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Letter to the Editor

Electrocorticographic high gamma language mapping: Mind the pitfalls of comparison with electrocortical stimulation

To the Editor

Several research groups have compared electrocorticographic (ECoG) high gamma language mapping (HGM) to language mapping using electrocortical stimulation (ESM) as the gold standard. The aim of these studies was to evaluate the clinical utility of ECoG HGM. The conclusion of a recently published review by Arya et al. [1], which included a meta-analysis, was that ECoG HGM is a specific but not sensitive method for language localization when compared to ESM. The authors state that the value of ECoG HGM remains unclear because of heterogeneity in study designs. For example, studies use different language tasks, different ECoG HGM procedures, and different ESM protocols. The authors conclude that ECoG HGM can only become a potential alternative for ESM if uniform methods are used.

We would like to draw attention to another important issue that influences sensitivity and specificity outcomes when comparing ECoG HGM with ESM. Electrocortical stimulation is usually performed by supplying currents to neighboring electrode pairs. If such currents cause language errors or hesitations, the electrode pair is considered language positive (ESM+ pair). However, it is unclear if the language area that is temporarily blocked by the electrical pulses is localized in the cortex between the two electrodes, in the cortex directly underneath one of the electrodes, or in the cortex underneath both electrodes. This uncertainty makes it difficult to compare ESM results with ECoG HGM results because ECoG HGM results are obtained per electrode. Arya et al. mention this issue briefly, but the different ways in which ESM and ECoG HGM results have been compared and the impact of each method on sensitivity and specificity were not addressed.

This letter discusses the papers included in the review by Arya et al. [2–15] and some additional papers that fulfilled the inclusion criterion of comparing language localization with ECoG HGM and ESM by calculating sensitivity and specificity [16–18]. We excluded studies if ESM was only performed to confirm ECoG HGM results [19]. In addition, we excluded a paper in which three out of four ECoG HGM sessions seem to have been performed while the patients were sedated [20]. Tables with patient characteristics suggested that two studies included the same three patients [12,21]; we excluded the one whose study aim was to answer a cognitive neuroscience question rather (or more) than a clinical research question [21]. Studies in which some, but not all, of the patients seemed to overlap with another study were not excluded.

The included studies contain four approaches for comparing ESM and ECoG HGM results, which are explained below and illustrated in Fig. 1. Sensitivity is calculated as true positive (TP) divided by TP + false negative (FN). Specificity is calculated as true negative (TN) divided by TN + false positive (FP).

- Method A [8,10,11,16–18]: Every electrode that is involved in at least one ESM+ electrode pair is considered ESM+. An ECoG HGM+ electrode is considered true positive if that electrode is also an ESM+ electrode.
- Method B [5,10,13]: Every electrode that is involved in two or more ESM+ electrode pairs is considered ESM+. This method is similar to method A, but the criteria for ESM+ electrodes are stricter.

Method A yields more ESM+ electrodes than method B. As a consequence, an ECoG HGM+ electrode is more likely to be true positive, but an ECoG HGM− electrode is more likely to be false negative. Studies with many ECoG HGM+ electrodes are therefore more likely to yield a high sensitivity with method A. On the other hand, if the number of ECoG HGM+ electrodes is low, sensitivity might be poor because of the large number of false negatives. The chance of finding false positive results is lower in method A than in method B. Thus, specificity is higher for method A.

- Method C [2,7,9,10]: This method determines whether ESM+ electrode pairs contain ECoG HGM+ electrodes. This method differs from method A and B because it looks at ESM+ pairs and then establishes whether those pairs contain ECoG HGM+ or ECoG HGM− electrodes. Thus, in method C, the pairwise ESM+ results are not converted to results per electrode, and one electrode can contribute to different ESM pairs. As a consequence, an ECoG HGM+ electrode that is connected to an ESM+ pair will result in a TP ESM pair, whereas that same ECoG HGM+ electrode will result in a FP ESM pair when connected to an ESM− pair. The higher number of TP results in relatively high sensitivity, but specificity is lower because of the higher number of FP results.
- Next-neighbor (NN) method [4,6,8]: This method applies the same rule for converting ESM pairs to ESM electrodes as method A. In addition, an ECoG HGM+ electrode is considered true positive if it is a neighbor of an ESM+ electrode. It is unclear if the reverse is also true, i.e., if ECoG HGM− electrodes that are neighbors of ESM+ are considered false negatives. If this is the case, sensitivity will drop because of the higher number of FN, but if this is not the case, sensitivity will be high because of the high number of TP. The chance of finding a FP result is low with this method, which therefore yields high specificity.

Some papers use a combination of two approaches: for example, method B if an electrode is stimulated in more than one pair and method A when an electrode is stimulated in only one pair [3,12] (method AB). One study used an adapted method C for calculating sensitivity in ESM+ pairs but calculated specificity by dividing ESM− pairs in two ESM− electrodes using method A [15] (method AC).

We plotted (1-specificity) against sensitivity for each study to demonstrate the effect of these methods in real data (Fig. 2). We deduced the method that was used in each paper from text, tables, and/or figures, but this information was not always readily available. If possible, we

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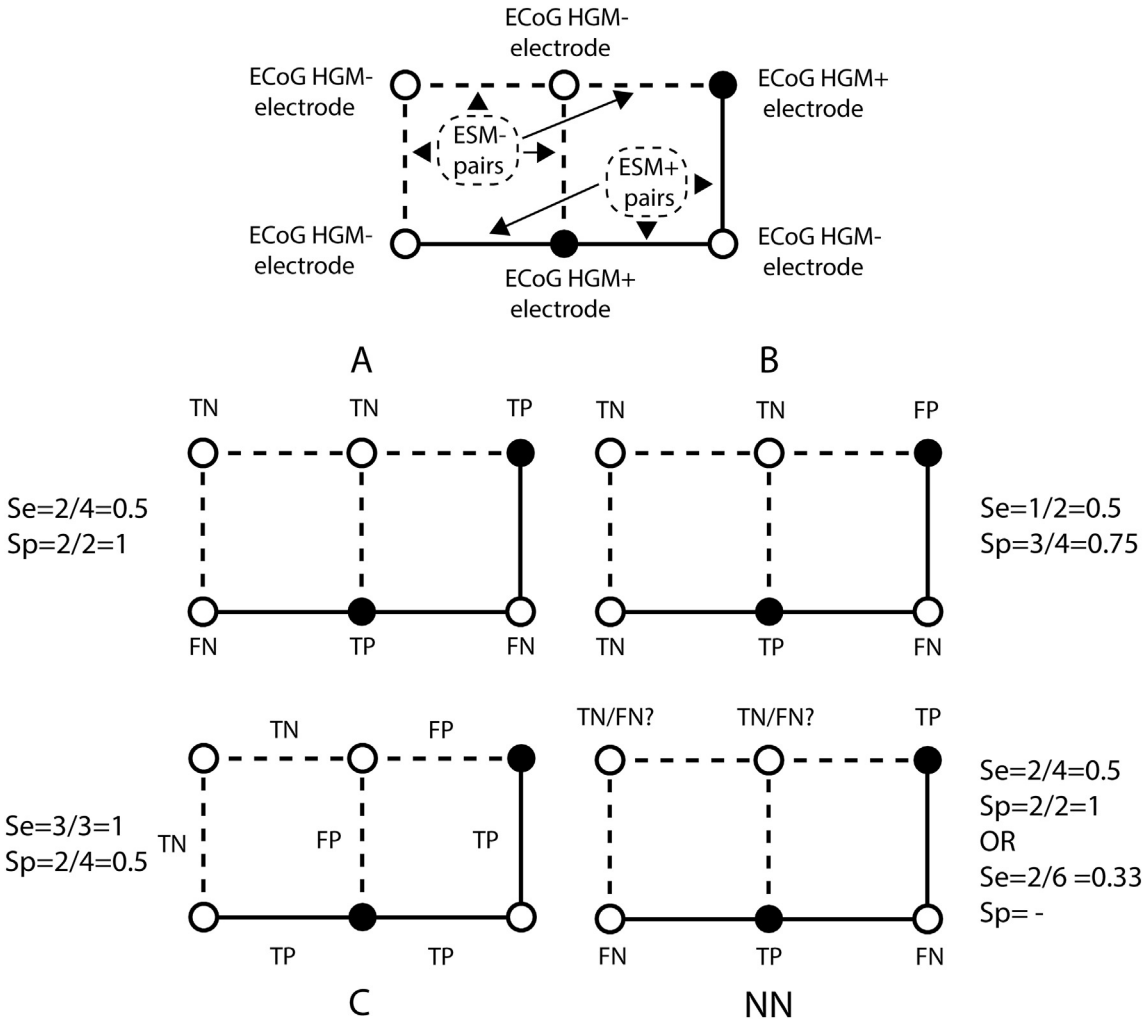

Fig. 1. Example of a three-by-two grid with two ECoG HGM + electrodes (filled circles) and three ESM + electrode pairs (solid lines). ECoG HGM − electrodes are depicted as open circles, ESM − electrode pairs as dashed lines. Below, the same grid is shown four times to demonstrate the four methods for determining whether electrodes (methods A, B, and NN), or electrode pairs (method C) are considered true positive (TP), false positive (FP), true negative (TN), or false negative (FN). The resulting sensitivity (Se) and specificity (Sp) are also supplied.

verified our classification by recalculating results for a patient based on a figure and comparing them to the results reported in a table. If it was clear that ECoG HGM and ESM results were compared per electrode but it was not specified which criteria were used to determine if an electrode was ESM + or ESM −, we assumed that the less strict criteria of method A were used [11,17,18]. One paper did not provide the information needed to determine if they used ESM pairs or ESM electrodes [14].

This figure shows a clustering of most of the studies using method C. All studies using method C report higher sensitivity than specificity. All studies using method B report low sensitivity but high specificity. There is no clear pattern in studies using method A. This is partly due to the fact that high and low sensitivity are both likely results of method A (see above). Another reason is that this category contains studies that were difficult to classify. We therefore cannot exclude the possibility that some studies were inadvertently misclassified.

Conclusion and recommendations

We showed that apart from the heterogeneity in testing methods as reported by Arya et al. [1], there are also different methods for calculating sensitivity and specificity, and these different methods influence outcome. Comparing sensitivity and specificity between studies is inappropriate as long as these differences in methods of comparison remain. Future research on ESM should clarify which method for converting ESM +/− pairs to ESM +/− electrodes best represents the actual situation in the electrically stimulated cerebral cortex. Until such a clarification is available, research groups should determine sensitivity and specificity using methods A, B, and C, or at least allow reviewers to recalculate values in one uniform method by providing the data required for these calculations. Recalculation requires information about all ECoG HGM positive and negative electrodes and all ESM positive and negative electrode pairs.

If sensitivity and specificity of all studies would be calculated using the same method of comparison, a new, valid attempt could be made to evaluate the effects of the variety in language tasks, ECoG HGM procedures, and ESM protocols.

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