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LETTER TO THE EDITOR

Where is the speech production area? Evidence from direct cortical electrical stimulation mapping

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We read the article by Gajardo-Vidal *et al.*[1] with great interest. The authors collected data from 134 stroke survivors with left lateral frontal lesions and built a series of multiple regression models to explain the contributions of Broca's area and adjacent structures to long-term speech production. Their findings challenge several traditional views. First, their data provide new evidence that damage to Broca's area rarely contributes to long-term speech production deficits. Second, the authors claim that a persistent speech production deficit after a lesion to the anterior arcuate fasciculus (aAF) is not caused by the disconnection of Broca's area. Third, the authors interpret the previously reported phenomenon of Broca's area lesion leading to long-term speech production deficits as co-occurring damage of the underlying aAF. This research not only has important reference value for the clinical brain mapping and preservation of language functions but also provides precious lesion-symptom evidence for neurolinguistic theories and models.

However, Gajardo-Vidal *et al.*[1] also mentioned several limitations of their study. For example, the stroke lesions are often diffuse[2]; thus, they cannot fully distinguish the contribution of Broca's area from that of the adjacent white and grey matter. For the same reason, it is difficult to map the disconnected cortex precisely after damage to a specific fibre bundle.[3] Herein, we would like to share the preliminary results of our fibre tractography and intraoperative direct cortical electrical stimulation (DES) study. The language interferences induced by DES can be regarded as a small-scale (~1-cm resolution) transient lesion to the language area.[4–8] In addition, previous studies have revealed a very low long-term aphasia rate (2.4% and 1.6%, respectively, for 3- and 6-months post operatively) after DES language mapping for glioma resection.[4] Thus, we believe our results are highly comparable with this lesion study.

We reviewed all right-handed glioma patients ($n = 77$) who underwent left frontal DES language mapping at Huashan Hospital between September 2017 and November 2018. Next, 18 patients were included for further analysis, because their tumors or oedema areas did not affect the regions of interest: Broca's area (pars opercularis, pars triangularis), the ventral precentral gyrus, the underlying aAF and long segment of the arcuate fasciculus (lAF). DES-induced speech arrest/anarthria (the stimulation-induced cessation of ongoing number counting, without twitching of the articulators) was selected as the gold standard for mapping the speech production area.[4,8] Subsequently, we reconstructed the cerebral distribution of the speech arrest sites (Fig. 1B and D) and the cortical terminations of aAF (Fig. 1E) and lAF (Fig. 1F) based on the intraoperative photos (Fig. 1A) and preoperative neuroimaging.[9,10] Considering the 1-cm resolution of DES and 1-cm margin of the tissue preservation to the functional area, we quantitatively measured these results with a 1-cm^2 square grid (Fig. 1C and G–I)[4] and then integrated them into group-level distribution maps (Fig. 1J). Finally, sensitivity and specificity analyses were performed for the regions of interest in predicting the stimulation-induced speech arrest sites (Fig. 1K).

Primarily, our results showed that the distribution of speech arrest sites is poorly consistent with Broca's area ($\kappa = -0.45$) or pars opercularis ($\kappa = -0.19$) (Fig. 1K). Among the 18 patients included, no speech arrest sites were found in the pars triangularis (Fig. 1J). Most of the speech arrest sites were located in the ventral precentral gyrus, especially the ventral premotor area (Fig. 1J). In addition, a moderate consistency was found between the ventral precentral gyrus and speech arrest area ($\kappa = 0.50$, $P < 0.0001$) (Fig. 1K). This distribution pattern is consistent with previous DES studies[4–8] and in

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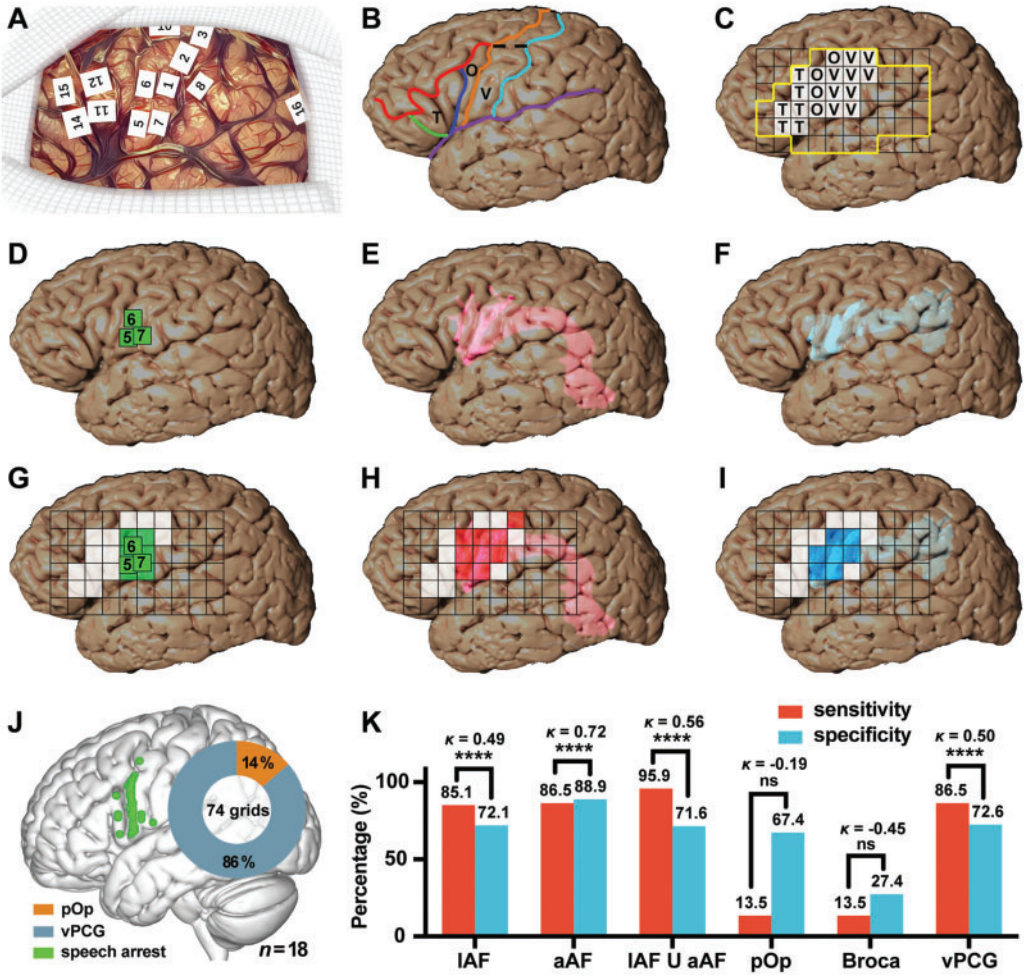

Figure 1 Sensitivity and specificity analysis for the regions of interest in predicting the stimulation-induced speech arrest sites. (**A**) The intra-operative photo of the cerebral surface with sterile tags labelling the DES-induced responses. The speech arrest sites are marked with the labels 5–7. (**B**) The anatomical landmarks (red line: inferior frontal sulcus; purple line: Sylvian fissure; green line: horizontal ramus; blue line: ascending ramus; orange line: precentral sulcus; light blue line: central sulcus; and black dotted line: the horizontal line from the intersection of the inferior frontal sulcus and the precentral sulcus) for delineating the pars opercularis (O), pars triangularis (T) and the ventral part of the precentral gyrus (V). (**C**) The distributions of the exposed cortex (delineated with a yellow line) and the regions of interest (1 cm^2 white squares and corresponding letters). (**D–I**) The distributions of (**D**) the speech arrest sites (1 cm^2 green squares), the frontal terminations of (**E**) the long segment (lAF, the termination marked in lighter red) and (**F**) anterior segment (aAF, the termination marked in lighter blue) of the arcuate fasciculus and (**G–I**) the corresponding squares containing these regions of interest. (**J**) At group-level ($n = 18$), the speech arrest sites (green) occupied 74 squares in total, with 86% of squares in the ventral precentral gyrus (vPCG, grey, 64 of 74 squares) and 14% of squares in the pars opercularis (pOp, orange, 10 of 74 squares). (**K**) The sensitivities and specificities of the regions of interest (lAF ∪ aAF: lAF and aAF complexes; Broca's area: pars opercularis and pars triangularis) in predicting the DES-induced speech arrest sites (κ = Cohen's kappa coefficient; $^{****}P < 0.0001$; ns = non-significant).

line with the poor contribution of the lesion load in Broca's area to predict the long-term speech production outcome,[1] as well as the low incidence of permanent speech production deficits after removing the Broca's area.[11]

Second, Gajardo-Vidal *et al.*[1] highlighted the critical rule of the aAF in explaining long-term speech production deficit among adjacent regions of Broca's area. However, the authors did not include a comparison between the aAF and lAF in their study. These two major fibres of the dorsal phonological stream tend to be underneath the frontal cortex and are likely to terminate in Broca's area and the ventral precentral gyrus.[9,10,12,13] We found that among all included regions of interest, the end points of the aAF have the best consistency with the DES-induced speech arrest area ($\kappa = 0.72$, $P < 0.0001$) (Fig. 1K). Furthermore, the sensitivity and specificity of the aAF end points were significantly higher than those of Broca's area or pars opercularis only ($P < 0.0001$ for all McNemar's tests). Although no statistical difference in sensitivity was found, aAF end points predicted speech arrest with significantly higher specificity than lAF ($P < 0.0001$) and ventral precentral gyrus ($P < 0.0001$). We also found that the end points of the lAF/aAF complex had a higher sensitivity than the aAF termination only ($P = 0.016$) but a lower specificity ($P < 0.0001$) and Yoden index (0.75 for the aAF versus 0.68 for the lAF/aAF complex). To conclude, we revealed that the termination of the aAF is the best predictor of the speech production cortex among the included regions of interest, and this is supported by various subcortical stimulation mapping and DTI studies.[13–16] Therefore, we believe that the cortical termination of the aAF may be the real speech production area. Finally, we hope our findings may supplement the excellent work by Gajardo-Vidal *et al.*[1]

Data availability

Data involved in this study are available upon reasonable request.

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Competing interests

The authors report no competing interests.

References

1. Gajardo-Vidal A, Lorca-Puls DL, Warner H, et al. Damage to Broca's area does not contribute to long-term speech production outcome after stroke. *Brain*. 2021;144(3):817–832.
2. Sperber C, Karnath HO. Impact of correction factors in human brain lesion-behavior inference. *Hum Brain Mapp*. 2017;38(3):1692–1701.
3. Basilakos A, Rorden C, Bonilha L, Moser D, Fridriksson J. Patterns of poststroke brain damage that predict speech production errors in apraxia of speech and aphasia dissociate. *Stroke*. 2015;46(6):1561–1566.
4. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. *New Engl J Med*. 2008;358(1):18–27.
5. Wu J, Lu J, Zhang H, et al. Direct evidence from intraoperative electrocortical stimulation indicates shared and distinct speech production center between Chinese and English languages. *Hum Brain Mapp*. 2015;36(12):4972–4985.
6. Chang EF, Breshears JD, Raygor KP, Lau D, Molinaro AM, Berger MS. Stereotactic probability and variability of speech arrest and anomia sites during stimulation mapping of the language dominant hemisphere. *J Neurosurg*. 2017;126(1):114–121.
7. Sarubbo S, Tate M, De Benedictis A, et al. Mapping critical cortical hubs and white matter pathways by direct electrical stimulation: An original functional atlas of the human brain. *NeuroImage*. 2020;205(1):116237.
8. Tate MC, Herbet G, Moritz-Gasser S, Tate JE, Duffau H. Probabilistic map of critical functional regions of the human cerebral cortex: Broca's area revisited. *Brain*. 2014;137(10):2773–2782.
9. Catani M, Jones DK, Ffytche DH. Perisylvian language networks of the human brain. *Ann Neurol*. 2005;57(1):8–16.
10. Catani M, De Schotten MT. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex*. 2008;44(8):1105–1132.
11. Rolston JD, Englot DJ, Benet A, Li J, Cha S, Berger MS. Frontal operculum gliomas: Language outcome following resection. *J Neurosurg*. 2015;122(4):725–734.
12. Hickok G. The architecture of speech production and the role of the phoneme in speech processing. *Lang Cogn Neurosci*. 2014;29(1):2–20.
13. Duffau H. Stimulation mapping of white matter tracts to study brain functional connectivity. *Nature Rev Neurol*. 2015;11(5):255–265.
14. Maldonado IL, Moritz-Gasser S, de Champfleur NM, Bertram L, Moulinié G, Duffau H. Surgery for gliomas involving the left inferior parietal lobule: New insights into the functional anatomy provided by stimulation mapping in awake patients. *J Neurosurg*. 2011;115(4):770–779.
15. Maldonado IL, Moritz-Gasser S, Duffau H. Does the left superior longitudinal fascicle subserve language semantics? A brain electrostimulation study. *Brain Struct Funct*. 2011;216(3):263–274.
16. Martino J, Hamer PCDW, Berger MS, et al. Analysis of the subcomponents and cortical terminations of the perisylvian superior longitudinal fasciculus: A fiber dissection and DTI tractography study. *Brain Struct Funct*. 2013;218(1):105–121.