Introduction: Despite temporal lobe epilepsy (TLE) being a focal syndrome, patients experience widespread brain deficits. It has been shown previously that intrinsic connectivity networks (ICNs) have abnormal connectivity in patients with epilepsy. Additionally, we have previously shown abnormal connectivity in arousal structures in TLE. Arousal structures may modulate these ICNs. Here, we investigate if patients with TLE have perturbations in functional connectivity (non-directed and directed) between arousal structures and ICNs.

Methods: We acquired resting-state functional magnetic resonance imaging (fMRI) in 50 adults with TLE and 50 controls. We calculated non-directed functional connectivity (correlation) and directed functional connectivity (Granger causality laterality index: GCLI) within ICNs (default mode network: DMN, salience network: SN, and central executive network: CEN) and between arousal structures and ICNs. We compared functional connectivity in patients versus controls and associated these functional connectivity measures with disease metrics and neurocognitive testing. Finally, we used an fMRI-based vigilance measurement to preliminarily relate vigilance changes to resting-state functional connectivity of arousal structures.

Results: We noted decreased non-directed functional connectivity within DMN in patients (5.73±1.44, mean±SD) versus controls (6.75±1.38, p=0.0008) and within SN in patients (9.27±2.19) versus controls (10.40±2.33, p=0.0008, t-test, corrected). We found decreased functional connectivity between arousal network and SN in patients (1.12±1.03) versus controls (2.04±1.27, p=0.0001, t-test, corrected). Larger decreases in non-directed functional connectivity between nucleus basalis of Meynert (NBM) and SN were associated with worse processing speed index (r=0.251, p=0.033, Pearson correlation, uncorrected, N=37). Lower non-directed functional connectivity between pedunculopontine nucleus (PPN) and SN associated with worse verbal comprehension index (r=0.350, p=0.015, Pearson correlation, uncorrected, N=48) and full-scale intelligence quotient (FSIQ) (r=0.296, p=0.043, Pearson correlation, uncorrected, N=47). We noted abnormal GCLI between arousal network and SN in patients (-0.095±0.21) vs. controls (-0.26±0.24, p=0.0012, t-test, corrected), meaning SN exerts influence on arousal structures in controls, but not in patients. After surgery, we noted some recovery of non-directed functional connectivity between the NBM and SN. Finally, in a preliminary analysis using an fMRI-based template with estimates of alertness, we found that patients, but not controls, may exhibit decreased vigilance during fMRI, but that functional connectivity did not change with vigilance.

Discussion: These results suggest that abnormal functional connectivity between subcortical arousal structures and ICNs may partially underlie neurocognitive deficits typically seen in patients with TLE, and that these networks may represent novel neuromodulation targets to treat neurocognitive comorbidities in patients with TLE.

Keywords: Temporal lobe epilepsy, Functional neuroimaging, Connectivity networks