
Brunner et al., 2009	10	Hand/Mouth	70–100Hz	SIGFRIED; r^2 weights	FPR and FNR <10%; with next-neighbor evaluation, approaches 0% and 0.46–1.1% respectively; 1.2% hand motor sites were ESM(+) but ECoG(−); 3.19% were ECoG(+) but ESM(−)
Crone 1998	5	Hand/Mouth/Leg	α 8–13Hz; β 15–25Hz; low γ 35–45, 40–50Hz; high γ 75–85, 80–90, 85–95, 90–100Hz	n/a	High and low ERS correlated with ESM(+) sites better than alpha ERD (which was less specific), but weren't always present on ESM(+) sites.
Miller et al., 2010	8	Overt and Imagined Hand/Mouth	LFB 8–32Hz; HFB 76–100Hz	r^2 weights	Direct comparisons with ESM not listed
Wray et al., 2012	50 patients; 36 had ESM attempted at first, 10 had ECoG only, 5 had both (children)	Hand	70–150Hz	n/a	Direct comparisons with ESM not listed; however of 7 patients failed attempts at ESM, of which 3 (8%) had successful ECoG mapping instead. All 10 patients with ECoG only attempts were successful.
Vansteensel et al., 2013	7	Hand/Arm (spontaneous, non-cued)	φ 4–7Hz; α 8–14Hz; β 15–25Hz; low γ 26–45Hz; high γ 65–95Hz	t-test $p<0.05$	single ESM sites: high γ sen .82, spe .83; other bands ~sen .50, spe >.80
Roland et al., 2010	2 (awake craniotomies)	Hand, Mouth (included speech tasks; awake intraoperative craniotomies)	75–115Hz	SIGFRIED; r^2 weights	Tongue motor: 2 ESM(+) and ECoG(+) sites overlap, 1 ECoG(+) and 1 ECS(+) only sites seen. Speech: 4 ESM(+) and ECoG(+) sites

Study	**Patients**	**Motor Task**	**Frequency Band**	**Methods**	**Correlation relative to ESM results**
					overlapped, 3 ESM(+) and 4 ECoG(+) only sites seen.
Breshears et al., 2012	8	Passive/non-task driven (during awake and anesthetized states)	<0.5Hz	Principal component analysis/systemic seed selection	asleep: sen .78-.9, spe .58-.67 awake: sen .83-.93, spe .55-.6
Ko et al., in preparation	6	Passive/non-task driven	<0.1Hz fluctations in 70–100Hz	Spectral clustering	sen .65, spe .98; NPV .95
Sinai et al., 2005	13	Mouth (Naming tasks also used)	80–100Hz	Varied	>50% power change threshold: sen .81-.85, spe .25-.29, No threshold: sen .41-.49, spe .74-.80 ECoG for motor tasks had better results than for naming tasks. Restricting to 12 ECoG(+) sites only: sen .38-.46, spe .78-.84