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Rest-fMRI—A Potential Substitute for Task-fMRI?

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Abstract

Objective The aim of this study was to assess the reliability of resting-state functional magnetic resonance imaging (rest-fMRI) in mapping language areas for preoperative planning, versus standard task-based techniques, which are at times difficult to perform in clinical settings. Our study also aimed to evaluate the overlap between language areas identified through rest-fMRI and the standard task-fMRI, in neurosurgical cases.

Materials and Methods Using a seed-based analysis of rest-fMRI with multiple template seeds, we identified functionally connected language regions in patients undergoing preoperative language mapping. Four language task paradigms (word, verb, picture, and semantics) were evaluated. We quantified the degree of overlap between language areas identified on rest-fMRI and task-fMRI, categorizing the results as more than 50% or less than 50% overlap.

Results Seventy-seven percent of patients demonstrated an overlap exceeding 50% between rest- and task-fMRI maps, with the left Broca's area being the most frequently observed region of overlap. This finding was noted even in cases with lesions in Broca's or Wernicke's areas, highlighting the method's robustness. The verb task showed the best blood-oxygen-level dependent activity and overlap with rest-fMRI, highlighting its reliability. To identify a specific language area, the contralateral seed of the same area most commonly displayed connectivity with the area of interest.

Conclusion Our findings demonstrate the potential of using rest-fMRI in accurately mapping eloquent language areas, in clinical settings The strong concordance observed, especially in the left Broca's area, underscores the reliability of this method. Further research and larger studies are essential to validate these results, potentially establishing the use of routine rest-fMRI, in clinical preoperative workup.

Keywords
- resting-state functional MRI
- magnetic resonance imaging
- neurosurgical cases
- task-fMRI

Introduction

Task-functional magnetic resonance imaging (fMRI) is routinely utilized for surgical planning near eloquent brain areas, but demands patient cooperation, posing challenges for children, cognitively impaired individuals, and anxious preoperative patients.

Resting-state functional MRI (rest-fMRI) is an emerging alternative, capturing spontaneous brain activity without tasks, saving time,[1] and has shown good concordance with task-fMRI for motor area mapping.[2,3] However, its reliability for language mapping in clinical settings is still the subject of an ongoing research.

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Our study assesses language mapping overlap accuracy between rest and task-fMRI in preoperative neurosurgical evaluation, exploring the potential for rest-fMRI to substitute task-fMRI as a preoperative tool.

Materials and Methods

Participants: Twenty-two patients ($n = 22$), between the age group of 9 to 65 years (M: F = 13: 9), underwent language task-fMRI (as requested by the referring surgeon), as a part of preoperative planning along with diffusion tensor imaging and routine brain sequences, to which we added a rest-fMRI sequence. As a part of the standard MR protocol, valid informed consent for MRI was obtained in all cases.

Only patients with intracranial lesions were included in our study. Patients who were claustrophobic and with MRI-incompatible devices (metallic implants, pacemakers, etc.) were excluded from the study.

fMRI Data Acquisition

The MRIs were performed on 3.0T Philips Ingenia, using a 32-channel head coil. Participants were thoroughly briefed on individual task paradigms before undergoing MRI. The language assessment tasks included word generation from a displayed alphabet, verb generation from a word, picture-to-verb generation (where a picture prompted thinking of an associated verb), and semantic tasks involving food or rhyming word identification using a response pad (yes/no). Each task involved a 30-second rest period with a fixation on + or #, followed by a 30-second task paradigm.

The MRI protocol began with task-blood-oxygen-level dependent (BOLD) fMRI following a localizer.

Rest-fMRI BOLD sequences were conducted next, where patients were instructed to keep their eyes closed and remain still. The rest-fMRI sequence utilized BOLD/echo-planar images covering the entire brain. The parameters included 250 dynamics, TR (repetition time) of 3,000 milliseconds, TE (echo time) of 35 milliseconds, FOV (field of view) of $220 \times 220 \times 152$ mm, slice thickness of 4 mm, matrix of 72×96 voxels, and voxel size of $3 \times 3 \times 4$ mm with a scan time of 9 minutes.

A three-dimensional T1-weighted turbo field echo sequence was performed as the base sequence, with parameters: FOV $250 \times 250 \times 181$ mm, TR/TE 7.4/3.4 milliseconds, voxel size $1.1 \times 1.1 \times 1.2$ mm, slice gap -0.6 mm, and a scan time of 5 minutes.

Processing

Both task- and rest-fMRI data were processed using the Food and Drug Administration (FDA)-approved Brainance MD software suite, a cloud-based tool developed by Advantis Medical Imaging in Eindhoven, The Netherlands. This comprehensive software analyzes clinically significant networks and is automated, ensuring accuracy and efficiency. This software automates the preprocessing for both task- and rest-fMRI, sequentially performing motion correction, optional slice timing correction, and spatial smoothing. Specifically for rest-fMRI, it also conducts nuisance variable removal and temporal filtering, The software automatically carries out these initial steps, preparing the data for further analysis.

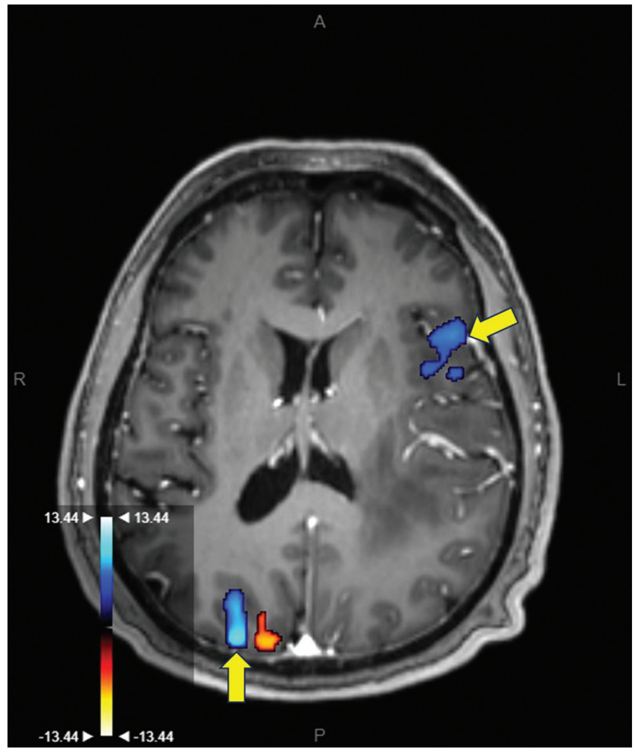

Fig. 1 Task-functional magnetic resonance imaging in a left Wernicke's area lesion case, using verb generation paradigm. Blue is a blood-oxygen-level dependent activity in left Broca's area. The visual cortex on the right (yellow arrow) is normally visible. Adjacent orange color indicates noise. No activity was observed in the right Broca's or bilateral Wernicke's area.

Our methodology was as follows:

Each task paradigm was individually processed.

In both task- and rest-fMRI, the threshold value was initially kept at the most optimum level to get the best BOLD activity. The overlap was only done post that. The thresholds used were based on Z scores which Brainance MD software provides, which in our case translates to the following p-values in rest-fMRI ranged: 0.344578 to 0.158655 and in task-fMRI: 0.00621–0.

On task-fMRI, traditionally, language areas are identified by localizing Broca's and Wernicke's areas based on previous studies.[4,5] Thereafter, BOLD activity detected in the inferior frontal gyrus on either side was considered likely Broca's area, while activity within the superior temporal gyrus and angular gyrus was interpreted as Wernicke's area (►**Fig. 1**).

1. Rest-fMRI was processed using the seed-voxel technique. This method has been found to be easy to understand and compute.[6] A "seed" is a specific area in the brain that is thought to be involved in the neural pathway under study. In the seed-based technique for language, the seed is either Broca's or Wernicke's area and on the placement of a seed, functionally connected areas in the contralateral hemisphere, as well as in the ipsilateral hemisphere, can be assessed (►**Fig. 2**).

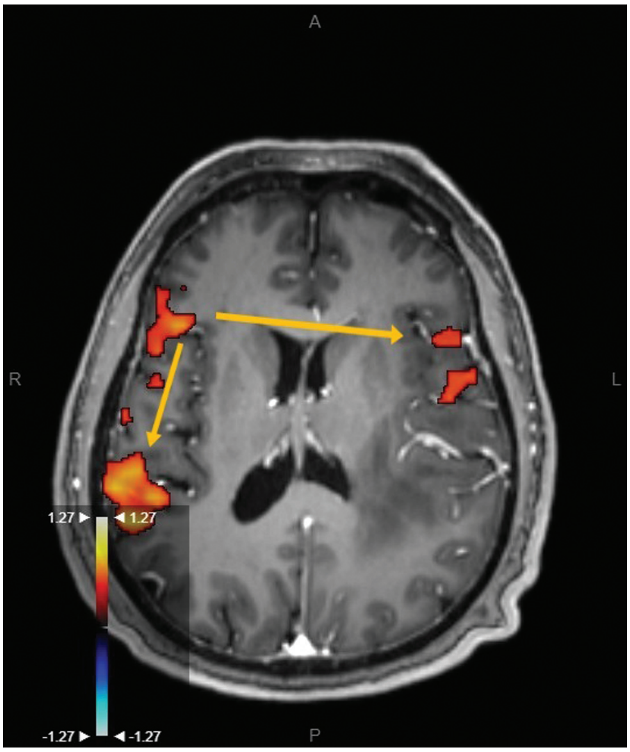

Fig. 2 Resting-state functional magnetic resonance imaging acquisition, in the same patient, using the right Broca's seed in orange, with resultant activity in left Broca's and right Wernicke's area (in orange) shown by yellow arrows.

The software uses the MNI (Montreal Neurological Institute) template to determine the seeds that represent Broca's and Wernicke's areas for individual patients. The MNI template is a standard brain atlas that is created from three-dimensional MRI images of many individuals. It offers a common coordinate system that helps to identify different regions of the brain.[7]

The T1 of each subject is coregistered with the MNI template. An affine matrix is created that is used to transform back to the subject's (T1) space, the coordinates of the center of each seed region. These coordinates are transferred to the rest-fMRI's space, which is coregistered with the T1's space. The coordinates are then used as centers to create seed regions by forming spheres with a specific diameter. Ultimately, the seed region for each correlation map is determined by MNI coordinates, with the entire process being automated.

The Brainance MD software provides four standard seeds, namely right inferior frontal gyrus/right Broca's, left inferior frontal gyrus or left Broca's, right superior temporal gyrus/right Wernicke's, and left superior temporal gyrus or left Wernicke's area.

2. Both maps, that is, rest-fMRI map obtained using language-seeds and the task-fMRI maps were then overlapped. The degree of overlap was assessed using a two-point grading: more than 50% and less than 50% (►**Fig. 3A–C**).

Two experienced readers, each with over 20 years of MRI interpretation experience, independently evaluated the degree of image overlap by meticulously examining the images across all three planes. This assessment was subsequently analyzed through an interobserver agreement calculation to ensure accuracy and consistency.

The aforementioned process was replicated for all other language areas utilizing the four standard seeds, and their overlap with task-fMRI was meticulously evaluated.

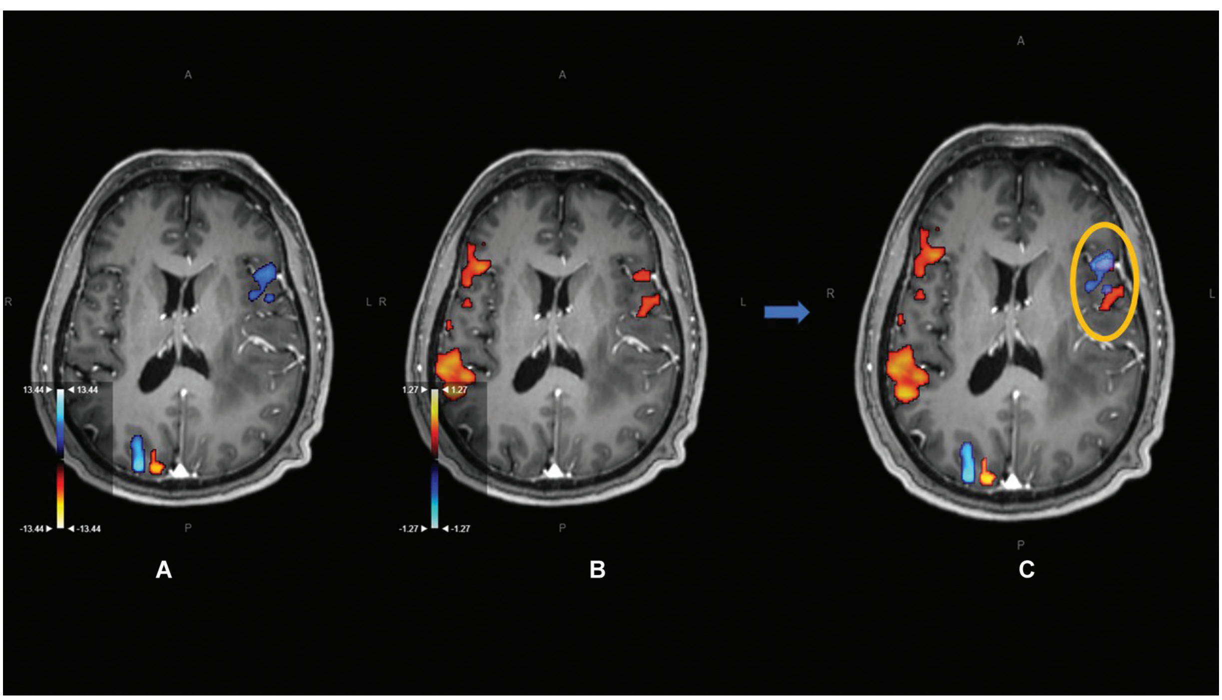

Fig. 3 On overlap of Task (**A**), in blue and rs-fMRI map using right Broca's seed (**B**) in orange more than 50% overlap observed in left Broca's area (yellow circle) in (**C**). Left Wernicke's area showed no BOLD activity on rest as well as on task. Right Wernicke's area was not seen on task but noted on rs-fMRI.

Table 1 The various lesions included in our study

Lesion	Number of patients ($n = 22$)	Percentage (%)
Glioma	8	36
AVM	4	18
Gliosis	3	14
Cavernoma	3	14
Meningioma	2	9
Primary CNS lymphoma	1	4.5
Mesial temporal sclerosis	1	4.5

Abbreviations: AVM, arteriovenous malformation; CNS, central nervous system.

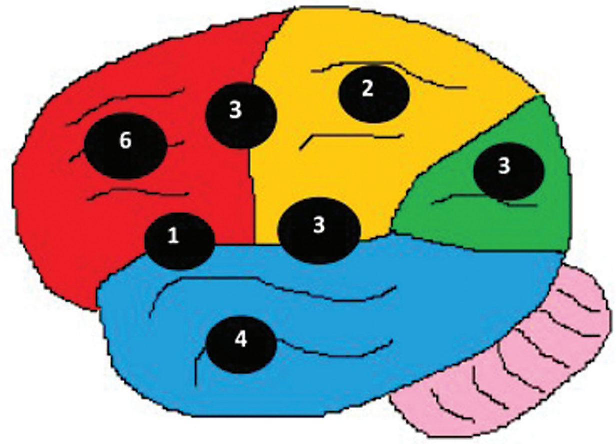

Fig. 4 Specific distribution of lesions in our study, in various lobes of the brain.

We documented which seed displayed the overlap and noted the task paradigm that best correlated with the findings on rest-fMRI.

Results

In our study group of 22 patients, five were children, ranging in age from 9 to 13 years old. Notably, none of these pediatric patients required sedation during the MRI sessions. Twenty out of the 22 patients were right-handed.

The study encompassed a diverse range of intracranial lesions, including gliomas of various grades, arteriovenous malformations, cavernomas, meningiomas, perinatal hypoxic lesions, mesial temporal sclerosis, and central nervous system lymphomas (►**Table 1**).

Distribution is as given below:

Lesions were found across multiple brain lobes, including the frontal, parietal, temporal, and occipital lobes. The specific distribution is detailed in ►**Table 2** and illustrated in ►**Fig. 4**, showcasing the varied locations of the lesions within the brain lobes.

During task-fMRI, language activity was most commonly seen in the left Broca's area.

In rest-fMRI, the left Broca's area (which was the most seen area of BOLD activity on task-fMRI) exhibited the most frequent overlap (91%; ►**Table 3**). A total of 17 patients showed language areas with >50% overlap in areas on rest and task fMRI (►**Table 4**).

Table 2 Distribution of lesions in different lobes of the brain in our study

Location	Number of patients ($n = 22$)
Frontal	6
Frontoparietal	3
Frontotemporal	1
Parietal	2
Parietotemporal	3
Temporal	4
Occipital	3

A total of 40 areas showed overlap between rest and task fMRI, and each overlap was individually assessed. Two independent radiologists assessed the degree of overlap, and interobserver agreement was calculated. This demonstrates a high level of concordance (with a concordance percentage over 90%) and significant agreement (indicated by a Weighted Kappa value greater than 0.7) between the two observers (►**Table 5**).

The language area of interest was predominantly activated using the contralateral seed (►**Table 6**).

Among the task paradigms, the verb task exhibited the highest degree of overlap with resting state results (►**Table 7**).

Discussion

fMRI using task-based language mapping remains the predominant noninvasive technique for the preoperative localization of the eloquent cortex, including the language areas. However, rest-fMRI is gaining popularity and acceptance, with increasing support in the literature, as it is much easier to obtain, and does not require patients to perform any explicit task.

Our study aimed to explore whether language areas identified individually on rest-fMRI overlapped with those on task-based mapping, suggesting concordance between the two language maps, in clinical presurgical settings. Numerous studies have demonstrated a strong correlation between rest- and task-fMRI in the motor cortex, as evidenced by research conducted by Kokkonen et al,[3] Zhang et al,[8] and Rosazza et al.[9] However, research on the same for language mapping has been limited.

We specifically focused on patients in preoperative neurosurgical settings who had brain pathologies and were undergoing language fMRI due to lesions proximate to or affecting the eloquent cortex. The objective was to evaluate whether rest-fMRI could pinpoint language areas in a manner comparable to task-fMRI assessments. We used a commercially available FDA-approved software for processing fMRI, to understand its applicability in routine clinical settings.

Our study yielded three key findings.

A) First, we utilized the seed-based technique for processing the rest-fMRI data, a method that proved to be straightforward and computationally easy. Interestingly, we observed that to identify a specific language area, for example, left Broca's, the contralateral seed (i.e., the right Broca's) most commonly displayed connectivity with the area of interest (in 14 of 22 patients).
B) Second, and more importantly, we found that in all patients, there was a certain degree of overlap between language areas identified during rest-fMRI and task-fMRI. Visually determined, 77% of patients displayed more than 50% overlap in these areas.
C) Additionally, among various task-fMRI paradigms, the language area was best identified during the verb generation task. This same area exhibited the highest degree of overlap with those identified during rest-fMRI.

The seed-based analysis, an early method for processing rest-fMRI, continues to be globally utilized. In our study, we employed all template seeds in both hemispheres to identify functionally connected language areas. The activation in the contralateral hemisphere was most significant and displayed the best overlap. This approach likely explained why the exact contralateral seed consistently elicited the language area under investigation, given its similar or identical anatomical location. It is difficult to determine the exact reason why the contralateral expressive Broca seed displayed a stronger connection compared with the receptive Wernicke's seed. One possible explanation could be due to the naturally strong connections between areas that serve similar functions. However, this hypothesis requires further research and understanding to be confirmed.

This technique was also found to be quite robust. Among the six patients in our study with lesions appearing to involve Broca's or Wernicke's area, two displayed no signal in the eloquent cortex during task paradigms. On rest-fMRI, the contralateral seed also exhibited no connectivity in the affected cortex, indicating its similarity to conventional task-fMRI (►**Fig. 5**).

Impaired BOLD activity is known in the eloquent cortex in the vicinity of brain tumors or other focal brain lesions, due to the disruption of coupling between neuronal activity and adjacent microvasculature, known as "neurovascular uncoupling," causing altered/decreased BOLD responses in both rest and task-fMRI.[10] Notably, in the four patients where task-fMRI identified language areas close to the lesion, rest-fMRI identified similar areas that overlapped with the task-based results. These areas were also found to be at a comparable distance from the pathology as determined in the task paradigms (►**Fig. 6**).

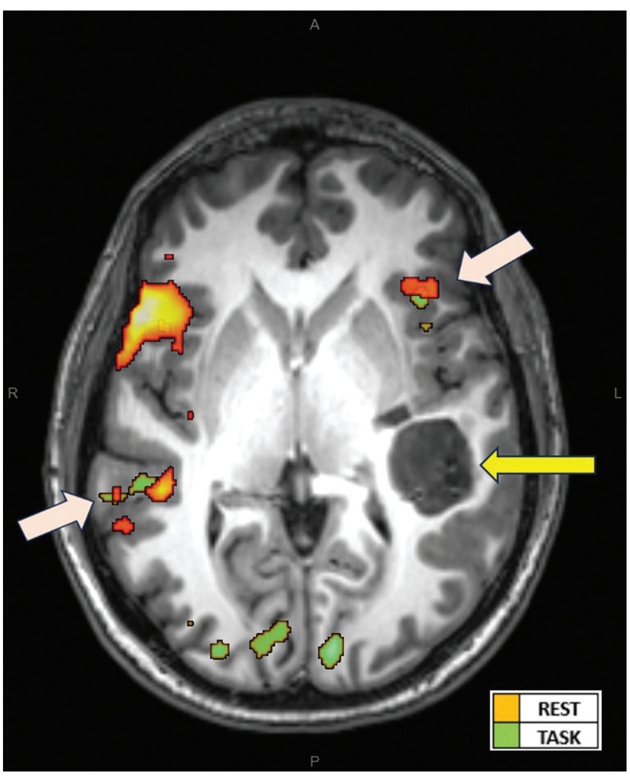

Fig. 5 MRI showing tumor, likely in the region of left Wernicke's (yellow arrow).BOLD activity on task shown in green and rs-fMRI activity generated using Right Broca's seed, shown in orange. >50% overlap noted in Left Broca's and Right Wernicke's areas (pink arrows).

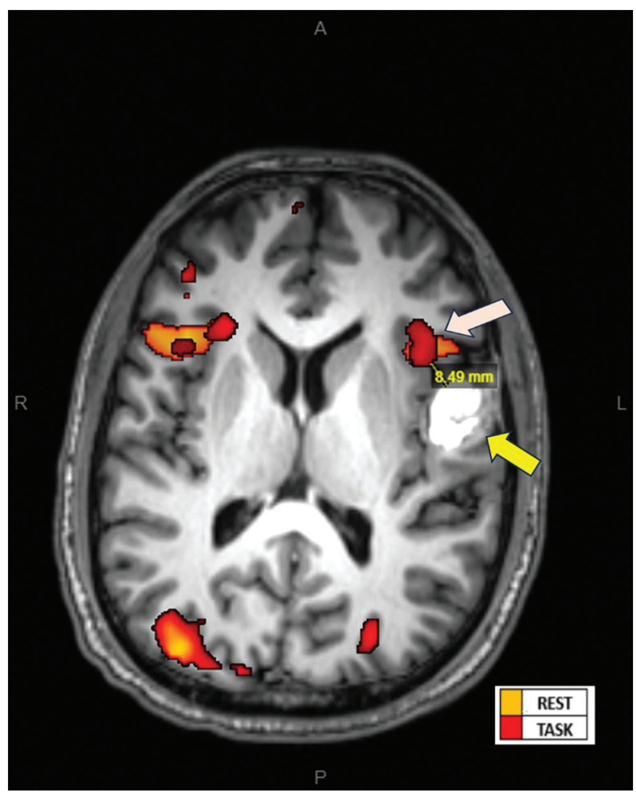

Fig. 6 Resting-state functional magnetic resonance imaging (rest-fMRI) map using right Broca's seed; task-word generation. Cavernoma was seen posterior to the left Broca's area (yellow arrow). More than 50% overlap was observed between rest and task areas, equidistant from the tumor as noted on task-fMRI (pink arrow).

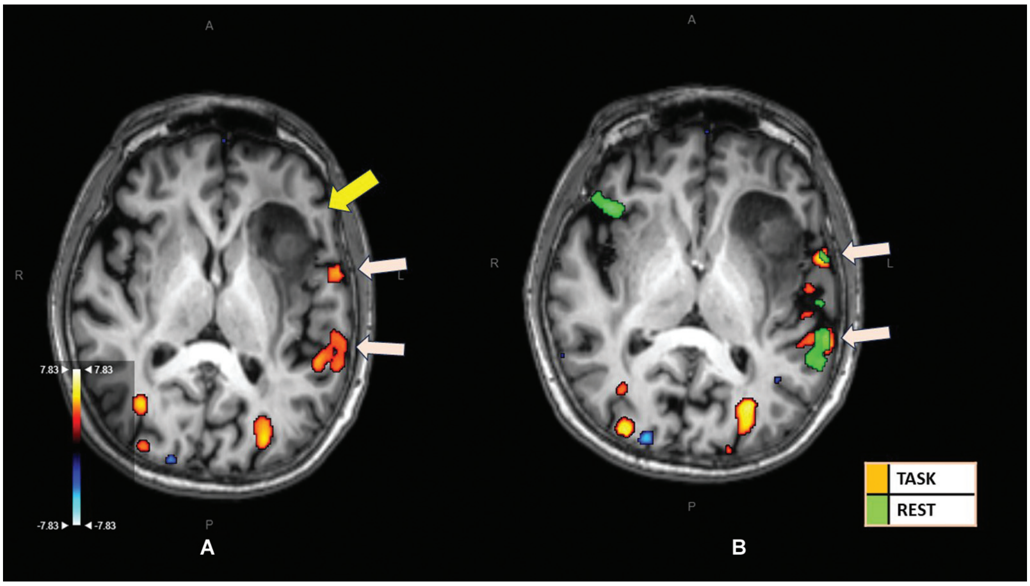

Fig. 7 (**A**) Lesion observed in the left Broca's area (yellow arrow). On the task-based examination, both the left Broca's and left Wernicke's areas were identified, located posterior to the lesion, highlighted by pink arrows. (**B**) During resting-state functional magnetic resonance imaging (rest-fMRI) analysis, outcomes from the right Broca's seed were overlapped onto the task map, with color codes in the legend. More than 50% overlap occurred in left Broca's and Wernicke's areas (pink arrows), situated posterior to the lesion, aligning with task-fMRI.

The overlap between language areas identified on rest- and task-fMRI was assessed visually, with the degree of overlap categorized as either greater than 50% or less than 50%. The overlap was checked in all three planes and were was interpreted by two individual radiologists with an interobserver agreement more than 90%.

The most frequently observed overlap occurred in the left Broca's area, which was also the most common area seen on task-fMRI (►**Figs. 5–7**). Other areas were also identified, albeit in fewer patients, and these areas also exhibited overlap. In total, 17 out of 22 patients, or 77% of the participants, demonstrated an overlap of more than 50% between the language areas identified in rest- and task-fMRI.

An earlier study by Tie et al[11] showed a significant overlap between rest- and task-fMRI, which was, however, among healthy subjects. Similarly, in a study by Branco et al,[12] conducted on patients with intracranial lesions, there was a notable concordance between task-related activity and rest-fMRI language maps, especially within the predefined language regions of interest. Worth mentioning is that this study employed the independent component analysis (ICA) technique for rest-fMRI processing. Additionally, in the same year, Sair et al[13] conducted a study using the ICA method and produced similar results, further supporting the consistency between task-related activity and rest-fMRI language maps.

In a study conducted by Smitha et al,[14] the ICA method was employed to analyze fMRI, with the overlap between

Table 3 The areas on rest-fMRI that revealed overlap on task-fMRI

Area overlapping with task	Number of patients	Percentage (%)
Left Broca's	20	91
Right Broca's	10	45
Right Wernicke's	6	27
Left Wernicke's	4	18

Abbreviation: Rest-fMRI, resting-state functional magnetic resonance imaging.

Table 4 the number of patients showing the degree of overlap as more than50% or less than50% of the areas on rest-fMRI and task

Degree of overlap (%)	Number of patients	Percentage (%)
>50	17	77.2
<50	4	22.8

Abbreviation: Rest-fMRI, resting-state functional magnetic resonance imaging.

Table 5 A total of 40 areas showed overlap between rest and task fMRI and each of these areas were individually assessed

	Observer 1		
Observer 2	<50	>50	Total
<50	16	2	18
>50	2	20	22
Total	18	22	40
Weighted Kappa	0.798		
Standard error	0.096		
95% CI	0.61–0.99		
% Concordance	90.00%		

Abbreviations: CI, confidence interval; fMRI, functional magnetic resonance imaging.

Table 6 The distribution of seeds responsible for identifying the Broca's and Wernicke's areas on rest-fMRI. These seeds were pivotal in the areas that exhibit overlap on task-fMRI

Left Broca's	
Right Broca's seed	14
Left Wernicke's seed	3
Right Wernicke's seed	3
Right Broca's	
Left Broca's seed	9
Right Wernicke's seed	1
Left Wernicke's seed	0
Right Wernicke's	
Left Wernicke's seed	3
Right Broca's seed	2
Left Broca's seed	1
Left Wernicke's	
Right Wernicke's seed	2
Right Broca's seed	1
Left Broca's seed	1

Abbreviation: Rest-fMRI, resting-state functional magnetic resonance imaging.

Table 7 The task paradigms alongside the number of patients where this task-fMRI overlapped with rest-fMRI results

Task	Number of patients showing overlap on this task	Percentage (%)
Verb generation	18/22	81
Word generation	16/22	72
Picture	11/22	50
Semantics	5/22	23

Abbreviation: Rest-fMRI, resting-state functional magnetic resonance imaging.

components being quantitatively evaluated using the Dice coefficient. However, our research has studied seed-based analysis and a qualitative assessment of overlap, with an interobserver agreement calculation, as described above.

Our study explored four language task paradigms: word, verb, picture, and semantics. Interestingly, verb generation closely mirrored the findings of rest-fMRI. In a study by Pang et al,[15] where localization of Broca's area was compared with findings on Magnetoencephalography (MEG), there was 100% concordance between MEG and fMRI findings on the picture-to-verb task. Picture tasks activated fewer language areas, likely due to simplicity, while semantics were not universally performed.

Language functions are intricate and their mapping, particularly in the presence of cortical distortion and brain plasticity, proves challenging. However, our study yielded promising results. Using a straightforward seed-based technique, we discovered encouraging overlap between rest-fMRI and standard task-fMRI, indicating the potential of rest-fMRI in accurately delineating complex language regions. These findings highlight the feasibility of incorporating rest-fMRI as a reliable tool in mapping eloquent brain areas, in clinical settings.

Strengths

Rest-fMRI is an emerging tool and is still being cautiously used in clinical presurgical settings for language mapping.

Some studies, like the one conducted by Smitha et al in 2017,[16] have extensively investigated the effectiveness of seed-based rest-fMRI as a substitute for task-fMRI. These studies primarily focused on the laterality index, while others[14] used ICA to analyze the data.

Our research focuses on the concordance of language area identification between rest-and task-fMRI, by assessing their overlap using seed-based analysis and a commercially available fMRI processing software. The goal is to evaluate the feasibility of using rest-fMRI in regular clinical settings, making it more accessible and useful for a wider population.

Encouragingly, 77% of patients exhibited good more than 50% overlap, particularly in Broca's areas, aligning with task-based results.

Limitation

All our patients underwent MRI without sedation. However, propofol anesthesia anesthesia, especially in pediatric cases, could interfere with rest-fMRI signals, an area that remains largely unexplored in pediatric language mapping,[17] which is a general limitation for rest-fMRI under sedation. Further studies with a larger sample size are necessary to validate our findings and assess the accuracy of rest-fMRI across various pathologies. Thresholding alters the size of BOLD activity, impacting its distance from the pathology—a limitation frequently encountered in task-fMRI studies, as well.[18]

Conclusion

The initial experience with rest-fMRI in clinical presurgical planning shows promise, particularly for patients unable to perform tasks, children, and those with language area involvement. However, further research is crucial to establish its role in presurgical planning. Larger scale studies, including intraoperative concordance, are essential to elaborate on these preliminary findings and to determine the technique's effectiveness.

Authors' Contributions

S.S.G. contributed to concept, design, definition of intellectual content, literature search, manuscript preparation, manuscript editing, data acquisition, and data analysis. R. S. helped in manuscript preparation, manuscript editing, literature search, and data analysis. S.M. was involved in data analysis, design, manuscript editing, and literature search. We thank and acknowledge Ms. Aditi Erande for helping in statistical analysis of our study.

Conflict of Interest

None declared.

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