Functional Connectivity MRI and Post-Operative Language Performance in Temporal Lobe Epilepsy: Initial Experience

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SUMMARY – Anterior temporal lobectomy is an effective treatment for drug-resistant epilepsy of temporal origin, although new language impairment may develop after surgery. Since correlations between functional connectivity (FC) MRI of the language network and verbal-IQ performance before surgery have recently been reported, we investigated the existence of correlations between the preoperative FC of the language network and post-operative verbal-IQ decline. FC between nodes of the language network of the two hemispheres (Interhemispheric-FC) and within nodes of the left hemisphere (LH-FC) and language lateralization indexes were estimated in five right-handed patients with non-tumoral left temporal lobe epilepsy undergoing anterior temporal lobectomy. Correlations between preoperative FC measures and lateralization indexes, and the post-operative (12 months) neuropsychological verbal-IQ decline were investigated. Verbal-IQ decline was inversely correlated with the degree of left lateralization and directly correlated with the strength of Interhemispheric-FC. No significant correlation was found between LH-FC and post-operative verbal-IQ change. The results from this limited number of patients suggest that a stronger preoperative connectivity between homologue regions, associated with the absence of a definite hemispheric lateralization, appears to be an unfavorable prognostic biomarker.

Introduction

Anterior temporal lobectomy (ATL) is routinely performed to treat drug-resistant temporal lobe epilepsy (TLE). Nonetheless, 25-60% of patients may present with new or worsened language deficits after surgery¹. Therefore, biomarkers that can predict post-operative language performance are clinically relevant.

Current predictors are age at seizure onset, seizure duration, language performance evaluated with neuropsychological tests, and language lateralization assessed through Wada and fMRI. However, the lateralization index (LI) obtained using a task-evoked BOLD activity¹⁻³ relies on patients' cooperation and may

be hampered by poor task performance. On the other hand, functional connectivity MRI (FC-MRI), based on the intrinsic cortical BOLD signal fluctuations at rest, does not depend on task execution^{4,5} and is therefore potentially more suitable when assessing language lateralization in partially compliant patients with epilepsy.

Recently, a decreased FC-MRI of the language network (LN) in epileptic patients and a relationship between FC-MRI and preoperative verbal-IQ (vIQ) were reported⁶⁻⁸.

The present short communication investigates the relationship between preoperative LI, FC of the LN and pre/post-operative change in language performance in patients with TLE.

Figure 1 Relationships between LI and Interhemispheric-FC (A), pre/post-surgical vIQ decline (B), and between Interhemispheric-FC and pre/post-surgical vIQ decline (C) (Spearman's rho).

Methods

Subjects

All the participants gave written informed consent prior to enrollment in the study, which was approved by our local ethics committee (G. d'Annunzio University of Chieti-Pescara). Patients' main demographic and clinical data are summarized in Table 1. FC-MRI of the LN was retrospectively evaluated in five right-handed patients (age range: 16-51 years; one male, four females) with drug-resistant, non-tumoral left TLE, who underwent fMRI to assess language lateralization before surgery. Large brain lesions causing epilepsy were not included in the study due to their tendency to destroy the normal anatomy of the brain and to directly affect (via contact or infiltration) the cortical regions for speech. Left ATL was performed in all subjects with sparing of the superior temporal gyrus and resection of the anterior hippocampus. All patients presented seizure onset before five years of age and were diagnosed using EEG, MRI, SPECT, and clinical assessment. Epilepsy was secondary to a cortical malformation in one patient, and to mesial temporal sclerosis in the others. Verbal-IQ (vIQ) was assessed using the Italian version of the Wechsler Adult Intelligence Scale IV- Revised⁹ administered by an expert neuropsychologist immediately before and 12 months after surgery.

fMRI data acquisition

Data were acquired on 1.5T scanners (Magnetom Vision, Siemens, Erlangen, Germany and Achieva, Philips Medical Systems, Best, The

Netherlands). Functional images were obtained using blood oxygen level dependent (BOLD) T2*-weighted echo-planar sequences (TR 2000 ms, TE 60 ms, matrix size 64×64, FOV 256 mm, in-plane voxel size 4 mm×4 mm, flip angle 90°, slice thickness 4 mm and no gap). Structural images were acquired with a MPRAGE T1-weighted sequence (matrix 256×256, FOV 256 mm, slice thickness 1 mm, in-plane voxel size 1 mm×1 mm, flip angle 12°, TR = 9.7 ms and TE = 4 ms). To localize cortical regions specialized for speech, subjects underwent BOLD fMRI while silently performing an orthographically-cued, block-designed, lexical verb generation task (VGt), with four task periods (30s each) and five rest periods (20s each). Visual stimuli were presented using E-Prime software, v.1.1 (Psychology Software Tools - Pittsburgh, USA), projected via an LCD projector and viewed with a mirror placed above the subject's head.

Task-dependent and FC fMRI analysis

Using Brain Voyager QX v.1.9 (Brain Innovation, Maastricht, The Netherlands), functional image volumes were first corrected for differences in slice acquisition times, detrended, realigned with the structural images and warped into standard Talairach anatomical space. To minimize the potential biasing influence from task execution nonconformity and/or illness-related issues, the fMRI statistical activation maps were generated according to a previously described method¹⁰ combining a classical hypothesis-driven general linear model analysis with independent component analysis for data-driven detection of the brain activation re-

sponse. This model was also used to eliminate the contribution of BOLD-evoked activity from the time series prior to assessment of the FC. fMRI time series were further pre-processed using in-house software according to previously described procedures^{5,11}. The pre-processing steps included: 1) band-pass filtering between 0.009 and 0.08 Hz; 2) regression of deterministic task-evoked components; 3) regression of signals from white matter and ventricles and of their first derivatives; 4) regression of three-dimensional motion parameters and their first derivatives.

Statistical analyses

LI were calculated in each subject by estimating beta-weight measures of each IFG, STS and TPJ peak in the left (Vl) and right (Vr) hemisphere, according to the following formula: $LI = (Vl - Vr) / (Vl + Vr)$ ¹¹. By definition, LI values range between -1 and +1. Language was considered left lateralized with $LI > +0.20$, right lateralized with $LI < -0.20$ and bilateral (i.e., not lateralized) with LI between +0.20 and -0.20, inclusive.

FC values were estimated in each subject between seed ROIs placed centered on the peaks of task-evoked activation in the left hemisphere (IFG, STS and TPJ), and their contralateral homologues. Pearson's correlation coefficient was used to estimate average FC between homologue ROI pairs (Interhemispheric-FC) and between ROIs of the left hemisphere (LH-FC). To obtain an approximately normal distribution of the FC values, the FC correlation r coefficients were converted to z -scores by means of Fisher's r -to- z transformation¹³. Spearman's ρ was used to investigate correlations between pre-surgical LI, FC and pre/post-operative vIQ-score decline. A p threshold $< .05$ was considered statistically significant.

Results

Preoperatively, language was left-lateralized in 3/5 patients ($LI > 0.2$) and non-lateralized in 2/5 patients ($0 < LI < 0.2$). Notably, the degree of left lateralization was negatively correlated with Interhemispheric-FC ($\rho = -1.00$; $p < .001$ Figure 1A) so that non-lateralized patients exhibited the strongest Interhemispheric-FC.

Following surgery, patients were seizure-free, and anti-epileptic medical therapy was not modified. Three patients suffered from a post-operative language decline, while no vIQ variation was detected in the other two. LI indexes, inter- and intra-hemispheric FC-MRI and vIQ decline for each subject are summarized in Table 1. vIQ decline was inversely correlated with the degree of left lateralization ($\rho = -.97$; $p < .005$; Figure 1B) and, crucially, positively correlated with the strength of Interhemispheric-FC ($\rho = .97$; $p < .005$; Figure 1C). Therefore, patients showing the greatest decline in language performance were those who previously showed the weakest left dominance and the strongest Interhemispheric-FC. Although a trend toward a positive correlation was observed between LH-FC and preoperative vIQ, (see also⁷) ($\rho = .90$; $p = .08$), no significant correlation was found between LH-FC and post-operative vIQ change ($\rho = .30$; $p = ns$).

Discussion

We explored the relationship between preoperative language lateralization of the LN and pre/post-operative vIQ change in five patients with left temporal lobe epilepsy (TLE) who underwent left anterior temporal lobectomy (ATL). We observed that weaker language lateralization to the dominant hemisphere was associated with stronger Interhemispheric-FC.

Table 1 Patients' characteristics, MRI results and verbal performance decline

Patient	Age	Gender	LI	Etiology	Interhemispheric FC (z-score)	LH-FC (z-score)	Post-op vIQ Decline
1	51	F	.04	Cortical Dysplasia	5.16	6.91	11
2	19	M	.38	MTS	1.32	4.13	2
3	29	F	.64	MTS	-0.24	5.21	0
4	16	F	.16	MTS	3.51	4.92	4
5	16	F	.54	MTS	.03	8.30	0

(LI = Lateralization index; LH-FC = Left hemisphere FC; Post-op vIQ = Post-operative verbal-IQ); MTS = Mesial temporal sclerosis.

Interestingly, this inverse relationship, which advises further investigations in healthy subjects, is reminiscent of the association between another lateralized system, the so called ventral attention network, and its peculiar pattern of low Interhemispheric-FC¹¹.

In contrast with previous observations^{1,2}, language lateralization was inversely correlated with vIQ decline. However, we hypothesize that this result reflects the fact that none of our patients was right-lateralized. Therefore, the lack of a hemispheric dominance in patients with left TLE may represent a condition of incomplete, insufficient reorganization of language functions towards the right hemisphere. In fact, right-lateralized patients in larger study groups^{1,2} suffered less or no decline compared to those with left-lateralization.

We previously reported that patients with stronger LH-FC obtained better results at pre-surgical language tests⁷. However, in the present short report, which includes a subset of the original patient group, a better post-surgical outcome was not correlated with strong LH-FC, but rather negatively correlated with Interhemispheric-FC. Thus, stronger preoperative connectivity between homologue regions, associated with the absence of a definite hemispheric lateralization, appears to be an unfavorable prognostic biomarker, possibly reflecting a non-functional spread of language activation across the two hemispheres. Notably, this moves in the opposite direction to evidence from less lateralized systems such as the motor network¹⁴, in which Interhemispheric-FC was found to be positively correlated with functional recovery after stroke.

Crucially, we note that the LI and FC were both associated with post-operative language outcome and may represent complementary measures of brain functional organization. Unlike the task-evoked BOLD response, FC-MRI does not depend on task execution⁴ and is therefore less influenced by patients' cooperation⁵. For this reason, FC-MRI may be potentially more

suitable for use in patients with reduced compliance. In addition, whereas the LI may be better conceptualized as a measure of hemispheric competition for language dominance, FC-MRI may be viewed as a measure of the status of the whole LN, which includes both cortical regions and their underlying interconnecting fibers.

Future perspectives and limitations

In addition to language function, FC-MRI measures are suitable to investigate the relationships between the integrity of other resting-state networks (i.e. default mode, attention and motor networks) and their corresponding behavioral domains (i.e. memory, visuospatial attention and somatomotor coordination skills) which may be assessed in future studies in TLE patients undergoing surgery. Furthermore, the existence of different patterns of FC-MRI in extratemporal epilepsy, and their relationships with post-operative behavioral outcomes should be also specifically investigated.

The main limitation of the present study is in the small number of subjects (five) who could be selected from our previous study group⁷ since they received the same surgical resection and a complete post-surgical neuropsychological examination. Studies on larger series, including patients with a definite right dominance, are needed to further explore the relationship between LI, Interhemispheric-FC and post-operative vIQ, and validate FC-MRI as a prognostic biomarker of post-operative outcome.

Conclusions

The results from this small number of patients suggest that a stronger preoperative connectivity between homologue regions of the language network, associated with the absence of a definite hemispheric lateralization, appears to be an unfavorable prognostic biomarker in epileptic patients undergoing left ATL.

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