Resting-state functional connectivity patterns from the **anterior hippocampi** to **temporo-parietal language regions** differentiates temporal lobe epilepsy patients whose seizures originate in the **right vs. left hippocampus**

Relating Resting-State Functional Connectivity of the Hippocampus and Language Cortex to Language Abilities in Temporal Lobe Epilepsy

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INTRODUCTION

- Language deficits are extremely common in temporal lobe epilepsy (TLE) patients due to:
  - repeated seizure propagation into the temporal lobe and beyond
  - surgery to remove the seizure focus that includes the removal of eloquent cortex
  - the crucial role of the hippocampus to language processing
- Functional connectivity (FC) between the hippocampus and language cortex during resting-state scans offers the unique opportunity to noninvasively assess plasticity and reorganization of connectivity patterns, and thus may predict language deficits following surgery.
- The purpose of the present study was to 1) characterize patterns of functional connectivity between the hippocampus and broad areas of language cortex in healthy controls, right TLE, and left TLE patients, and 2) determine whether FC patterns show associations with language abilities. The *long-term goal* of the present work is to use hippocampal-language FC as a predictor of post-surgical language outcome.

METHODS

Subjects:

- 54 healthy controls (age: M: 37.00 years, SD: 13.78)
- 40 unilateral presurgical TLE patients with seizures identified using standard clinical assessments by neurosurgery team (video-EEG, MRI, PET)
  - 27 right TLE patients (age: M: 39.44 years, SD: 10.52)
  - 13 left TLE patients (age: M: 37.62 years, SD: 15.23)

Imaging: 3T MRI resting-state T2* weighted BOLD fMRI [TR: 2 s, 10 mins, voxel size: 3 x 3 x 4 mm^3]
Neuropsych Language Tests: Verbal Comprehension Index (WAIS), NAB Naming Test, Word Generation: Categories & Letters, Wechsler Memory Scales (WMS), California Verbal Learning Test (CVLT)
Segmentation of ROIs: Bilateral hippocampi were segmented into anterior and posterior sections using FreeSurfer, and 11 language regions in the frontal, temporal, and parietal lobes were segmented using MultiAtlas
FC Analysis: FC was measured as the pairwise partial correlation between the time series of the hippocampus sections to each language region, and then averaged into single FC values for anterior and posterior hippocampus to Frontal and Temporo-Parietal regions
Hippocampal Volume: Gray matter volume of the anterior and posterior hippocampi were calculated using FreeSurfer

RESULTS

- FC from the bilateral anterior hippocampus was significantly stronger than the bilateral posterior hippocampus to both the frontal and temporo-parietal language regions in all three groups ($p < 0.001$).
- No significant differences were found between groups from the bilateral anterior hippocampi to the frontal language regions. In contrast, FC from the bilateral anterior hippocampus to temporo-parietal language regions revealed a significant group x hippocampus interaction ($p = 0.01$), such that in the right TLE group, the right (impaired) hippocampus was significantly less connected to temporo-parietal language cortex, while in the left TLE group the left (impaired) hippocampus was significantly less connected.
- No significant differences were found between groups from the bilateral posterior hippocampi to frontal or temporo-parietal language regions
- Significant but distinct correlations to neuropsychological tests were found in RTLE and LTLE
- No significant correlations were found between hippocampal volume and resting-state FC measures in controls or RTLE. However, in LTLE significant negative correlations were found between both left and right hippocampal volume and resting-state FC ($p < .05$)
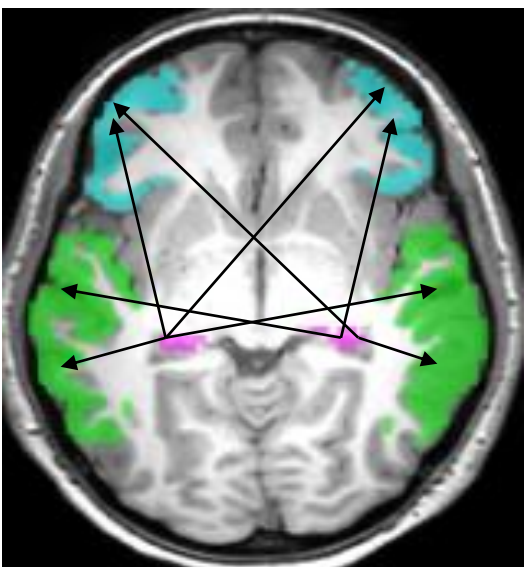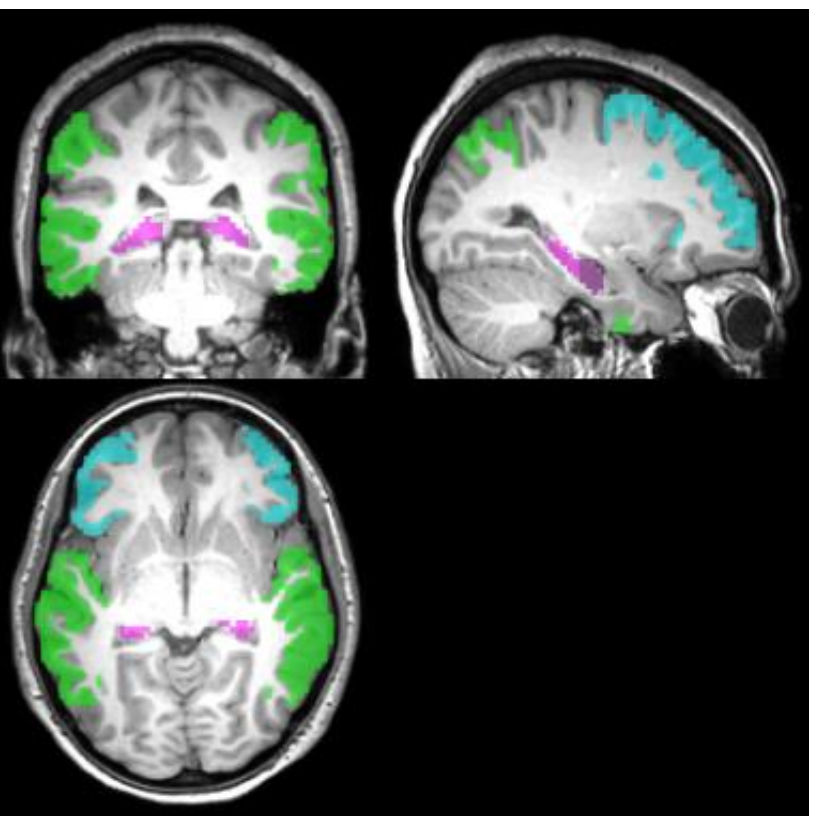
CONCLUSIONS

- Temporal lobe epilepsy patients whose seizures originate in the left vs. right hippocampus showed different patterns of FC between the anterior hippocampi and temporo-parietal language regions, and these patterns showed significant associations to language abilities that may inform novel mechanistic models of language impairment in patients with TLE.
- This work suggests that FC from the bilateral hippocampi to language cortex can be used to understand pre-surgical organization and current language abilities, and these relationships may be robust enough to predict post-surgical outcomes using resting state pre-surgical scans. Work is currently ongoing to collect longitudinal data from these patients to assess the prediction of postsurgical language outcomes, and/or whether specific patterns of reorganization lead to better language outcomes.
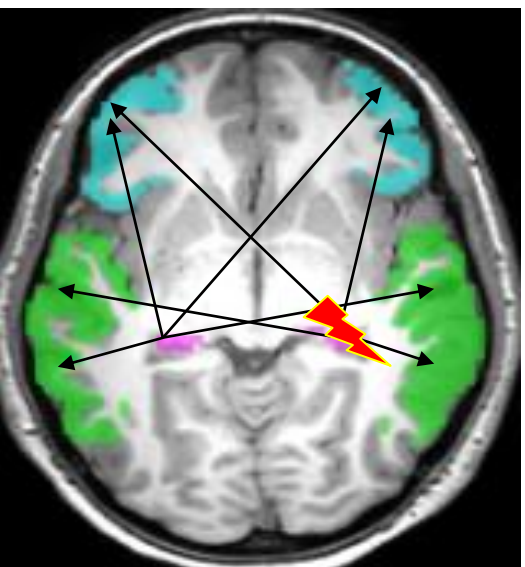
REGIONS OF INTEREST (ROIS)

- **Bilateral Hippocampi**
  - Segmented into anterior and posterior sections using FreeSurfer
- Language Regions
  - Segmented using MultiAtlas
    Frontal Regions:
    Middle frontal gyrus
    Orbital inferior frontal gyrus
    Triangular inferior frontal gyrus
    Temporo-Parietal Regions:
    Inferior temporal gyrus
    Middle temporal gyrus
    Planum polare
    Superior temporal gyrus
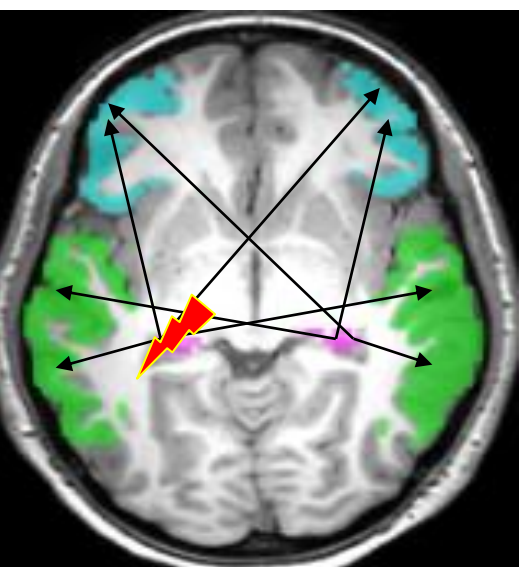   Transverse temporal gyrus
    Angular gyrus
    Supramarginal gyrus

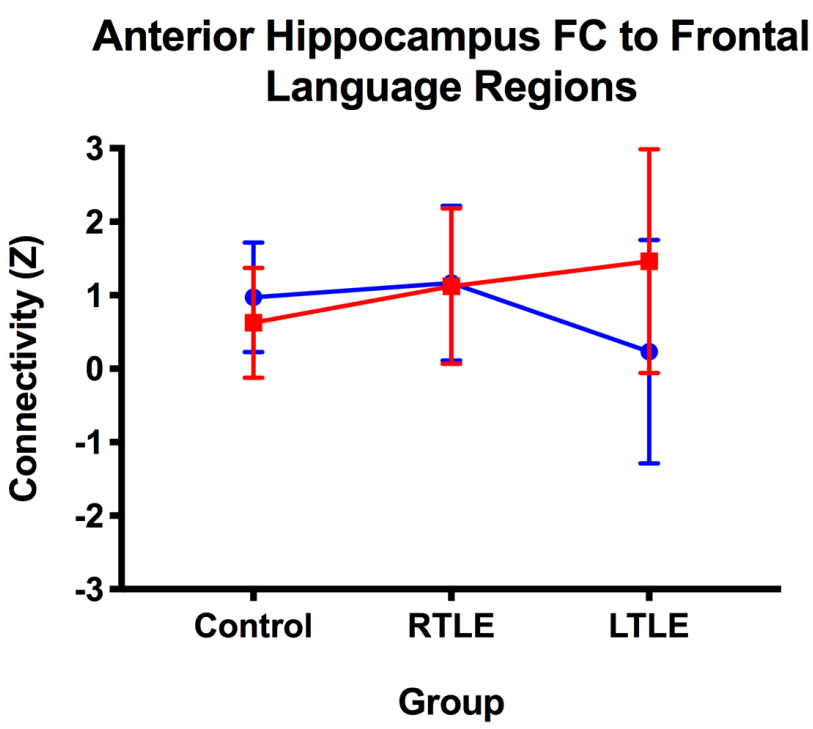**Voxels included in Functional Connectivity Analysis**
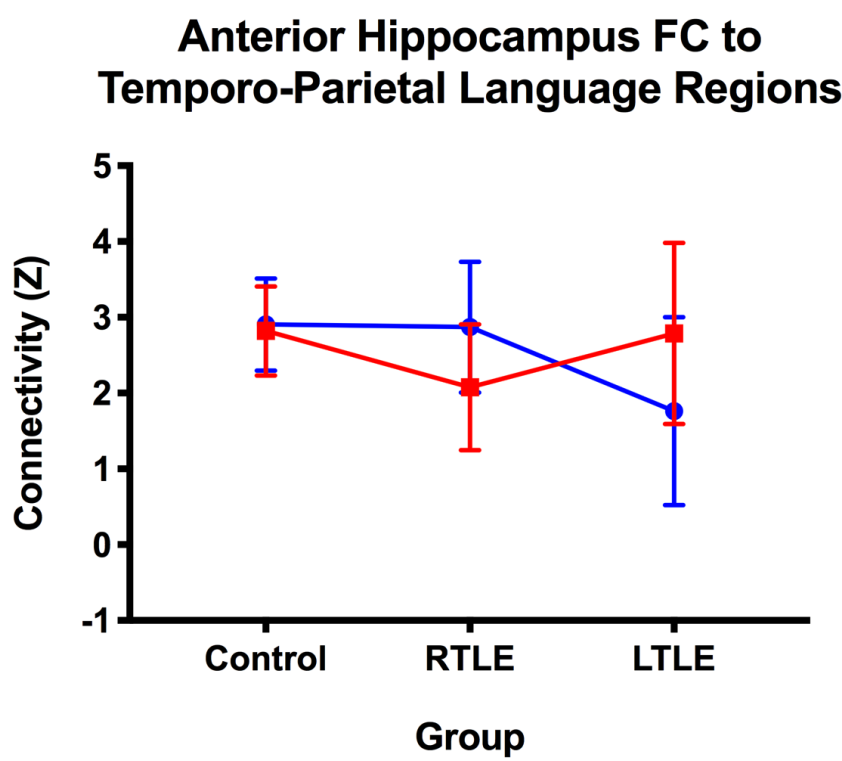

Healthy Controls   Right TLE   Left TLE

FC of Anterior Hippocampi to Frontal Language Regions

Anterior Hippocampus FC to Frontal Language Regions

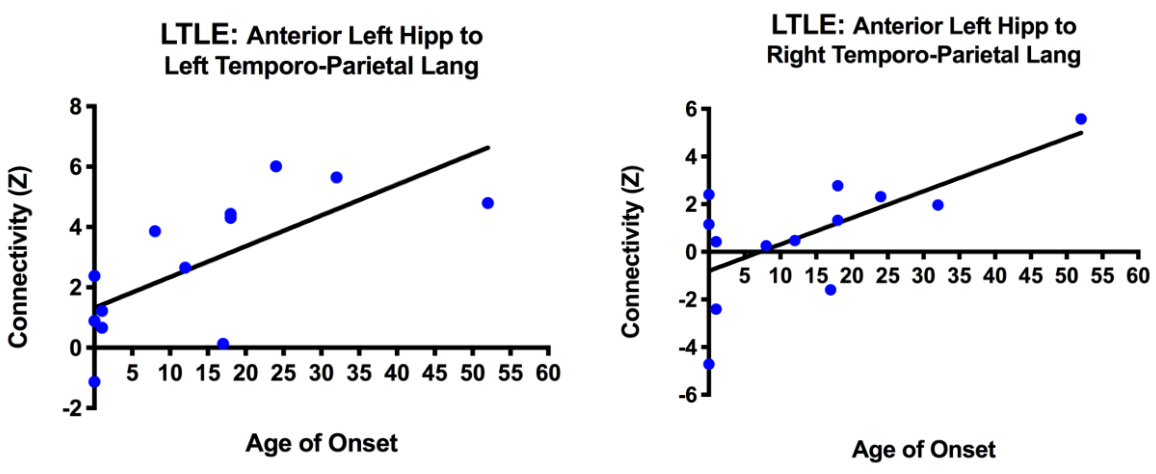*Across groups: No significant differences between anterior hippocampal-frontal language connectivity*

Within groups: no significant differences between right vs. left anterior hippocampus FC

FC of Anterior Hippocampi to Temporo-Parietal Language Regions

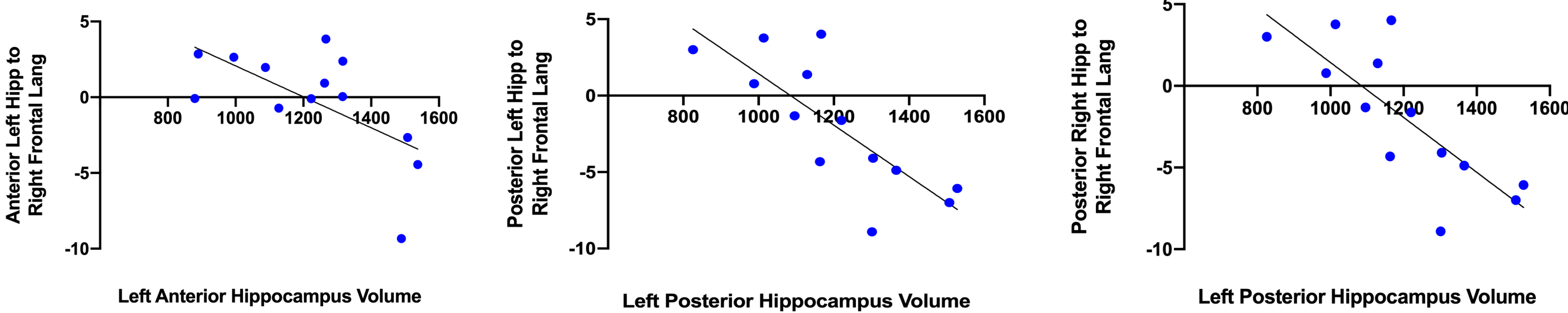Anterior Hippocampus FC to Temporo-Parietal Language Regions

Across groups: Significant interaction (p = 0.01) between groups and left vs. right anterior hippocampal FC

Within groups:
Control = no significant differences (p = 0.73)
RTLE = significantly stronger FC to left anterior hippocampus (p = 0.02)
LTLE = significantly stronger FC to right anterior hippocampus (p = 0.04)

LTLE: Anterior Left Hipp to Left Temporo-Parietal Lang   LTLE: Anterior Left Hipp to Right Temporo-Parietal Lang
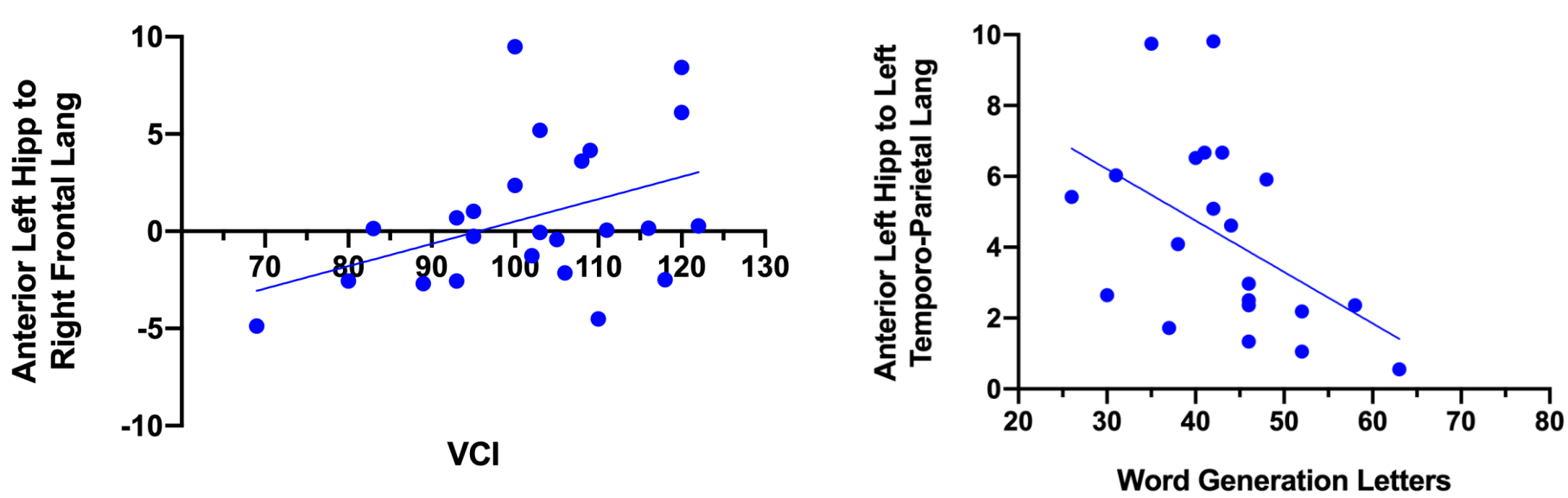
Within LTLE group only, significant correlations found between Age of Onset of epilepsy and connectivity of the left anterior hippocampus temporo-parietal language regions of both left and right hemisphere
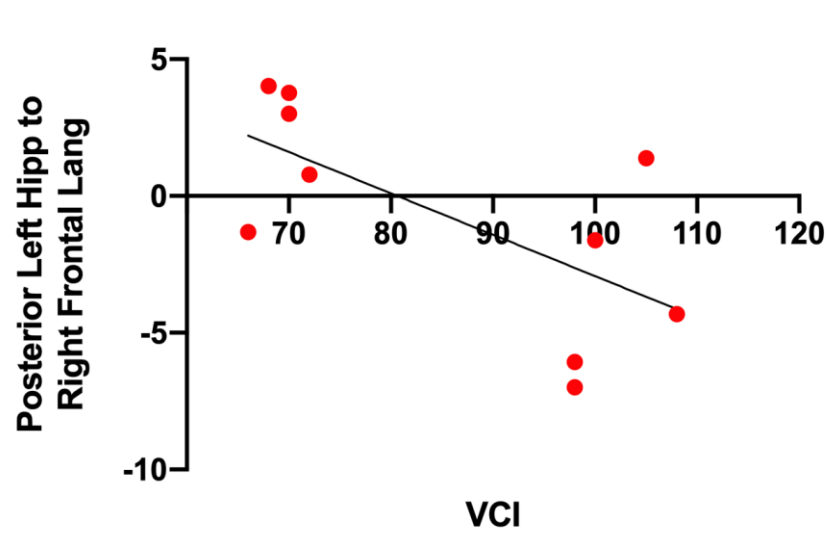
Relation to Hippocampal Volume: LTLE

In LTLE only, significant negative correlations between left anterior hippocampal volume and anterior left hippocampus to right frontal language (r = -0.63, p = .02), and both the left and right posterior hippocampus to posterior left hippocampus to right frontal language (r = -0.79 and -0.62, both p < .05).

Relation to Language Abilities: Right TLE

Relation to Language Abilities: Left TLE

Significant positive correlations between the Verbal Comprehension and the left anterior hippocampus to left frontal language regions (r = 0.41,) and Word Generation from Letters and left anterior hippocampus to left temporo-parietal language regions (r = -0.45; both p < .05)

Significant positive correlations between Verbal Comprehension Index and the left posterior hippocampus to right frontal language regions (r = 0.44, p < .05)

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