Rationale
Predicting seizure outcome (SO) after anterior temporal lobectomy (ATL) is a major clinical goal. With clear evidence that even focal epilepsies disrupt large scale brain networks, resting-state functional connectivity (FC) methods have been increasingly used on a pre-surgical basis to characterize the impact of seizures on brain activity. In this project, we sought to determine whether the functional integrity of resting-state networks (RSNs) prior to surgery can discriminate between patients who obtain good versus poor seizure control after ATL.

Methods
We collected 5-minute resting state fMRI data on 56 refractory adult unilateral TLE patients prior to their brain surgery (ATL). Seizure outcome at least six months post-surgery was identified (“good” outcome, GO= no seizures since surgery, Engel Class I, n=35; “poor”=at least one seizure after surgery, Engel ≥ II, n=21) (Engel et al. 1993). A standard pipeline was run to preprocess the data, using FMRIB.

Twenty-three RSNs obtained from a large sample of normal healthy participants were used as normative templates (Doucet et al., 2011; Figure 1). For each network and each participant, an “intra-connectivity coefficient” (ICC) was computed as the average correlation between the time-series of all the voxels within the RSN and the averaged time-series within the RSN. A high value indicates strong temporal coherence between the voxels of the network while a low value indicates the network lacks functional coherence and strength.

Using the ICCs, two analyses were then done to predict seizure outcome:

1. A logistic regression was computed, using the 23 RSN ICCs as the continuous independent variables (forward stepwise likelihood ratio option). We then re-ran the regression to compare the predictive power of these variables with the predictive power of a more standard clinical predictor (presence/absence of mesial temporal sclerosis (MTS)).

2. A recursive partitioning analysis was computed, using the 23 RSN ICCs to classify the patients with GO vs. PO. Of note, laterality of the pathology (Right / Left TLE) was also tested a potential predictor in each model.

Results

• Participants: The 2 experimental groups did not differ in age (GO: 41 ± 12 y.o.; PO: 40 ± 12 y.o.) and in gender (GO= 17; PO= 18 of females), age at seizure onset, seizure duration, size of the resection (p>0.05). However, the two groups differ in the proportion of patients showing sign of MTS (GO: 21 vs PO: 5, p=0.013).

• Logistic Regression: The results revealed that the RSN 7 had the only significant predictor (Cox and Snell R²= 0.12, p=0.032), classifying correctly 89% of the GO patients, and 43% of the PO patients (Total: 71% of patients classified correctly). In a model solely with non-MTS (non-lesional) TLE, RSN 7 again emerged the best predictor, producing classification rates comparable to above.

The model with only the MTS variable did not classify as well the GO patients (66% total: 60% of the GO, 76% of the PO; Cox and Snell R²= 0.12, relation to the RSN 7 ICC variable. Together, they classified 64% of the patients (74% of the GO, 48% of the PO; Cox and Snell R²= 0.22) (Table 1). When tested, the laterality of the pathology was not a significant predictor of seizure outcome.

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Table 1: Result of the logistic regression testing the predictive power of the RSN7 ICC and the MTS presence.

The results from the recursive partitioning method were consistent with the logistic regression method, showing that, among the networks, the RSN 7 is the most significant network to predict SO. In detail, a lower ICC (e.g., less coherent, less strong network) was associated with poor seizure outcome. However, when adding MTS in the model, the presence of MTS becomes a better predictor of SO, showing that patients with MTS have a better chance to become seizure free, post-surgery. Also, the networks involving sensory-motor regions showed some power to predict seizure outcome. The functionality of the RSN 7 is not definitive known, though it bears similarity to a working memory as defined by fMRI, though some resemblance as well to attention and object recognition networks.

The RSNs with strong temporal overlaps (such as the Default-mode network) were not reliable predictors of seizure outcome.

Discussion
Our results suggest that prior to surgery the functional network organization of the brain may differ for patients who experience a good versus poor outcome following ATL. Importantly, networks at least partially covering mesial temporal lobe regions were not predictors of seizure outcome. The networks most reliably predicting seizure outcome involved lateral frontal and temporal regions. These findings suggest that, pre-surgery, a less coherent functional network specifically involving lateral frontal and temporal cortex predicts worse seizure outcome. In contrast, stronger connections between these regions is associated with better seizure outcome.

This functional result converges with our recent structural study showing that abnormal gray matter volume in the frontal, not mesial temporal, lobe predicts seizure outcome (Doucet et al., 2015). Together, these imply that both structural and functional information may be needed to optimize prediction of seizure outcome. The current findings suggest that the functional integrity of extra-temporal networks plays a role in the development of good seizure control following ATL, perhaps reflecting the presence of cognitive/fronational reserve. Further research is needed, but our data also provide some indication that in non-lesional TLE knowledge of the integrity of specific RSNs, such as the RSN7 (bilaterial frontal-temporal), may provide added value to the pre-surgical prediction of seizure outcome.

Conclusion
This study highlights the value of exploring the functional integrity of regions/networks outside the mesial temporal lobe when trying to predict seizure outcome. This study provides specific evidence of the value one particular RSN, all toward evaluating its status as a potential biomarker of outcome. Future investigations are needed to confirm these findings.

Acknowledgments
The brain networks are visualized with the BrainNet Viewer (www.nitrc.org/projects/bnv/) (Xia et al., 2013).

References