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Resting State Functional Networks in Gliomas: Validation With Direct Electric Stimulation of a New Tool for Planning Brain Resections

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BACKGROUND AND OBJECTIVES: Precise mapping of functional networks in patients with brain tumor is essential for tailoring personalized treatment strategies. Resting-state functional MRI (rs-fMRI) offers an alternative to task-based fMRI, capable of capturing multiple networks within a single acquisition, without necessitating task engagement. This study demonstrates a strong concordance between preoperative rs-fMRI maps and the gold standard intraoperative direct electric stimulation (DES) mapping during awake surgery.

METHODS: We conducted an analysis involving 28 patients with glioma who underwent awake surgery with DES mapping. A total of 100 DES recordings were collected to map sensorimotor (SMN), language (LANG), visual (VIS), and speech articulation cognitive domains. Preoperative rs-fMRI maps were generated using an updated version of the ReStNeuMap software, specifically designed for rs-fMRI data preprocessing and automatic detection of 7 resting-state networks (SMN, LANG, VIS, speech articulation, default mode, frontoparietal, and visuospatial). To evaluate the agreement between these networks and those mapped with invasive cortical mapping, we computed patient-specific distances between them and intraoperative DES recordings.

RESULTS: Automatically detected preoperative functional networks exhibited excellent agreement with intraoperative DES recordings. When we spatially compared DES points with their corresponding networks, we found that SMN, VIS, and speech articulatory DES points fell within the corresponding network (median distance = 0 mm), whereas for LANG a median distance of 1.6 mm was reported.

CONCLUSION: Our findings show the remarkable consistency between key functional networks mapped noninvasively using presurgical rs-fMRI and invasive cortical mapping. This evidence highlights the utility of rs-fMRI for personalized presurgical planning, particularly in scenarios where awake surgery with DES is not feasible to protect eloquent areas during tumor resection. We have made the updated tool for automated functional network estimation publicly available, facilitating broader utilization of rs-fMRI mapping in various clinical contexts, including presurgical planning, functional reorganization over follow-up periods, and informing future treatments such as radiotherapy.

KEY WORDS: Brain surgery, Brain mapping, Functional MRI, Glioma, Presurgical planning, Resting state

ABBREVIATIONS: BOLD, blood oxygenation level dependent; **CC,** cross-correlation; **DES,** direct electrical stimulation; **DMN,** default mode network; **EOR,** extent of resection; **FPN,** frontoparietal network; **HGGs,** high-grade gliomas; **ICA,** independent component analysis; **ICs,** independent components; **IOM,** intraoperative monitoring; **LANG,** language; **LGGs,** low-grade gliomas; **pICA,** probabilistic ICA; **rs-fMRI,** resting-state fMRI; **RSNs,** resting -state networks; **SAN,** speech articulation; **SMN,** sensorimotor; **T1w,** T1-weighted; **tb-fMRI,** task-based fMRI; **VIS,** visual ; **VSN,** visuospatial network.

Supplemental digital content is available for this article at neurosurgery-online.com.

Gliomas, the most frequent intrinsic brain tumors in adults, occur at an annual rate of 4.7 to 5.7 cases per 100 000 people.[1] Current standard treatment involves surgical resection followed by radio and/or chemotherapy.[2,3] The extent of resection (EOR) significantly affects overall survival for both high-grade gliomas (HGGs) and low-grade gliomas (LGGs).[4,5] Balancing EOR with preserving eloquent brain networks to prevent cognitive deficits[6] is thus a critical consideration in neurosurgery and neuro-oncology.

Therefore, awake surgery with intraoperative direct electrical stimulation (DES) and asleep surgery with intraoperative monitoring (IOM) are recommended for functional-tailored resections, minimizing risks of permanent sensorimotor (SMN) and cognitive deficits.[7-10] Although both awake surgery with DES[11] and asleep surgery with IOM[12] have shown improved outcomes, both present challenges. Awake surgery requires patient cooperation during intraoperative cognitive tasks, which may not always be possible. When awake surgery is not feasible, IOM has a limited predictive value for outcomes beyond primary motor and somatosensory functions.[13]

To help address these challenges, noninvasive functional MRI (fMRI) has been proposed to preoperatively identify critical functional networks. Most studies reporting preoperative mapping in brain tumors exploited task-based fMRI (tb-fMRI).[14,15] Although tb-fMRI helps map specific networks like motor and language (LANG), it relies on patient cooperation in structured tasks, limiting its applicability for some patients.

Recently, resting-state fMRI (rs-fMRI) has shown promise for enhancing the clinical use of fMRI in presurgical mapping.[16,17] It offers advantages over tb-fMRI, including (1) facilitating large-scale applications in patient populations, since it does not require patients to perform specific tasks; (2) absence of specific hardware and software to deliver stimuli in the magnetic resonance scanner room; (3) ability to detect multiple functional networks within a single acquisition with methods that make no assumptions related to the hemodynamic response; and (4) exploring essential networks, like the default mode network (DMN) and frontoparietal network (FPN), not yet explored with current methods like DES mapping or tb-fMRI. Despite these advantages, there is limited information about the accuracy of rs-fMRI in mapping cortical networks, especially when using data-driven methods in comparison with invasive cortical mapping methods.

Independent component analysis (ICA) is a data-driven technique that decomposes the blood oxygenation level dependent (BOLD) signal into spatial maps and their associated time-courses, characterizing underlying independent components (ICs).[18] Only 3 previous studies used ICA to compare preoperative rs-fMRI with gold standard DES for mapping SMN,[19] LANG[20] or multiple networks including SMN, LANG, visual (VIS), and speech articulation (SAN).[21] In the study by Rosazza of 7 patients with frontal lesions, ICs were compared with 13 DES points, revealing an average distance of 8.3 ± 7.3 mm between them. Lu and colleagues examined 7 gliomas, finding that 14/23 DES points were located within the ICs maps, and 6/23 were within a 10 mm radius. Zacà and colleagues examined 4 LGGs and 2 cavernous angiomas and introduced ReStNeuMap, an open-access tool integrating rs-fMRI data preprocessing, quality control, and mapping of SMN, LANG, VIS, and SAN networks. They found that the distance between DES points and corresponding ICs was within 10 mm in 78% of cases for SMN, 100% for VIS, 87.5% for LANG, and 100% for SAN mapping.

These studies suggest a strong agreement (within a 10 mm range) between presurgical rs-fMRI maps and DES mapping. However, the sample size is a common limitation. In addition, the original version of ReStNeuMap successfully mapped networks in eloquent brain regions but overlooked other critical resting-state networks (RSNs) like DMN, FPN, and visuospatial network (VSN). In fact, a recent longitudinal study[22] highlighted that the neurocognitive profile of patients with glioma is associated with spatial features of the functional connectome, mainly within the DMN. In addition, performance in attention and executive function tests strongly predicts dynamic functional connectivity features, particularly in VSN and FPN.[23]

Within this context, this study has 2 primary aims. First, expand the validation of the functional relevance of presurgical rs-fMRI ICs maps by comparing them with awake DES data, employing a larger sample size of 28 patients with either LGGs or HGGs, and 100 DES points. Second, we intend to enhance the accessibility of ReStNeuMap as a complementary tool for the comprehension of the functional assessment at individual level. This updated public version incorporates the automatic selection of 3 additional RSNs (DMN, FPN, and VSN) in addition to the ones covered in the original version (SMN, LANG, VIS, and SAN).

METHODS

Participants

This study included 28 consecutive patients with brain gliomas (18 HGGs/10 LGGs; 24 men; age 46.2 ± 15.5 years). Table 1 and **Supplemental Digital Content 1** (http://links.lww.com/NEU/E288), provide the clinical information at the group and individual levels, respectively.

The research was conducted at the Department of Neurosurgery of the "S. Chiara" University-Hospital in Trento (Italy). The use of data was approved by the local ethical committee (authorization ID A734), and patients provided written informed consent. The study was conducted according to the ethical standards of the Declaration of Helsinki. Exclusion criteria for awake surgery included severe linguistic or executive cognitive deficits, anxiety disorders, and anesthesiologic contraindications.[13,24,25]

MRI Data Acquisition

Data were acquired with a 1.5 T GE Healthcare MRI scanner. The MRI presurgical acquisition protocol[21,22] included 3-dimensional T1-weighted (T1w) inversion recovery gradient-echo images with and without contrast-agent injection (repetition time /echo time = 10.08/4.28 ms, voxel resolution = 0.5 × 0.5 × 1 mm^3, flip angle = 12°, field of view = 264 × 264 mm^2) and 12 minutes of rs-fMRI scans acquired with a

2-dimensional T2*-weighted gradient-echo echo-planar imaging sequence (repetition time /echo time = 2600/45 ms, voxel resolution = 4 × 4 × 4.8 mm^3, flip angle = 87°, field of view = 256 × 256 mm^2, acceleration factor array coil spatial sensitivity encoding = 2, volumes = 275).

ReStNeuMap-v2 to Extract Individual Functional Maps

ReStNeuMap-v2, the upgraded version of ReStNeuMap, runs within MATLAB (The MathWorks Inc. [2022]. MATLAB version: 9.8 [pR2020a]: The MathWorks Inc. https://www.mathworks.com) and uses SPM12 (fil.ion.ucl.ac.uk/spm/software/spm12/) for MRI data preprocessing, ICA-AROMA[26] for motion artifacts removal, and MELODIC (version 3.14; fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC) for ICA. ReStNeuMap-v2 was tested on a Mac (Apple Computer Inc.; v10.11.5, 4 GHz Intel i7, 16 GB RAM at 1867 MHz) and on a DELL (Dell Inc.; Ubuntu v16.04, Intel Core i5-4590 3.3 GHz, 32 GB RAM at 1600 MHz). Figure 1 shows a schematic workflow of the new pipeline.

ReStNeuMap-v2 comprises 2 modules: the first for rs-fMRI data preprocessing and the second for extracting spatial maps of functional networks. To be easily used by clinicians, all the processing steps have been fully automated, without any further need of user's interaction when starting the pipeline after selecting the raw input MRI data. The first module includes an additional denoising step, performed with the ICA-AROMA package,[26] to remove head motion-related noise. After preprocessing, subject-level probabilistic ICA (pICA)[18] is performed to extract RSN using the FMRIB Software Library melodic function. A template matching procedure automatically selects the ICs belonging to 7 RSNs of interest: SMN, LANG, VIS, SAN, DMN, FPN, and VSN. Two functional atlases serve as reference templates for these networks,[27,28] and spatial cross-correlation (CC) is employed as a metric[29,30] to select the best IC for each target network. As a result, in addition to quality metrics output (eg, anatomical-to-functional coregistration, ICA-AROMA motion correction report, and CC values between ICs and templates), ReStNeuMap-v2 generates spatial maps of the top 3 ICs with the highest CC coefficient for each target RSN. We opted to keep 3 ICs because many networks may be split into multiple nodes during pICA. In addition, the pipeline offers an optional step for manual selection of other ICs if necessary. To verify that the amount of lesions present in a given network did not influence the method's performance, we conducted a correlation analysis between CC values and lesion amount normalized by network extension.

Awake Glioma Surgery

All patients underwent awake surgery, during which a total of 100 positive cortical sites were collected with DES (5 mm bipolar probe; 60 Hz; 1 ms; 2 to 4 mA intensity range across the series) to map motor, motor

TABLE 1. Demographic and Clinical Information of the Study Sample

Variable	Total	LGGs	HGGs
Patients	28	10	18
Sex (No. male)	24	7	17
Age (y mean, SD)	46.25 ± 15.50	41.70 ± 14.39	50.11 ± 12.36
Tumor characteristics			
Tumor lateralization (No. Left)	15	6	9
Tumor WHO grade (No. patients)	—	Grade I (0); Grade II (10)	Grade III (11); Grade IV (7)
IDH-mutation (No. patients)	12	4	8
MGMT-methylation (No. patients)	6	1	5
Tumor location (No. Frontal)	11	1	10
Tumor location (No. Fronto-insular/No. Insular)	2	—	2
Tumor location (No. Fronto-temporal)	2	—	2
Tumor location (No. Fronto-cingular)	1	1	—
Tumor location (No. Occipital)	1	1	—
Tumor location (No. Parietal)	3	1	2
Tumor location (No. Temporal)	5	4	1
Tumor location (No. Temporo-mesial)	1	1	—
Tumor location (No. Temporo-parietal)	1	—	1
Tumor location (No. SMA)	1	1	—

HGG, high-grade glioma; IDH, isocitrate dehydrogenase 1; LGG, low-grade glioma; MGMT, 06-methylguanine-DNA methyltransferase; SMA, supplementary motor area; WHO, World Health Organization.

arrest, sensorial, coordination, semantic, phonemic, anomia, VIS, and SAN cognitive functions. Patient-specific DES coordinates were grouped into 4 functional domains: SMN, LANG, VIS, and SAN (see Table 2 for all DES-related information). After intraoperative mapping, the DES coordinates were projected onto a postsurgical T1w image after gadolinium injection with the same acquisition parameters of the presurgical T1w image.

Comparison of RestNeuMap-v2 Maps With Awake Surgery Stimulation Data

To verify the spatial accuracy of the noninvasive presurgical rs-fMRI SMN, LANG, VIS, and SAN network predictions, we calculated the patient-specific distances between them and awake surgery DES points causing functional interference. This involved resampling DES into rs-fMRI space, where ICs maps were generated. For each patient, we thus computed the shortest distance of each DES point from the ReStNeuMap-v2 derived network representing the corresponding functional system: SMN vs motor, motor arrest, sensorial and coordination, LANG vs semantic and anomia, VIS vs visual, SAN vs speech articulation. The computation considered a confidence interval of 8 mm, encompassing the 5 mm distance between bipolar probe electrodes and the 3 mm average spread of stimulation current (range 2-4 mA).[31,32]

To evaluate the extent of improvement achieved by employing our patient-specific approach rather than atlases, we calculated distances between network templates and DES points.

The data analyzed in this study are available from the corresponding author on reasonable request.

RESULTS

Automatic Identification of Patients' Presurgical Functional Networks

First, we analyzed rs-fMRI data of 28 patients with glioma using ReStNeuMap-v2, obtaining the single-subject functional

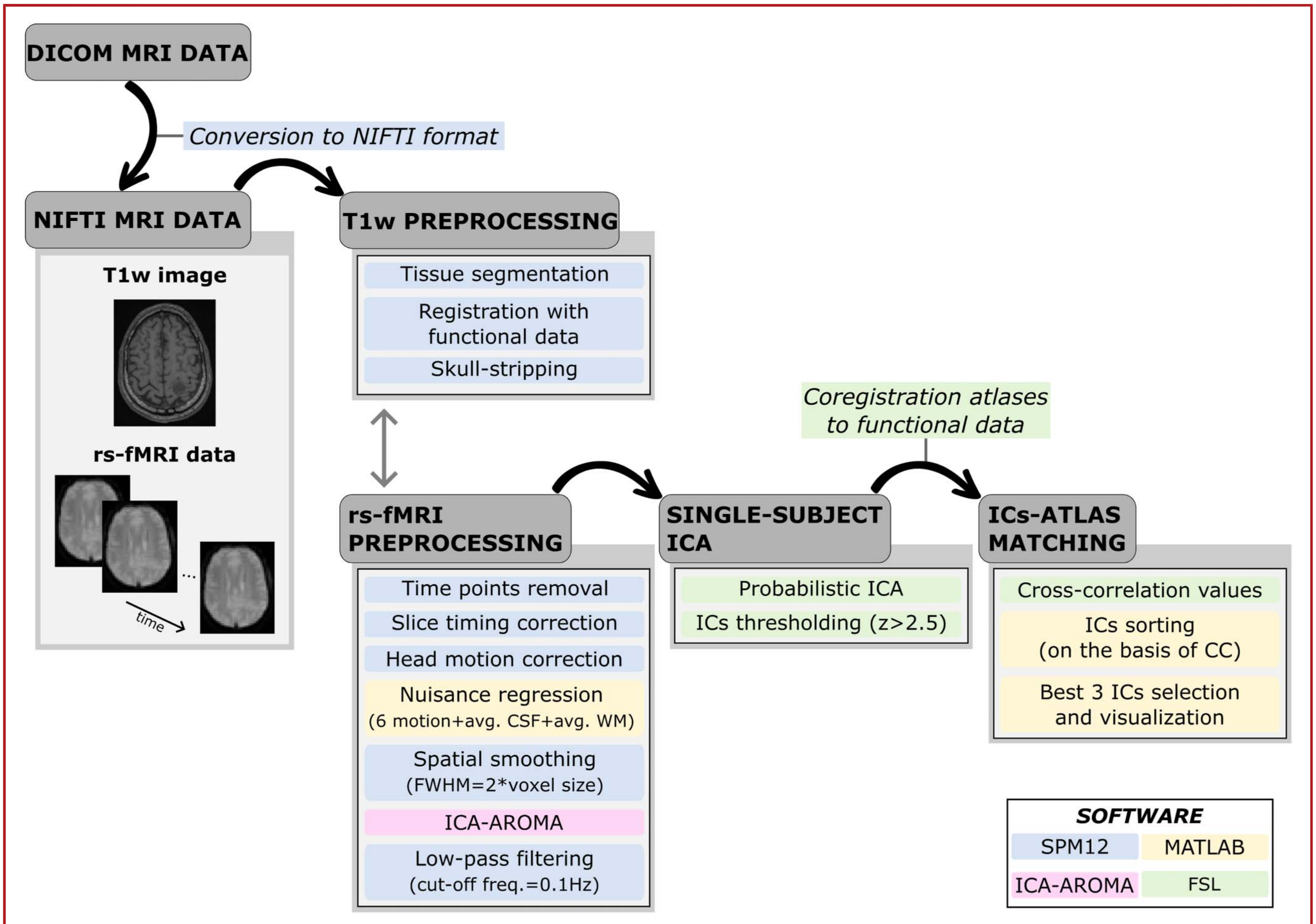

FIGURE 1. *Automated detection of target presurgical functional networks: ReStNeuMap-v2 pipeline workflow. AROMA, automatic removal of motion artifacts; avg, mean; CC, cross-correlation; CSF, cerebrospinal fluid; freq, frequency; FWHM, full width half maximum; FSL, FMRIB Software Library; ICA, independent component analysis; ICs, independent components; pICA, probabilistic ICA; MATLAB, MATrix LABoratory; NIFTI, Neuroimaging Informatics Technology Initiative; rs-fMRI, resting-state functional MRI; SPM, statistical parametric mapping; WM, white matter.*

TABLE 2. Classification of 100 DES Points Collected During Awake Surgery on the Basis of the Corresponding Cognitive Function

Function	Total	LGGs	HGGs
No. DES points	100	28	72
Sensorimotor	44	10	34
Motor	29	6	23
Motor arrest	3	2	1
Sensorial	11	1	10
Coordination	1	1	—
Language	24	9	15
Semantic	8	1	7
Anomia	16	8	8
Visual	5	—	5
Speech articulation	27	9	18

DES, direct electrical stimulation; HGG, high-grade glioma; LGG, low-grade glioma.

maps of the 3 best ICs (top1, top2, top3) for the 7 target networks (SMN, LANG, VIS, SAN, DMN, FPN, VSN).

The implemented template-matching procedure yielded median CC value across patients above 0.5 for all the 7 RSNs when considering the top1 IC (see **Supplemental Digital Content 2**, http://links.lww.com/NEU/E289). Figure 2 showcases the spatial agreement between target template networks (white) and the 3 automatically selected top ICs (red-yellow scale) with the highest CC scores for representative cases. Tumors (blue) near relevant networks are highlighted, emphasizing network reorganization and tumor proximity. Notably, each target network was consistently identifiable in at least one of the top 3 automatically selected ICs. Additional processing outputs of ReStNeuMap-v2 are detailed in **Supplemental Digital Content 3** (http://links.lww.com/NEU/E290).

The correlation analysis between the method's performance in identifying the top 3 ICs and the amount of lesion present in a given network yielded no statistically significant results.

Validation of rs-fMRI Maps: Proximity With Intraoperative DES Mapping

Figure 3 displays the distances between cortical DES points and associated functional networks derived by ReStNeuMap-v2 across 4 cognitive domains. From left to right, the panels represent the group results for the first, second, and third IC choices. For the SMN domain (N = 44 DES points), the median distance from the 3 best ICs associated with the SMN was, respectively, 0 ± 3.3 mm, 4.9 ± 9.8 mm, and 5.7 ± 5.2 mm. For LANG (N = 24), median distances were 1.6 ± 5.7 mm, 2.3 ± 6.1 mm, and 1.6 ± 5.2 mm. Visual domain (N = 5) showed median distances of 0 ± 0.3 mm, 6.4 ± 3.2 mm, and 14.2 ± 2.5 mm, and speech articulatory domain (N = 27) exhibited median distances of 0 ± 2.9 mm, 0 ± 1.5 mm, and 1.3 ± 1.5 mm. Generally, the top1 IC with the highest spatial CC had the shortest distance to the DES point in each network, whereas distances tended to increase for top2 and top3 IC selections. Spatial overlap (distance ≤ 8 mm) between DES sites and preoperative top-ranking ICs occurred in 65.9% for SMN, 41.7% for LANG, 80% for VIS, and 59.3% for speech articulatory domains. Overall, 59% of recorded DES points were within an 8 mm range from the corresponding functional network. Tables in **Supplemental Digital Content 4** (http://links.lww.com/NEU/E291), **Supplemental Digital Content 5** (http://links.lww.com/NEU/E292), and **Supplemental Digital Content 6** (http://links.lww.com/NEU/E293) provide detailed distance values at the single-subject level.

Patient-specific ICs to DES points were closer than network templates to DES points. Specifically, the median distance was 6.9 ± 7.7 mm for SMN, 10.7 ± 10.6 mm for LANG, 9.2 ± 1.5 mm for VIS, and 0 ± 2.4 mm for the speech-articulatory domain.

Figure 4 illustrates, for some representative cases, ReStNeuMap-v2's capabilities in mapping rs-fMRI networks near DES points. Each 3-dimensional brain map displays the top1 IC in red, DES sphere in green, and lesion in blue, separately for the 4 cognitive domains. Complete figures can be found in **Supplemental Digital Content 7** (http://links.lww.com/NEU/E294), **Supplemental Digital Content 8** (http://links.lww.com/NEU/E295), and **Supplemental Digital Content 9** (http://links.lww.com/NEU/E296).

DISCUSSION

Automated neuroimaging holds promise for enhancing both patient outcomes and the overall efficiency of brain tumor resection and subsequent treatments, particularly when validated against DES mapping data. The study compares preoperative rs-fMRI with intraoperative cortical DES outcomes in 28 patients diagnosed with LGGs or HGGs. Our main finding is that considering 100 DES points, the mean distance was within 5 mm between presurgical and cortical mapping of eloquent areas.

Automatic Estimation of Resting-State Networks at the Single-Subject Level

The first step in our study consisted in deriving individual presurgical RSNs of the main cognitive functions assessed during awake surgery with DES. Existing tools for this process (eg, MELODIC: http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC, GIFT: http://mialab.mrn.org/software/gift, etc.) typically require high expertise to integrate signal denoising, ICs selection, and quality assurance, not always available in clinical settings. The first version of ReStNeuMap[21] addressed this by offering an easy-to-use pipeline that automatically generates spatial maps of RSNs from raw Digital Imaging and Communications in Medicine

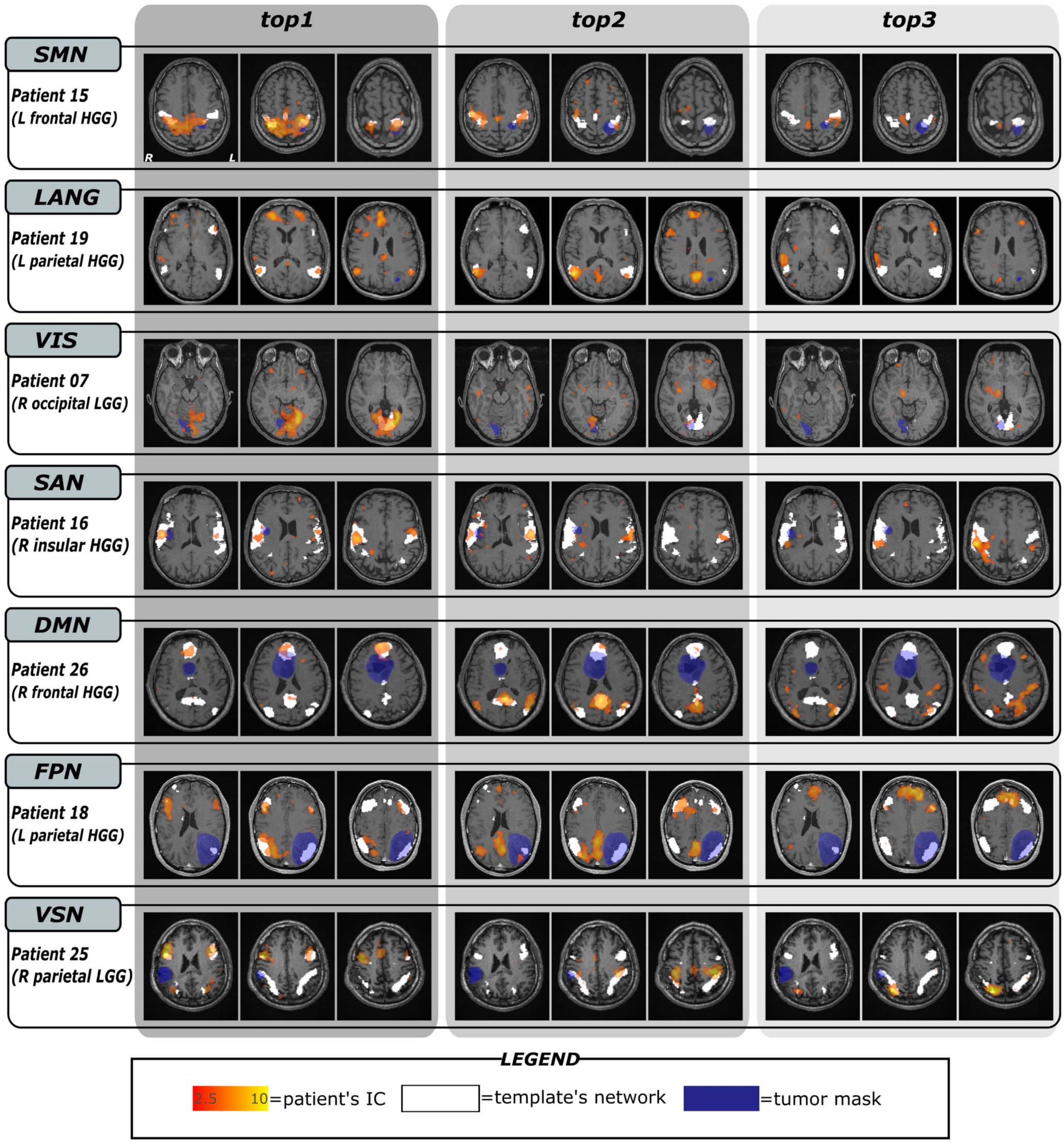

FIGURE 2. *Patients' presurgical functional networks maps: top 3 candidates. For some example patients, whose IDs are indicated on the left, the figure depicts, for each of the 7 templates' target networks shown in white (SMN, LANG, VIS, SAN, DMN, FPN, VSN) in each row, the 3 best resting-state independent components automatically chosen by the ReStNeuMap tool (top1, top2, top3). These components are presented in each column using a red-yellow scale, with z-score values ranging from 2.5 to 10. The tumor mask is colored in blue. DMN, default mode network; FPN, frontoparietal network; HGG, high-grade glioma; IC, independent component; LANG, language; LGG, low-grade glioma; SAN, speech articulation; SMN, sensorimotor; VIS, visual; VSN, visuospatial network.*

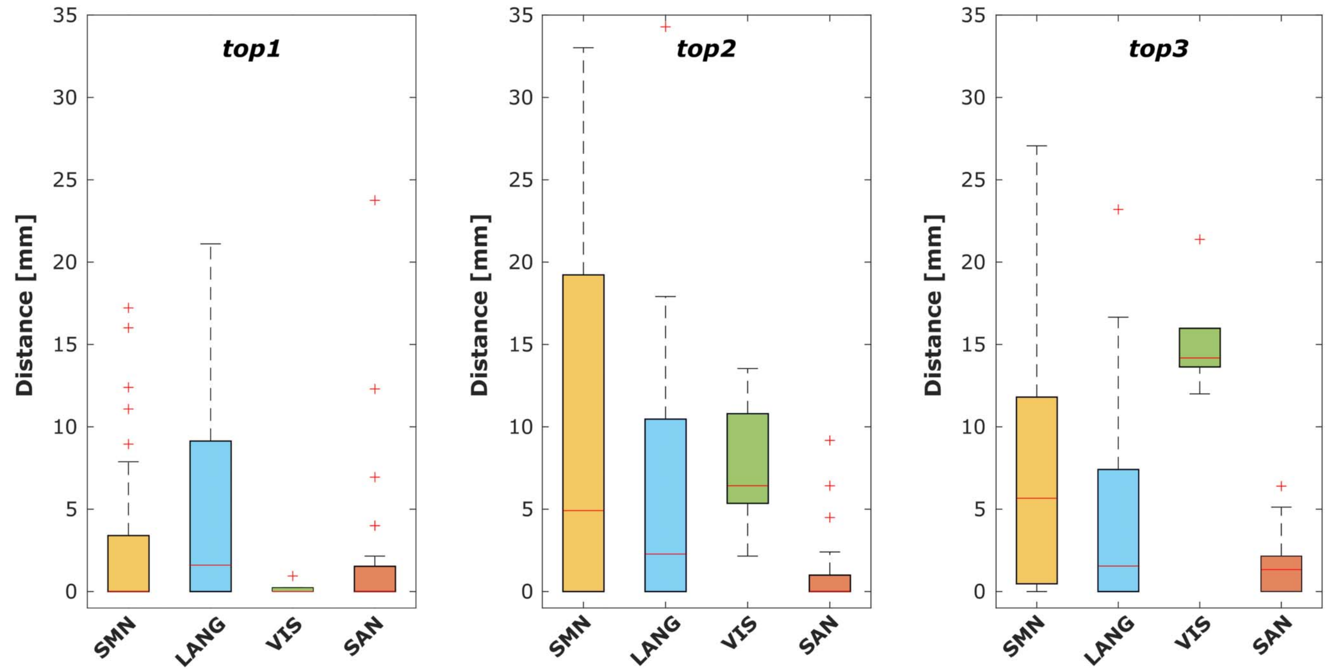

FIGURE 3. *Distance between intraoperative DES points and automatically defined presurgical resting-state functional MRI networks. Closest distance (mm) between each DES point and the relevant functional network for each one of the 3 automatically selected independent components (top1, top2, top3). It can be seen how the distances are shortest for the first component. On each box, the central red horizontal line indicates the median. DES, direct electrical stimulation; LANG, language; SAN, speech articulation; SMN, sensorimotor; VIS, visual.*

MRI data in approximately 60 minutes. The tool has been further developed to offer several improvements, including (1) validation in a larger and diverse cohort of glioma patients; (2) incorporation of ICA-AROMA for improved denoising; (3) extension to include 7 functional networks (SMN, LANG, VIS, SAN, and DMN, FPN, VSN); (4) automatic validation of ICs through a template-matching procedure; and (5) spatial comparison of 4 of 7 networks with gold standard cortical DES sites.

This study demonstrates ReStNeuMap-v2's effectiveness in automatically identifying target RSNs in all 28 patients, even in cases where the previous version failed, as demonstrated in **Supplemental Digital Content 10** (http://links.lww.com/NEU/E297). This indicates that incorporating ICA-AROMA improves network identifiability, as previously demonstrated in a previous study,[33] and CC proves to be a reliable metric for selecting the best IC for each target network. Indeed, the median CC values across patients exceeded 0.5 in all the 7 RSNs (as shown in **Supplemental Digital Content 2**, http://links.lww.com/NEU/E289). Notably, the VIS network was particularly well-identified (median CC = 0.87), likely due to the absence of occipital lesions in our data set and the fact that this network is the only one not divided into multiple nodes, making the identification of the matching IC more reliable.

For the clinical perspective of quality assurance of the automatically defined networks, the tool provides not only the patient-specific best-matching IC (top1) for each target network but also offers 2 alternative choices (top2, top3). This feature is valuable for presurgical planning, especially when the top1 IC only partially aligns with the network of interest (eg, Figure 2, patients 16, 19 and 26) or when artifacts may be present (eg, Figure 2 patient 15).

Correspondence Between Presurgical Resting-State Networks and Cortical Direct Electric Stimulation

The study aimed to evaluate the proximity between automatically defined RSNs and corresponding cortical DES points. After obtaining individual functional maps, it is crucial to ensure their specificity, as fMRI using the BOLD contrast is an indirect measure of neural activity, particularly at low fields such as 1.5 T.[34] The mean distance of all 100 recorded DES points from the ReStNeuMap-v2's top1 IC was less than the distance between the electrodes of the stimulation probe of 5 mm: 2.4 ± 4.5 mm for SMN, 5 ± 6.8 mm for LANG, 0.2 ± 0.4 mm for VIS, and 2.1 ± 5.1 mm for SAN. Language function showed the highest distances, a result consistent with previous task-based[35-37] and rs-fMRI studies,[38] which suggested that fMRI mapping is less effective for LANG. Furthermore, previous studies[39,40] showed greater functional connectivity variability within associative regions (eg, LANG, executive, and attention nodes) compared with unimodal regions (eg, VIS and SMN nodes). This may explain

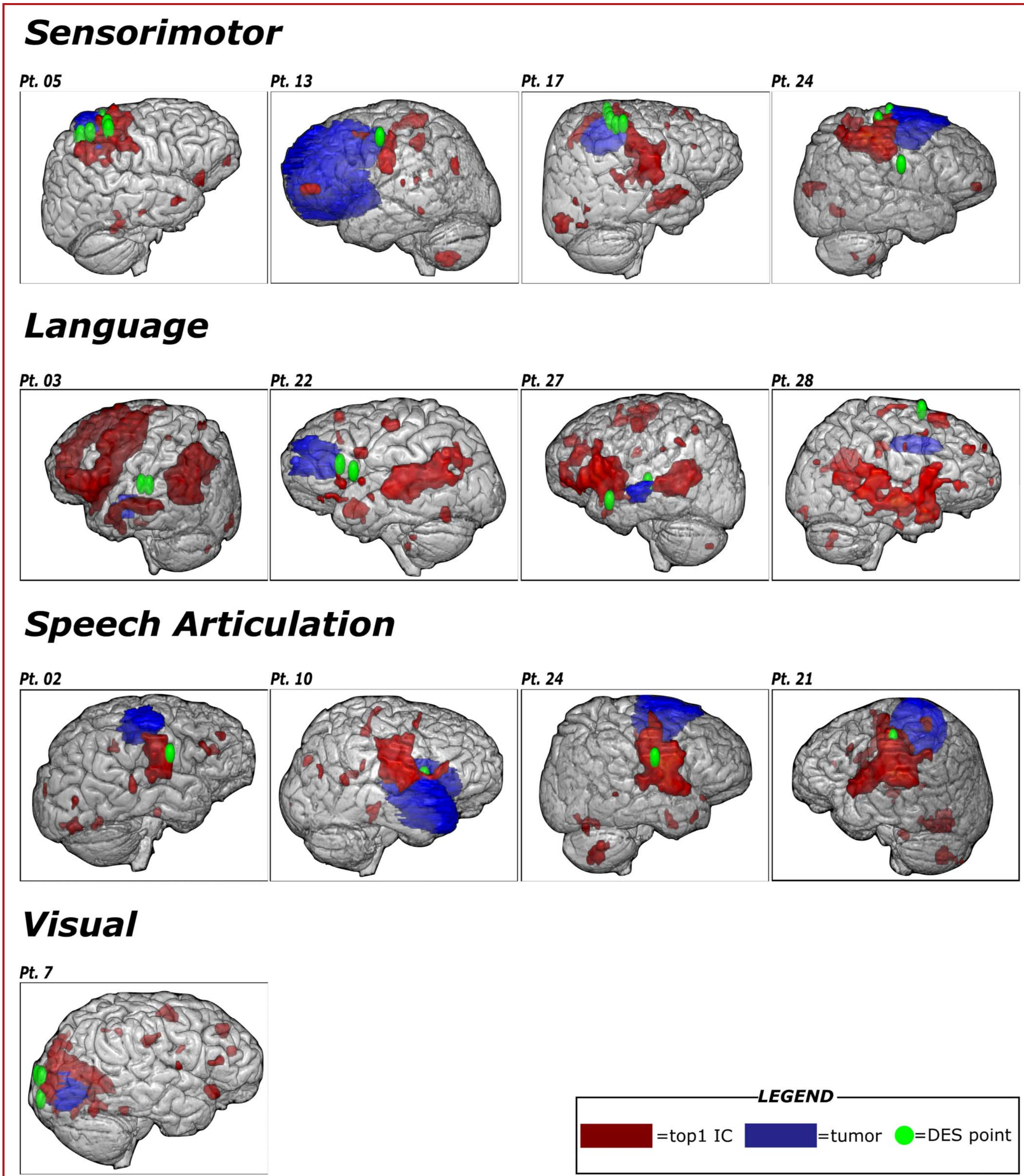

FIGURE 4. *Spatial proximity between DES recordings and presurgical resting-state functional MRI networks. Each brain view displays a 3D representation of the single-subject T1w image in gray with the best-matching IC (top1) overlaid in red, the DES sphere in green, and the tumoral lesion in blue, for some representative cases. DES, direct electrical stimulation; IC, independent component.*

why LANG mapping seemed less robust than mapping of the unimodal cortex. Nonetheless, these shorter distances compared with those between DES points and network templates highlight the improvement gained from our patient-specific approach over predefined rs-fMRI atlases from healthy subjects.

Although awake surgery with DES remains the gold standard for tumor resection, balancing EOR and cognitive outcomes, our results underscore the high sensitivity and value of intrinsic functional mapping. These rs-fMRI maps, while less specific than DES, offer valuable indications on the localization of specific functional networks, with an unprecedented precision of 5 mm range, compared with other mapping techniques.

Added Value of Resting-State Functional Mapping

Presurgical rs-fMRI data hold significant value in several clinical contexts. First, it can expedite functional mapping in cases planned to undergo DES during awake surgery by providing insights into functional reorganization in regions surrounding the lesion. This also reduces the induced current and the risk of epileptic seizures. Second, it serves as a crucial guide for preoperative planning in patients undergoing IOM during asleep surgery. This is particularly critical for adults not candidates to awake surgery or pediatric patients. Last, it provides crucial information, like linguistic dominance, particularly important for left-handed patients.

Rs-fMRI provides a unique opportunity to automatically map essential higher cognitive networks (DMN, FPN, VSN) that would otherwise be challenging to monitor in the operating room or preoperative settings using alternative techniques like transcranial magnetic stimulation. These networks significantly affect patients' quality of life and contribute to both presurgical[23,41] and longitudinal[22,42] neurocognitive outcomes in patients with glioma.

In a broader perspective, these functional maps can enhance the planning of future treatments, particularly radiotherapy or proton beam therapies, focusing on crucial networks like the FPN and DMN. Moreover, they can be leveraged to explore functional plasticity changes over treatments and follow-ups, aiding in prognosis and treatment evaluation along with cognitive recovery.

Limitations

ReStNeuMap-v2 has some limitations and areas for improvements. The current 1.5 T fMRI protocol does not include data for correcting static field inhomogeneity,[43,44] which can affect anatomic-functional data coregistration. Correcting such distortions, especially at higher magnetic fields (≥3 T), can enhance RSNs[45] detection. Despite this, our clinical protocol aligns with similar studies[46,47] where distortion correction was not performed. While minor geometric distortions were observed, functional-structural coregistrations were deemed acceptable (see **Supplemental Digital Content 11**, http://links.lww.com/NEU/E298). Notably, the comparison between presurgical functional maps and cortical mapping solely used our 1.5 T fMRI data. Future studies should extend and validate ReStNeuMap-v2 across larger samples, different MRI vendors, and higher field strengths, with appropriate preprocessing adaptations. Finally, our study does not determine whether presurgical rs-fMRI network mapping improves glioma resection outcomes. This necessitates a large-scale study, employing a 2 × 2 design (rs-fMRI presence/absence, awake/nonawake surgery). We hypothesize rs-fMRI enhances outcomes, particularly when awake DES mapping is impractical, similar to prior tb-fMRI vs DES evaluations.[48]

CONCLUSION

Our study affirms a strong alignment between rs-fMRI maps of key intrinsic networks (SMN, LANG, VIS, SAN) and DES mapping in both LGGs and HGGs. ReStNeuMap-v2 demonstrated high sensitivity in detecting functional networks in all cases, making it a valuable complementary preoperative tool, particularly for patients ineligible for awake surgery. It also offers the unique opportunity to extract fundamental networks like DMN, FPN, and VSN, which may not be otherwise mappable. With its flexibility, ReStNeuMap-v2 can provide comprehensive insights into whole-brain plasticity changes over follow-up. The availability of ReStNeuMap-v2, which is freely accessible at: https://github.com/CIMeC-MRI-Lab/ReStNeuMap, is expected to facilitate broader standardized utilization and assessment of rs-fMRI mapping in various clinical applications, including presurgical planning for gliomas, radiotherapy, stroke treatment, rehabilitation, neuromodulation, epilepsy, and more.

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Disclosures

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Supplemental Digital Content 1. **Table**. Demographic and clinical information of each patient. Abbreviations: F = female; M = male; TM = tumor; L = left; R = right; SMA = supplementary motor area; IDH = isocitrate dehydrogenase 1.

Supplemental Digital Content 2. **Figure**. Cross-correlation values between functional network templates (color coded differently) and the best 3 automatically selected ICs by ReStNeuMap-v2 (top1, top2, top3). On each box, the central black horizontal line indicates the median. The most identifiable network is the visual network (top1's cross-correlation median value = 0.87).

Supplemental Digital Content 3. **Table**. The table reports, for each patient: (1) the percentage of head motion-related components over the total components identified by ICA-AROMA (2nd column); (2) the number of ICs identified automatically by probabilistic ICA (3rd column); (3) the cross-correlation values of the best three ICs, for each RSN (4th-10th column).

Supplemental Digital Content 4. **Table**. For each patient and separately for each DES functional domain (sensorimotor, language, visual, speech articulation), the table reports the number of DES collected for that domain (#DES), the mean, and standard deviation of the distances between DES points and the corresponding best IC.

Supplemental Digital Content 5. **Table**. For each patient and separately for each DES functional domain (sensorimotor, language, visual, speech articulation), the table reports the number of DES collected for that domain (#DES), the mean, and standard deviation of the distances between DES points and the corresponding 2nd best IC.

Supplemental Digital Content 6. **Table**. For each patient and separately for each DES functional domain (sensorimotor, language, visual, speech articulation), the table reports the number of DES collected for that domain (#DES), the mean, and standard deviation of the distances between DES points and the corresponding 3rd best IC.

Supplemental Digital Content 7. **Figure**. Spatial proximity between sensorimotor DES recordings and presurgical rs-fMRI networks. Each brain view displays a 3D representation of the single-subject T1w image in gray with the best-matching IC (top1) overlaid in red, the DES sphere in green, and the tumoral lesion in blue.

Supplemental Digital Content 8. **Figure**. Spatial proximity between language/visual DES recordings and presurgical rs-fMRI networks. Each brain view displays a 3D representation of the single-subject T1w image in gray with the best-matching IC (top1) overlaid in red, the DES sphere in green, and the tumoral lesion in blue.

Supplemental Digital Content 9. **Figure**. Spatial proximity between speech articulatory DES recordings and presurgical rs-fMRI networks. Each brain view displays a 3D representation of the single-subject T1w image in gray with the best-matching IC (top1) overlaid in red, the DES sphere in green, and the tumoral lesion in blue.

Supplemental Digital Content 10. **Figure**. The 2 panels report, for 2 different patients, the resting-state networks of SMN, LANG, VIS, and SAN automatically identified by the first version of ReStNeuMap with Goodness-of-Fit (second row) and by ReStNeuMap-v2 with cross correlation (third row). In the first case, the original ReStNeuMap version could automatically select two ICs which were poorly related to the target networks. Such findings were not observed in the patient sample studied with ReStNeuMap-v2. The second example shows a patient where both the original and new pipelines find suitable network components with respect to the target ones. The green ticks indicate visual agreement between the target network (first row) and the automatically identified networks of the different versions. Red tickets indicate disagreements.

Supplemental Digital Content 11. **Figure**. Each panel reports, for four example patients, the sagittal views of preprocessed mean rs-fMRI scan (gray-scale image) aligned with the anatomic T1w image, with boundaries depicted as red dots. These views also reveal minor geometric distortions induced by the static magnetic field, particularly in frontal and temporal regions.