Feasibility, Sensitivity and Network Specificity of fMRI Language Lateralization for Epilepsy and Brain Tumor Surgery

Vasileios Kokkinos¹,²,⁴*, Panagiotis Selviaridis³, Ioannis Seimenis⁴

¹Department of Neurosurgery, Massachusetts General Hospital, Boston, MA, USA.

²Harvard Medical School, Boston, MA, USA.

³Department of Neurosurgery, St. Luke’s Hospital, Greece.

⁴Department of Medicine, School of Health Sciences, Democritus University of Thrace, Greece.

* Corresponding author: Department of Neurosurgery, Massachusetts General Hospital, 55 Fruit Street, Boston, 02114, MA, USA. Email: vasileios.kokkinos@mgh.harvard.edu

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INTRODUCTION

Language fMRI has become an important part of the presurgical process as lateralization of language highly impacts both the decision-making processes in terms of surgical options, as well as the surgical planning itself in terms of determining the optimal approach trajectory to the surgical target and the extent of the resection. The use of presurgical fMRI mapping has been shown to reduce morbidities and mortality in brain tumor patients, as well as contribute to a post-operative life of higher quality.

However, the variability of the language fMRI process is wide in all aspects of the workflow, including pivotal nodes such as the task and baseline selection, the interpretation of results and the degree of contribution to the surgical process. Moreover, the added value of language fMRI in clinical practice has not been robustly established yet, mainly because there are more parameters that affect the process than the task features. In a meta-analysis study performed by the American Academy of Neurology (AAN), the committee concluded that the fMRI process has significant confounding factors both on the provider side (task design, analysis methodology and tools) as well as on the patient side (lobular location and hemispheric lateralization of pathology). The later type of confounds have not been systematically investigated in the literature.

In this study, we investigate how these confounds affect the ability of the patient to perform each of our fMRI tasks (feasibility) and the efficiency of the task from a contrast point of view (blood oxygen level-dependent / BOLD sensitivity). In addition, we address the specificity of our fMRI protocols (covering both expressive and receptive language skills) in terms of anatomical localization and, in conjunction with the statistics, approach optimal strategies to maximize lateralization and localization efficiency in patient groups.
METHODS

104 patients were referred for fMRI to determine both expressive and receptive language lateralization in the context of their presurgical procedure for epilepsy and brain tumor surgery. To cover the most basic levels of expressive (vocabulary management & sentence formation) and receptive (reading & listening) language skills, we developed four tasks to map each skill separately: 1) a verbal fluency task (VF) to map vocabulary use, 2) a semantic description task (SD) to map sentence formation / semantic integration skills, 3) a reading comprehension (RC) task and 4) a listening comprehension (LC) task. Upon referral, all patients underwent a full screening procedure where they were presented with samples of all four tasks and were asked to perform each task out loud for feasibility of performance to be assessed.

After image acquisition, a General Linear Model (GLM) was built for each task separately. We used multiple regression with seven covariate vectors accounting for the group variability in: 1) age, 2) gender, 3) handedness, 4) education level, 5) lobe of lesion, 6) hemisphere of lesion, and 7) lesion severity. Group-analysis results for each language task are presented family-wise error (FWE) corrected for multiple comparisons ($p < 0.05$).

To assess the degree of association between the categorical covariates of our study and our variables of interest (fMRI test feasibility and BOLD sensitivity) we used two-sided Chi$^2$, accompanied by symmetric measures of Phi and Kramer’s V for evaluation of statistically significant results. To assess the effect of age on fMRI test feasibility and BOLD sensitivity, we used Point Biserial Correlation.
Verbal Fluency task flow
- 1 x stimulus item: K
- 10 x baseline items
- 1 x stimulus item: B

Semantic Description task flow
- 4 x stimulus items: Tree, Factory, Window
- 10 x baseline items

Reading Comprehension task flow
- 10 x stimulus items: The door was open, The sun is shining
- 10 x baseline items: The roof is red, The sea was calm
- 10 x stimulus items: The day is warm, The ship will sail

Listing Comprehension task flow
- 1 x stimulus item: 20''
- 1 x baseline item: 20''
RESULTS

Feasibility was excellent in the LC task (100%), while in the acceptable to mediocre range for the rest of the tasks (SD: 87.50%, RC: 85.57%, VF: 67.30%). Feasibility of the VF task was significantly confounded by age (p=0.020) and education level (p=0.003). Feasibility of the SD task was confounded by education level (p=0.004) and the laterality of the lesion (p=0.019). Feasibility of the RC task was confounded by age (p=0.001), lesion laterality (p=0.007) and lesion severity (p=0.048).
RESULTS

All tasks were comparable in terms of sensitivity in generating statistically significant BOLD contrast (VF: 90.00%, SD: 92.30%, RC: 93.25%, LC: 88.46%). The lobe of the lesion (p=0.005) and age (p=0.009) confounded the VF and SD tasks respectively.

<table>
<thead>
<tr>
<th>fMRI tasks: BOLD sensitivity %</th>
<th>Age</th>
<th>Gender</th>
<th>Handedness</th>
<th>Education Level</th>
<th>Lesion Lobe</th>
<th>Lesion Laterality</th>
<th>Lesion Severity</th>
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<tbody>
<tr>
<td>Verbal Fluency 90.00%</td>
<td>r(68)=0.046, p=0.352</td>
<td>x²(1, N=70)=0.312, p=0.576</td>
<td>x²(2, N=70)=0.476, p=0.788</td>
<td>x²(2, N=70)=2.137, p=0.343</td>
<td>x²(4, N=70)=14.894, p=0.005*</td>
<td>x²(2, N=70)=0.353, p=0.553</td>
<td>x²(2, N=70)=0.959, p=0.619</td>
</tr>
<tr>
<td>Semantic Description 92.30%</td>
<td>r(89)=0.247, p=0.009*</td>
<td>x²(1, N=91)=3.751, p=0.053</td>
<td>x²(2, N=91)=1.264, p=0.532</td>
<td>x²(2, N=91)=1.582, p=0.453</td>
<td>x²(4, N=91)=2.344, p=0.673</td>
<td>x²(2, N=91)=3.033, p=0.082</td>
<td>x²(2, N=91)=4.928, p=0.085</td>
</tr>
<tr>
<td>Reading Comprehension 93.25%</td>
<td>r(87)=0.151, p=0.078</td>
<td>x²(1, N=89)=0.020, p=0.887</td>
<td>x²(2, N=89)=1.101, p=0.577</td>
<td>x²(2, N=89)=2.618, p=0.270</td>
<td>x²(4, N=89)=3.337, p=0.503</td>
<td>x²(2, N=89)=0.764, p=0.382</td>
<td>x²(2, N=89)=2.557, p=0.278</td>
</tr>
<tr>
<td>Listening Comprehension 88.46%</td>
<td>r(102)=0.071, p=0.235</td>
<td>x²(1, N=104)=0.020, p=0.887</td>
<td>x²(2, N=104)=0.067, p=0.967</td>
<td>x²(2, N=104)=1.021, p=0.600</td>
<td>x²(4, N=104)=2.992, p=0.559</td>
<td>x²(2, N=104)=1.306, p=0.520</td>
<td>x²(2, N=104)=3.984, p=0.136</td>
</tr>
</tbody>
</table>
RESULTS

Language network specificity also varied among tasks. The VF task was bilaterally highly sensitive for Broca’s (for the right-handed group: $Z_L=12.71$, $Z_R=9.27$) and weakly unilateral for Wernicke’s ($Z_L=6.24$). The SD task was bilaterally sensitive for Broca’s ($Z_L=13.81$, $Z_R=7.25$), although clearly predominant on the left, and bilaterally sensitive for Wernicke’s ($Z_L=9.99$, $Z_R=8.07$). The RC task was bilaterally weakly sensitive for Broca’s ($Z_L=9.22$, $Z_R=6.01$) and bilaterally highly sensitive for Wernicke’s ($Z_L=10.32$, $Z_R=6.99$), although slightly predominant on the left. The LC task was unilaterally weakly sensitive for Broca’s ($Z_L=5.40$) and unilaterally highly sensitive for Wernicke’s ($Z_L=10.41$).
Brain areas involved in the verbal fluency (VF) task.

**Inferior frontal cluster (Broca's Area):**
- Left: $Z=12.71 (x=-32, y=22, z=0, \text{ Brodmann areas 44/45})$ (A);
- $Z=12.20 (x=-48, y=36, z=12, \text{ Brodmann area 46})$ (B);
- $Z=12.22 (x=-38, y=18, z=6, \text{ Anterior Insula})$ (C) | Right: $Z=9.27 (x=36, y=28, z=2, \text{ Brodmann area 44 / Anterior Insula})$ (E).

**Superior mesial frontal cluster:** Left: $Z= 12.40 (x=-4, y=8, z=66, \text{ Brodmann area 9})$ (D).

**Precentral gyrus and operculum cluster:** Left: $Z=9.25 (x=-50, -6, 34, \text{ Brodmann area 4})$ (F); Right: $Z=6.48 (x=50, -8, 38, \text{ Brodmann area 4})$ (G).

**Posterior superior temporal cluster (Wernicke's area):** Left: $Z=6.24 (x=-54, y=-38, z=10, \text{ Brodmann areas 41/42})$ (H).

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Brain areas involved in the semantic description (SD) task.

**Inferior frontal cluster (Broca's Area):**
- Left: $Z=13.44 (x=-46, y=26, z=2, \text{ Brodmann areas 44/45})$ (A);
- $Z=13.81 (x=-48, y=26, z=18, \text{ Brodmann area 46})$ (B);
- $Z=12.02 (x=-30, y=24, z=2, \text{ Anterior Insula})$ (C) | Right: $Z=7.25 (x=36, y=24, z=4, \text{ Brodmann area 44 / Anterior Insula})$ (E).

**Superior mesial frontal cluster:** Left: $Z= 14.24 (x=-4, y=24, z=36, \text{ Brodmann area 9})$ (D).

**Precentral gyrus and operculum cluster:** Left: $Z=12.30 (x=-42, 4, 52, \text{ Brodmann area 4})$ (F).

**Posterior superior temporal cluster (Wernicke's area):** Left: $Z=9.99 (x=-48, y=-40, z=2, \text{ Brodmann areas 41/42})$ (G); Right: $Z=8.07 (x=52, -28, 0, \text{ Brodmann areas 41/42})$ (I).
Brain areas involved in the reading comprehension (RC) task.

Inferior frontal cluster (Broca’s Area): Left: Z=9.22 (x=-46, y=28, z=2, Brodmann areas 44/45) (A); Z=9.17 (x=-48, y=18, z=16, Brodmann area 46) (B) | Right: Z=6.01 (x=40, y=28, z=0, Brodmann area 44) (H).

Precentral gyrus and operculum cluster: Left: Z=8.52 (x=-46, y=-6, z=42, Brodmann area 4) (C) | Right: Z=5.92 (x=48, y=-10, z=36, Brodmann area 4) (I).

Posterior superior temporal/angular gyrus (Wernicke’s area): Left: Z=10.32 (x=-48, y=-44, z=8, Brodmann areas 41/42) (F); Z=6.72 (x=-44, y=-38, z=24, Brodmann area 40) (F); Z=7.92 (x=-55, y=-6, z=-10, Brodmann area 41) (G); Z=6.94 (x=-44, y=-70, z=4, Brodmann areas 39/19) (G) | Right: Z=6.99 (x=46, -36, 6, Brodmann areas 41/42) (J); Z=8.00 (x=46, y=-68, z=6, Brodmann areas 39/19) (K).

Brain areas involved in the listening comprehension (LC) task.

Inferior frontal cluster (Broca’s Area): Left: Z=5.40 (x=-50, y=30, z=8, Brodmann areas 44/45) (A).

Precentral gyrus and operculum cluster: Left: Z=8.88 (x=-46, y=16, z=26, Brodmann area 4) (B).

Posterior superior temporal/angular gyrus (Wernicke’s area): Left: Z=10.41 (x=-62, y=-34, z=2, Brodmann areas 41/42) (D); Z=9.25 (x=-58, y=-52, z=14, Brodmann area 40) (D); Z=9.44 (x=-56, y=2, z=-12, Brodmann areas 41/38) (D); Z=6.77 (x=-48, y=-66, z=22, Brodmann areas 39/19) (F) | Right: Z=6.38 (x=54, 2, -18, Brodmann areas 41/38) (G).
CONCLUSIONS

Tasks that require minimal patient engagement (passive tasks: LC) have the higher chance of feasibility. Feasibility is significantly confounded by age and education level of the patient in tasks that require significant patient engagement (active tasks: VF, SD, RC). The lateralization and severity of pathology can also confound feasibility. All tasks, once rendered feasible, have a high chance of generating statistically significant BOLD contrast. Only the LC task resulted in robust hemispheric lateralization of language in both expressive and receptive language regions. Our study highlights the effects of patient-related confounding factors on language fMRI efficiency and proposes the LC task as the most efficient (given its excellent feasibility, normal sensitivity, robust specificity and lateralization) in the presurgical context.