

1 **Default Mode Network Ventral Hub Connectivity Associated with Memory Impairment**  
2 **in Temporal Lobe Epilepsy Surgery**

3 Elliot G. Neal <sup>1</sup>, Long Di <sup>1</sup>, You Jeong Park <sup>1</sup>, Austin Finch <sup>1</sup>, Ferdinand Korneli <sup>1,2</sup>,  
4 Stephanie Maciver <sup>2</sup>, Yarema B. Bezchlibnyk <sup>1</sup>, Mike R. Schoenberg <sup>1,2</sup>, Fernando L. Vale <sup>3</sup>

5

6 <sup>1</sup> Department of Neurosurgery and Brain Repair, University of South Florida at Tampa

7 General Hospital, Tampa, FL, USA

8 <sup>2</sup> Department of Neurology, University of South Florida at Tampa General Hospital, Tampa,

9 FL, USA

10 <sup>3</sup> Department of Neurosurgery, Medical College of Georgia, Augusta University, Augusta,

11 GA

12

13 Corresponding Author: Fernando L. Vale, MD

14 Department of Neurosurgery

15 Medical College of Georgia at Augusta University

16 1120 15<sup>th</sup> Street, BI 3088

17 Augusta, GA 30912

18 [fvalediaz@augusta.edu](mailto:fvalediaz@augusta.edu)

19

20 Keywords: epilepsy surgery, epilepsy imaging, source localization, temporal lobe epilepsy,

21 epilepsy prognosis

22 **Abbreviations**

- 23 <sup>18</sup>Fluoro-2-Deoxyglucose Positron Emission Tomography ((<sup>18</sup>F-FDG) PET)
- 24 Blood Oxygenation Level Dependent (BOLD)
- 25 Boston Naming Test (BNT)
- 26 Controlled Oral Word Association Test (COWAT-FAS)
- 27 Default Mode Network (DMN)
- 28 Electroencephalography (EEG)
- 29 Long-Term Video-EEG Monitoring (LTM)
- 30 Magnetoencephalography (MEG)
- 31 Mesial temporal sclerosis (MTS)
- 32 Montreal Neurological Institute (MNI)
- 33 National Institutes of Health (NIH)
- 34 Resting state functional MRI (rsfMRI)
- 35 Rey Auditory Verbal Learning Test, Trial 6 (RAVLT6)
- 36 Rey Auditory Verbal Learning Test, Trial 7 (RAVLT7)
- 37 Ruff Figural Fluency Test - Unique Designs (RFFT-UD)
- 38 Ruff Figural Fluency Test – Error Ratio (RFFT-ER)
- 39 Single-Photon Emission Computed Tomography (SPECT)
- 40 Temporal Lobe Epilepsy (TLE)
- 41 Wechsler Adult Intelligence Scale-4<sup>th</sup> Ed. – Full Scale Intelligence Quotient (FSIQ)
- 42 Wechsler Memory Scale-4<sup>th</sup> Ed. (WMS-IV)
- 43 Wechsler Memory Scale-4<sup>th</sup> Ed., Logical Memory Immediate recall subtest (LM-I)
- 44 Wechsler Memory Scale-4<sup>th</sup> Ed., Logical Memory Delayed recall subtest (LM-II)
- 45 Wechsler Memory Scale-4<sup>th</sup> Ed., Visual Reproduction Immediate Recall subtest (VR-I)
- 46 Wechsler Memory Scale-4<sup>th</sup> Ed., Visual Reproduction Delayed Recall subtest (VR-II)

47 Abstract

48

49 In patients undergoing surgery for intractable temporal lobe epilepsy, the relationship  
50 between the default mode network and patients' neurocognitive outcome remains unclear.

51 The objective of this study is to employ non-invasive network mapping to identify the  
52 relationship between subdivisions of the default mode network and neurocognitive function  
53 before and after epilepsy surgery in patients with temporal lobe epilepsy.

54 Twenty-seven medically patients with medically refractory temporal lobe epilepsy  
55 were prospectively enrolled and received resting state functional MRI and  
56 neuropsychological testing both pre- and post-operatively. Connectivity within the default  
57 mode network was modeled and average connectivity within the networks was calculated.

58 Higher pre-operative connectivity in the ventral default mode network hub correlated  
59 with impaired baseline performance in a visual memory task. Post-operatively, a decrease in  
60 ventral but not dorsal default mode network connectivity was correlated with a deterioration  
61 of verbal and logical memory after surgery.

62 Overall, higher connectivity in the ventral default mode network hub was associated  
63 with poor memory function in patients with temporal lobe epilepsy both before and after  
64 temporal lobe surgery. Pre-operatively, higher ventral connectivity was associated with worse  
65 visual function. Post-operatively, decreased connectivity of the ventral and dorsal default  
66 mode network was correlated with a greater decrease in logical and verbal memory when  
67 compared with the pre-operation baseline. An imbalance in default mode network  
68 connectivity towards the ventral stream and more widespread epilepsy networks may be used  
69 to predict memory impairments following surgical intervention and may lead to more tailored  
70 surgical decision making based on this non-invasive network modeling.

## 71 1. Introduction

### 72 *1.1 Temporal Lobe Epilepsy*

73 Temporal lobe epilepsy (TLE) is the most common focal epilepsy in adults [1].  
74 Persistence of seizures leads to decline in verbal and visual memory, which may be  
75 associated with progressive hippocampal atrophy and it is possible that uncontrolled seizures  
76 will lead to deterioration in extratemporal faculties including executive function, attention,  
77 psychomotor speed, and general cognitive function [2-9].

### 78 *1.2 Network Analysis in Epilepsy Surgery*

79 Patients with medically refractory TLE may be candidates for potentially curative  
80 epilepsy surgery, and decline in memory function seen with persistent seizures can be  
81 arrested and possibly reversed with control of seizures following surgical intervention [2].  
82 The role of resting state fMRI (rsfMRI) and network analysis in epilepsy surgery has not  
83 been clearly established, but promising data has demonstrated its ability to help lateralize  
84 epileptogenesis and predict seizure recurrence after surgery [10-12]. Since uncontrolled  
85 seizures in patients with TLE leads to deterioration in extra-temporal neurocognitive  
86 function, a more nuanced approach might consider functional connectivity not only within  
87 the epilepsy network, but with networks underlying brain function more broadly, such as the  
88 default mode network (DMN).

### 89 *1.3 Default Mode Network*

90 The DMN is an intrinsic connectivity network that activates during periods of restful  
91 wakefulness – when the brain is not involved in externally oriented tasks – and deactivates  
92 during task performance [13, 14]. Functionally, the DMN can be subdivided into two  
93 integrated hubs, one more ventral and one more dorsal [15]. In general, studies conducted in  
94 patients with TLE have observed decreased connectivity between their temporal lobes and the  
95 DMN [16-20]. This finding appears to be related to the duration of TLE [17, 18], and studies

96 correlating data from rsfMRI and tractography suggest that the decreased connectivity may  
97 be related to microstructural damage in white matter bundles due to persistent seizures [21].  
98 Combined magnetoencephalography (MEG)/EEG and rsfMRI studies in patients with TLE  
99 have shown that during spike-free intervals, connectivity is increased between regions of the  
100 temporal lobe and the DMN [22]. Furthermore, left-sided mesial temporal sclerosis (MTS)  
101 appears to be associated with decreased functional connectivity of the temporal lobe and the  
102 DMN, while increased connectivity is seen in patients with right-sided MTS [22-24]. After  
103 surgery, McCormick et al. have shown that the decreased functional connectivity between the  
104 contralateral hippocampus and the posterior cingulate cortex (PCC)/precuneus – a critical  
105 node within the DMN – predicts postoperative memory decline [25].

#### 106 *1.4 Objective*

107 As regions of the DMN are also involved in episodic and autobiographical memory  
108 [26, 27], aberrant connectivity within this network may be associated with cognitive  
109 impairment in patients with TLE [28]. Here, we more broadly explore DMN connectivity and  
110 its correlation with neuropsychological measurements both pre- and post-operatively. The  
111 hypothesis for this study is that DMN ventral and dorsal hub connectivity will correlate with  
112 memory function both pre- and post-operatively in patients with TLE undergoing surgery.

## 113 2. Materials and Methods

### 114 *2.1. Patient Demographics*

115 All reported data followed the Strengthening the Reporting of Observational studies  
116 in Epidemiology (STROBE) guidelines for observational trials. DMN connectivity and  
117 epilepsy networks were modeled in twenty-seven patients with TLE. The patients included in  
118 this study represent a consecutive series of patients with TLE who signed consent and agreed  
119 to participate in this study (Table 1). The period of data collection started in May 2017 and  
120 concluded in October 2020. Each patient underwent a pre-surgical workup for epilepsy

121 surgery including: MRI, long-term video-EEG monitoring (LTM), Wada testing, <sup>18</sup>Fluoro-2-  
122 deoxyglucose positron emission tomography ((<sup>18</sup>F-FDG) PET), and quantitative  
123 neuropsychological evaluation. Five of those patients underwent subsequent phase II invasive  
124 monitoring for further clarification of epileptogenic focus. EEG and imaging interpretation  
125 were performed by a multidisciplinary team blinded to the network modeling parameters. The  
126 dominant hemisphere was defined as the hemisphere that supported expressive language  
127 when the contralateral side was injected during the Wada test. Additional data points  
128 collected included the side of surgery, pathologic MTS diagnosis, and age at surgery.

129

130 Table 1. Demographics

<b>Patient Number</b>	<b>Gender</b>	<b>Age at Surgery</b>	<b>MTS (Tissue Specimen)</b>	<b>Surgery Side</b>	<b>Dominant Hemisphere (Wada)</b>	<b>Seizure Free</b>
1	Female	50	No	Right	Left	No
2	Male	26	Yes	Left	Left	No
3	Male	17	No	Left	Right	No
4	Female	26	No	Right	Left	No
5	Female	35	No	Left	Left	No
6	Female	32	No	Left	Right	No
7	Female	40	No	Right	Left	No
8	Female	36	No	Left	Left	No
9	Female	47	Yes	Left	Left	Yes
10	Male	30	N/A	Right	N/A	Yes
11	Male	23	N/A	Left	Left	Yes
12	Female	34	Yes	Left	Right	Yes
13	Female	58	No	Left	Left	Yes
14	Female	32	N/A	Left	Bilateral	Yes
15	Female	19	Yes	Right	Left	Yes
16	Female	40	Yes	Right	Left	Yes
17	Female	30	No	Right	Left	Yes

18	Male	26	Yes	Left	Left	Yes
19	Male	44	N/A	Right	Right	Yes
20	Female	33	Yes	Left	Left	Yes
21	Female	32	N/A	Left	Left	Yes
22	Female	36	Yes	Left	Right	Yes
23	Male	32	No	Left	Left	Yes
24	Female	28	Yes	Left	Left	Yes
25	Female	24	No	Left	N/A	Yes
26	Male	25	Yes	Left	Left	Yes
27	Female	53	Yes	Left	Left	Yes

131

132

### 133 2.2. Data Acquisition

134 EEG and rsfMRI were obtained on two separate visits. EEG was acquired with  
135 twenty-four scalp electrodes in an International 10-20 configuration. rsfMRI was conducted  
136 in a three tesla MRI with a blood oxygenation level dependent (BOLD) MRI sequence,  
137 consisting of a single five-minute acquisition (eyes closed) with parameters as follows: echo  
138 time (TE) of 35 ms, repetition time (TR) of 3000 ms, and a voxel size of 4 x 3.75 x 3.75 mm.

### 139 2.3. Default Mode Network Connectivity

140 rsfMRI datasets were normalized to Montreal Neurological Institute (MNI) space  
141 using the six-parameter rigid body spatial transformation algorithm using SPM12 (Wellcome  
142 Department of Imaging Neuroscience, University College London, UK). An atlas of ROIs  
143 generated in a prior study of rsfMRI datasets was overlaid on the rsfMRI to extract the time  
144 series signature from regions of interest (ROIs) involved in the ventral and dorsal DMN [[13](#),  
145 [29](#)]. An important consideration in this analysis is that of the ROIs used to define the DMN  
146 hubs. Whereas other studies have used individual component analyses (ICA) to define the  
147 DMN on an individual level [[30](#)], in the current study we opted to use an atlas-based, ROI  
148 approach. The DMN ROIs were adapted from a previous study using *a priori* methods to

149 identify networks in healthy patients using rsfMRI [29]. The ventral DMN ROI included: a  
150 large cluster in the medial parietal cortex, including the precuneus, PCC, and retrosplenial  
151 cortex, regions of the bilateral angular gyri, the anterior ventral area of the medial prefrontal  
152 cortex as well as bilateral parahippocampal gyri, bilateral inferior temporal cortices, and  
153 bilateral superior/middle frontal cortices. Dorsal DMN ROIs included: a major cluster in the  
154 medial prefrontal cortex/anterior cingulate cortex (ACC), and the bilateral caudate nuclei. To  
155 a lesser degree, the PCC was also included as well as the bilateral hippocampi, thalami, the  
156 right angular gyrus, the left superior temporal cortex, and the right calcarine cortex (Figure  
157 1). The average time series for each ROI was used to generate a connectivity matrix of  
158 Pearson correlation values grouped into the ventral and dorsal DMN groups. Average  
159 connectivity for both the ventral and dorsal DMN was calculated and used as a marker for  
160 functional connectivity within the respective network both pre- and post-operatively.

161

162 *Figure 1: Default Mode Network Regions of Interest: The regions of interest (ROIs)*  
163 *applied for connectivity analysis in the default mode network (DMN) are overlaid on coronal*  
164 *MRI sections. Regions in blue represent the ventral DMN, while those in red represent the*  
165 *dorsal DMN.*

166

#### 167 *2.4. Neuropsychological Testing*

168 Pre-operatively, all twenty-seven patients completed a comprehensive  
169 neuropsychological assessment following National Institutes of Health (NIH) Epilepsy  
170 common data elements recommendations. Due to differences in how one patient's assessment  
171 was documented, the data for that patient could not be included. Thus, twenty-six patients  
172 had pre-operative neuropsychological data which were available and were included for  
173 analysis. Sixteen of these patients also had post-operative testing. Subtests of the Wechsler



174 Memory Scale-4th Ed. (WMS-IV) and RAVLT were used to measure verbal immediate  
175 memory (LM-I, RAVLT trial 6) and verbal delayed memory (LM-II, RAVLT trial 7) [31].  
176 Visual immediate memory tests included the WMS-IV VR-I subtest and visual delayed  
177 memory task including WMS-IV VR-II subtest and the ROCFT-delay task. Letter and  
178 semantic verbal fluency tasks including the Controlled Oral Word Association Test (FAS)  
179 and animal semantic fluency task was measured. Confrontation naming was measured using  
180 the Boston Naming Test (BNT). Executive function including the Wisconsin Card Sorting  
181 Test and the Ruff Figural Fluency Test (RFFT). The RFFT provides a measure of nonverbal  
182 mental flexibility including unique designs and perseverative errors error ratio. Finally, each  
183 patient completed the Wechsler Adult Intelligence Scale – 4th Ed (WAIS-IV) prorated full-  
184 scale intelligence index (Table 2). Age-corrected scores for all neuropsychological tests  
185 except for WAIS-IV IQ scores were used in analyses. Descriptive statistics for this cohort are  
186 given in Table 3.

187

188 Table 2. Neuropsychological Tests

<b>Cognitive Domain</b>	<b>Test</b>
Immediate Verbal Memory	Wechsler Memory Scale-4 <sup>th</sup> Ed. LM-I
	RAVLT Trial 6
Delayed Verbal Memory	Wechsler Memory Scale-4 <sup>th</sup> Ed. LM-II
	RAVLT Trial 7
Immediate Visual Memory	Wechsler Memory Scale-4 <sup>th</sup> VR-I
Delayed Visual Memory	Wechsler Memory Scale-4 <sup>th</sup> VR-II
Semantic Verbal Fluency	Controlled Oral Word Association Test (FAS)
	Animal Semantic Fluency
Confrontation Naming	Boston Naming Test
Executive Function	Ruff Figural Fluency Test
Full-Scale Intelligence	Wechsler Adult Intelligence Scale – 4 <sup>th</sup> Edition

189

190 Table 3. Neuropsychological Testing Values

191 Difference score = Post-op score – pre-op score

<b>Test Name</b>		<b>Minimum</b>	<b>Maximum</b>	<b>Mean</b>	<b>Standard Deviation</b>
<b>FSIQ</b>	Pre-op score	64.00	112.00	85.50	14.70
	Post-op score	61.00	118.00	84.86	15.27
	Difference score	-18.00	16.00	1.08	7.99
<b>LM-I</b>	Pre-op score	20.00	64.00	37.83	13.66
	Post-op score	20.00	59.00	36.79	13.47
	Difference score	-29.00	10.00	-3.46	10.65
<b>LM-II</b>	Pre-op score	20.00	66.00	38.78	12.26
	Post-op score	20.00	59.00	37.80	11.77
	Difference score	-15.00	13.00	-1.92	7.69
<b>VR-I</b>	Pre-op score	20.00	63.00	38.70	12.70
	Post-op score	19.00	60.00	36.87	12.42
	Difference score	-23.00	17.00	-0.69	10.23
<b>VR-II</b>	Pre-op score	20.00	73.00	40.70	11.17
	Post-op score	20.00	66.00	39.13	14.81
	Difference score	-12.00	22.00	1.85	9.33
<b>FAS</b>	Pre-op score	21.00	60.00	37.56	10.71
	Post-op score	23.00	58.00	39.33	7.90
	Difference score	-7.00	19.00	4.57	6.91
<b>Animal Naming</b>	Pre-op score	24.00	60.00	39.20	9.60
	Post-op score	17.00	53.00	33.93	10.61
	Difference score	-26.00	12.00	-2.79	11.05
<b>RAVLT-6</b>	Pre-op score	0.00	80.00	40.82	17.23
	Post-op score	0.00	57.00	36.75	16.88

	Difference score	-22.00	21.50	0.50	11.58
<b>RAVLT-7</b>	Pre-op score	5.00	64.00	38.24	15.19
	Post-op score	10.00	56.00	37.71	16.05
	Difference score	-14.00	31.00	4.46	12.76
<b>BNT</b>	Pre-op score	8.00	53.00	34.92	11.08
	Post-op score	8.00	53.00	33.87	11.49
	Difference score	-15.00	15.00	-1.14	8.29
<b>RFFT-UD</b>	Pre-op score	33.00	120.00	67.76	22.40
	Post-op score	42.00	116.00	68.27	20.23
	Difference score	-17.70	12.00	0.61	7.51
<b>RFFT-ER</b>	Pre-op score	36.00	73.00	55.51	14.27
	Post-op score	38.00	73.00	55.83	10.93
	Difference score	-21.00	9.20	-3.47	8.91

192

### 193 2.5. Statistical Analysis

194 Neuropsychological data and the network metrics were compared using a Spearman  
 195 Rho correlation coefficient analysis. Connectivity differences between the subgroups was  
 196 analyzed using an independent-sample t-test. All statistical tests were conducted using IBM  
 197 SPSS Statistics Version 26 (IBM Corp., Armonk, New York, United States). P-values less  
 198 than  $\alpha = 0.05$  were considered significant.

### 199 2.6. Data Availability

200 The data will be made available to anyone within reason who requests it from the  
 201 corresponding author. The network mapping algorithm will also be made available for  
 202 purposes of validation and corroboration of presented results if requested.

203 3. Results

204 3.1. *Demographics*

205 Twenty-seven patients with TLE underwent pre-operative rsfMRI scanning and  
206 network analysis. The time from the first lifetime seizure to the surgery was an average of  
207 14.9 +/- 10.2 years. The average time to most recent follow-up after surgery was 30.2 +/-  
208 8.69 months. Nineteen (70%) of the patients underwent surgery on the left temporal lobe.  
209 Twenty-five patients (93%) completed Wada testing, and fifteen of those patients (60%) had  
210 a surgery in the dominant hemisphere. In the cohort, four patients underwent stereotactic  
211 laser amygdalohippocampotomy (SLAH) while the remaining twenty-three underwent  
212 microsurgical resection with either selective amygdalohippocampectomy (SAH; sixteen),  
213 anterior temporal lobectomy (ATL; one), or resection of the temporal pole with  
214 amygdalectomy and minimal hippocampal resection (HC-sparing; six). Of these patients,  
215 eleven (41%) had tissue specimen proven MTS, eleven (41%) did not have MTS, and five  
216 (19%) patients had no hippocampus specimens collected.

217 3.2. *Pre-operative DMN Connectivity in TLE*

218 Pre-operative connectivity within the ventral and dorsal DMN and the ratio of ventral  
219 to dorsal DMN connectivity were compared to pre-operative neuropsychometric  
220 performance. To control for possible differences in DMN connectivity between patients, we  
221 analyzed the relationship between the ratio of ventral to dorsal DMN connectivity. Patients  
222 with a higher ventral:dorsal DMN connectivity ratio (DCR; i.e. those with a relatively higher  
223 ventral DMN connectivity when compared to dorsal DMN connectivity) performed worse in  
224 immediate (VRI I,  $R = -0.401$ ,  $p = 0.042$ ) and delayed (VRI II,  $R = -0.446$ ,  $p = 0.022$ )  
225 visuoconstructional memory tasks. Higher DCR (ventral > dorsal) also correlated with  
226 impaired immediate and delayed verbal memory function (RAVLT6,  $R = -0.434$ ,  $p = 0.024$ ;  
227 RAVLT7  $R = -0.383$ ,  $p = 0.049$ ) (Figure 2).

228

229 *Figure 2: Increased pre-operative DMN ventral hub connectivity correlates with*  
230 *relatively worse visual memory. A. Immediate visual memory (LMI) pre-operative*  
231 *performance, scaled to age-matched controls, is lower in patients who's DMN connectivity is*  
232 *relatively higher in the ventral hub compared to the dorsal hub. B. The same trend is also*  
233 *found when comparing the ratio of ventral to dorsal DMN hub connectivity to delayed visual*  
234 *memory. The connectivity ratio is skewed towards the ventral hub in patients who performed*  
235 *worse on the delayed visual memory task (LMII).*

236

### 237 *3.3. Post-operative Changes in the DMN*

238 DMN connectivity and neuropsychological function were also measured post-  
239 operatively in the same way as the pre-operative assessment. Change in connectivity of both  
240 the ventral and dorsal DMN after surgery was measured by the ratio of the average pre- and  
241 post-operative Pearson correlation within the respective network. For example, when the  
242 post-operative network connectivity was close to that of the pre-operative network (ratio  
243 approaches unity), then that patient's network connectivity was relatively preserved after  
244 surgery. Pre-operative ventral DMN connectivity was compared to post-operative ventral  
245 DMN connectivity, and pre-operative dorsal DMN was compared to post-operative dorsal  
246 DMN. It was found increase in connectivity within the ventral DMN after surgery was  
247 associated with a decline post-operatively in both immediate (LM I,  $R = -0.668$ ,  $p = 0.006$ )  
248 and delayed (LM II,  $R = -0.747$ ,  $p = 0.001$ ) (RAVLT 7,  $R = -0.622$ ,  $p = 0.013$ ) verbal  
249 memory (Figure 3).

250

251 *Figure 3: Post-operative connectivity in the ventral hub is increased in patients who*  
252 *exhibit a relative decline in memory compared to their pre-operative performance. Difference*

253 scores are calculated by subtracting the pre-operative score from the post-operative score so  
254 that higher difference scores indicate improvement post-operatively compared to before  
255 surgery. Increased connectivity within the ventral DMN hub correlated with decline in  
256 immediate logical memory (A), delayed logical memory (B), and delayed verbal memory  
257 (C).

258

### 259 *3.4. Subgroup Analysis*

260 DMN connectivity was also assessed in patients segregated by several factors,  
261 including presence of MTS, left vs. right side surgery, and dominant vs. non-dominant side  
262 surgery. First, comparison was made with regards to the pre-operative DMN connectivity.  
263 When comparing patients with pathology-proven MTS to those without ( $n=x, y$ ,  
264 respectively), neither ventral nor dorsal DMN connectivity at baseline were significantly  
265 different (ventral  $p = 0.754$ , dorsal  $p = 0.815$ ). The same results were found when comparing  
266 patients with surgery on the left side vs. the right ( $n=x, y$ , respectively; ventral  $p = 0.722$ ,  
267 dorsal  $p = 0.366$ ) and between patients with surgery on the dominant vs. non-dominant side  
268 ( $n=x, y$ , respectively; ventral  $p = 0.626$ , dorsal  $p = 0.738$ ). At the post-operative timepoint,  
269 again there was no difference in ventral or dorsal DMN connectivity with respect to presence  
270 of MTS on pathology (ventral  $p = 0.603$ , dorsal  $p = 0.282$ ), side of surgery (ventral  $p = 0.182$ ,  
271 dorsal  $p = 0.690$ ), or surgery on the dominant vs. non-dominant side (ventral  $p = 0.544$ ,  
272 dorsal  $p = 0.721$ ). Pathological specimens were not available for five patients, so the analysis  
273 was also performed based on radiographic features of MTS. Again, there were no significant  
274 differences in the ventral or dorsal DMN connectivity either pre-operatively ( $n=x, y$ ,  
275 respectively; ventral DMN  $p = 0.646$ , dorsal DMN  $p = 0.938$ ) or post-operatively ( $n=x, y$ ,  
276 respectively; ventral DMN  $p = 0.684$ , dorsal DMN  $p = 0.323$ ).

## 277 4. Discussion

278        4.1. *Main Findings and Impact*

279            In the present study, we show that increased ventral hub connectivity in patients with  
280 medically refractory temporal lobe epilepsy was correlated with impaired memory function  
281 both before and after temporal lobe surgery. Pre-operatively, we found that increased ventral,  
282 but not dorsal, DMN connectivity in patients with TLE is associated with poorer immediate  
283 and delayed verbal and visual. After surgery, it was shown that relative increase in  
284 connectivity within the ventral DMN was associated with a decrease in immediate and  
285 delayed logical memory and delayed verbal memory. Subgroup analyses revealed no  
286 difference in DMN connectivity either pre-operatively or post-operatively in patients with  
287 pathological or radiological diagnoses of MTS, patients undergoing surgery on the left or  
288 right side, or patients undergoing dominant or non-dominant hemisphere surgeries.

289            Here, increased connectivity within the ventral DMN at baseline was generally found  
290 to be a poor prognostic indicator in that it was associated with impaired verbal and visual  
291 memory pre-operatively and relative increase in ventral DMN connectivity after surgery was  
292 associated with a greater decline in verbal and logical memory. These findings may relate to  
293 the more global effects on network connectivity seen in patients with TLE. One possible  
294 explanation is that with longstanding epilepsy, the epileptogenic temporal lobe becomes  
295 progressively disconnected from the DMN over time [[16-20](#)], resulting in an associated  
296 dysregulation in the DMN which is measured as an increase in functional connectivity of the  
297 ventral stream of the DMN, perhaps by way of compensation. The dysregulated ventral DMN  
298 may then become less “resilient” to surgical interventions and may result in it becoming  
299 abnormally hyperactivated after surgery, with an end effect in impairments of memory and  
300 visuoconstructional abilities.

301            Interestingly, we failed to identify any significant differences between patients with  
302 either pathological or radiographic diagnoses of MTS vs. no-MTS, left vs. right sided

303 surgery, or dominant vs. non-dominant surgery side. The lack of an association is not clear,  
304 but an unknown compensatory network may play an important role in these patients. One  
305 prior study done in patients with MTS found a decreased connectivity between the PCC,  
306 precuneus, and mesial temporal lobes, but there was no comparison of patients with MTS and  
307 those without MTS [21].

308 In future studies, we will include stereo-encephalography (SEEG) results into this  
309 analysis to incorporate seizure spread as it relates to the DMN hubs. We do not yet know how  
310 seizure propagation disrupts the DMN, and different patterns of spread may help to explain  
311 why some patients have a more dysregulated ventral hub than others. Furthermore, semiology  
312 has been related to anatomy [32, 33], but not yet to network connectivity analysis. In future  
313 studies we will incorporate semiology into this analysis to differentiate subgroups of patients  
314 who may more preferentially have disrupted DMN hub connectivity.

315 While not detracting from the findings of the present study, there are some  
316 limitations. First, the sample size is somewhat limited. This is a preliminary study showing  
317 that is intended to inform larger prospective studies into the DMN connectivity in patients  
318 undergoing temporal lobe surgery for epilepsy. Furthermore, while the sample size is limited,  
319 follow up is rigorous including post-operative neuropsychological testing and rsfMRI.  
320 Another limitation of this study is that only one method is used to assess connectivity, and in  
321 future studies we hope to use SEEG to corroborate these connectivity findings.

322 Connectivity within the DMN was investigated in patients with TLE undergoing  
323 surgery both pre- and post-operatively using rsfMRI. Increased connectivity within the  
324 ventral DMN was found to be a poor prognostic indicator in that it was associated with worse  
325 visual and verbal memory pre-operatively, and increased connectivity in the ventral DMN  
326 after surgery was found in patients who had relatively more decline in verbal and logical  
327 memory post-operatively.



328 5. Acknowledgements: None

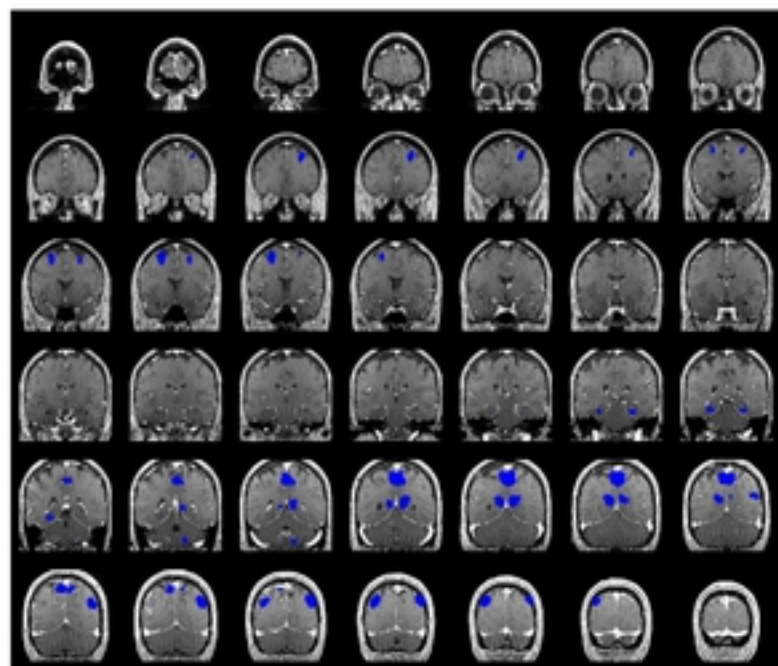
329 6. References

- 330 1. Tellez-Zenteno JF, Hernandez-Ronquillo L. A review of the epidemiology of  
331 temporal lobe epilepsy. *Epilepsy Res Treat.* 2012;2012:630853. Epub 2012/09/08. doi:  
332 10.1155/2012/630853. PubMed PMID: 22957234; PubMed Central PMCID:  
333 PMCPMC3420432.
- 334 2. Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE. Chronic epilepsy and  
335 cognition: a longitudinal study in temporal lobe epilepsy. *Ann Neurol.* 2003;54(4):425-32.  
336 Epub 2003/10/02. doi: 10.1002/ana.10692. PubMed PMID: 14520652.
- 337 3. Fuerst D, Shah J, Shah A, Watson C. Hippocampal sclerosis is a progressive disorder:  
338 a longitudinal volumetric MRI study. *Ann Neurol.* 2003;53(3):413-6. Epub 2003/02/26. doi:  
339 10.1002/ana.10509. PubMed PMID: 12601713.
- 340 4. Dodrill CB. Neuropsychological effects of seizures. *Epilepsy Behav.* 2004;5 Suppl  
341 1:S21-4. Epub 2004/01/17. doi: 10.1016/j.yebeh.2003.11.004. PubMed PMID: 14725843.
- 342 5. Bergen DC. Do seizures harm the brain? *Epilepsy Curr.* 2006;6(4):117-8. Epub  
343 2007/01/30. doi: 10.1111/j.1535-7511.2006.00116.x. PubMed PMID: 17260030; PubMed  
344 Central PMCID: PMCPMC1783429.
- 345 6. Hermann B, Loring DW, Wilson S. Paradigm Shifts in the Neuropsychology of  
346 Epilepsy. *J Int Neuropsychol Soc.* 2017;23(9-10):791-805. Epub 2017/12/05. doi:  
347 10.1017/S1355617717000650. PubMed PMID: 29198272; PubMed Central PMCID:  
348 PMCPMC5846680.
- 349 7. Helmstaedter C, Witt JA. How neuropsychology can improve the care of individual  
350 patients with epilepsy. Looking back and into the future. *Seizure.* 2017;44:113-20. Epub  
351 2016/10/30. doi: 10.1016/j.seizure.2016.09.010. PubMed PMID: 27789166.
- 352 8. Hwang G, Hermann B, Nair VA, Conant LL, Dabbs K, Mathis J, et al. Brain aging in  
353 temporal lobe epilepsy: Chronological, structural, and functional. *Neuroimage Clin.*  
354 2020;25:102183. Epub 2020/02/15. doi: 10.1016/j.nicl.2020.102183. PubMed PMID:  
355 32058319; PubMed Central PMCID: PMCPMC7016276.
- 356 9. Dabbs K, Becker T, Jones J, Rutecki P, Seidenberg M, Hermann B. Brain structure  
357 and aging in chronic temporal lobe epilepsy. *Epilepsia.* 2012;53(6):1033-43. Epub  
358 2012/04/05. doi: 10.1111/j.1528-1167.2012.03447.x. PubMed PMID: 22471353; PubMed  
359 Central PMCID: PMCPMC3710695.
- 360 10. Ofer I, LeRose C, Mast H, LeVan P, Metternich B, Egger K, et al. Association  
361 between seizure freedom and default mode network reorganization in patients with unilateral  
362 temporal lobe epilepsy. *Epilepsy Behav.* 2019;90:238-46. Epub 2018/12/13. doi:  
363 10.1016/j.yebeh.2018.10.025. PubMed PMID: 30538081.
- 364 11. Bettus G, Bartolomei F, Confort-Gouny S, Guedj E, Chauvel P, Cozzone PJ, et al.  
365 Role of resting state functional connectivity MRI in presurgical investigation of mesial  
366 temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry.* 2010;81(10):1147-54. Epub  
367 2010/06/16. doi: 10.1136/jnnp.2009.191460. PubMed PMID: 20547611.
- 368 12. Morgan VL, Sonmezturk HH, Gore JC, Abou-Khalil B. Lateralization of temporal  
369 lobe epilepsy using resting functional magnetic resonance imaging connectivity of  
370 hippocampal networks. *Epilepsia.* 2012;53(9):1628-35. Epub 2012/07/12. doi:  
371 10.1111/j.1528-1167.2012.03590.x. PubMed PMID: 22779926; PubMed Central PMCID:  
372 PMCPMC3436984.
- 373 13. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy,  
374 function, and relevance to disease. *Ann N Y Acad Sci.* 2008;1124:1-38. Epub 2008/04/11.  
375 doi: 10.1196/annals.1440.011. PubMed PMID: 18400922.
- 376 14. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A  
377 default mode of brain function. *Proc Natl Acad Sci U S A.* 2001;98(2):676-82. Epub

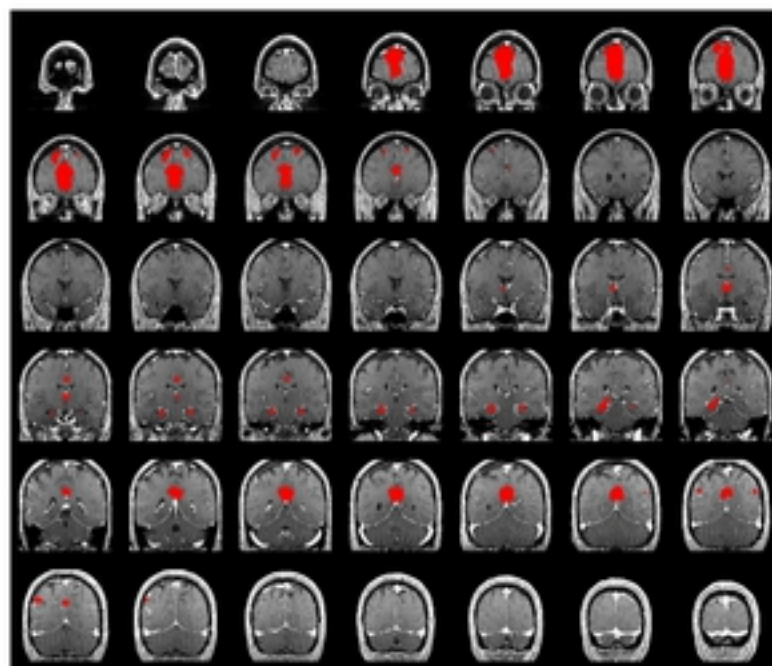
- 378 2001/02/24. doi: 10.1073/pnas.98.2.676. PubMed PMID: 11209064; PubMed Central  
379 PMCID: PMCPMC14647.
- 380 15. Raichle ME. The brain's default mode network. *Annu Rev Neurosci.* 2015;38:433-47.  
381 Epub 2015/05/06. doi: 10.1146/annurev-neuro-071013-014030. PubMed PMID: 25938726.
- 382 16. Cook CJ, Hwang G, Mathis J, Nair VA, Conant LL, Allen L, et al. Effective  
383 Connectivity Within the Default Mode Network in Left Temporal Lobe Epilepsy: Findings  
384 from the Epilepsy Connectome Project. *Brain Connect.* 2019;9(2):174-83. Epub 2018/11/07.  
385 doi: 10.1089/brain.2018.0600. PubMed PMID: 30398367; PubMed Central PMCID:  
386 PMCPMC6444922.
- 387 17. Voets NL, Beckmann CF, Cole DM, Hong S, Bernasconi A, Bernasconi N. Structural  
388 substrates for resting network disruption in temporal lobe epilepsy. *Brain.* 2012;135(Pt  
389 8):2350-7. Epub 2012/06/07. doi: 10.1093/brain/aws137. PubMed PMID: 22669081.
- 390 18. Liao W, Zhang Z, Pan Z, Mantini D, Ding J, Duan X, et al. Altered functional  
391 connectivity and small-world in mesial temporal lobe epilepsy. *PLoS One.* 2010;5(1):e8525.  
392 Epub 2010/01/15. doi: 10.1371/journal.pone.0008525. PubMed PMID: 20072616; PubMed  
393 Central PMCID: PMCPMC2799523.
- 394 19. Pereira FR, Alessio A, Sercheli MS, Pedro T, Bilevicius E, Rondina JM, et al.  
395 Asymmetrical hippocampal connectivity in mesial temporal lobe epilepsy: evidence from  
396 resting state fMRI. *BMC Neurosci.* 2010;11:66. Epub 2010/06/08. doi: 10.1186/1471-2202-  
397 11-66. PubMed PMID: 20525202; PubMed Central PMCID: PMCPMC2890013.
- 398 20. Pittau F, Grova C, Moeller F, Dubeau F, Gotman J. Patterns of altered functional  
399 connectivity in mesial temporal lobe epilepsy. *Epilepsia.* 2012;53(6):1013-23. Epub  
400 2012/05/15. doi: 10.1111/j.1528-1167.2012.03464.x. PubMed PMID: 22578020; PubMed  
401 Central PMCID: PMCPMC3767602.
- 402 21. Liao W, Zhang Z, Pan Z, Mantini D, Ding J, Duan X, et al. Default mode network  
403 abnormalities in mesial temporal lobe epilepsy: a study combining fMRI and DTI. *Hum  
404 Brain Mapp.* 2011;32(6):883-95. Epub 2010/06/10. doi: 10.1002/hbm.21076. PubMed PMID:  
405 20533558.
- 406 22. Hsiao FJ, Yu HY, Chen WT, Kwan SY, Chen C, Yen DJ, et al. Increased Intrinsic  
407 Connectivity of the Default Mode Network in Temporal Lobe Epilepsy: Evidence from  
408 Resting-State MEG Recordings. *PLoS One.* 2015;10(6):e0128787. Epub 2015/06/04. doi:  
409 10.1371/journal.pone.0128787. PubMed PMID: 26035750; PubMed Central PMCID:  
410 PMCPMC4452781.
- 411 23. Zhang Z, Lu G, Zhong Y, Tan Q, Chen H, Liao W, et al. fMRI study of mesial  
412 temporal lobe epilepsy using amplitude of low-frequency fluctuation analysis. *Hum Brain  
413 Mapp.* 2010;31(12):1851-61. Epub 2010/03/13. doi: 10.1002/hbm.20982. PubMed PMID:  
414 20225278.
- 415 24. Zanao TA, Lopes TM, de Campos BM, Yasuda CL, Cendes F. Patterns of default  
416 mode network in temporal lobe epilepsy with and without hippocampal sclerosis. *Epilepsy  
417 Behav.* 2019;106523. Epub 2019/10/28. doi: 10.1016/j.yebeh.2019.106523. PubMed PMID:  
418 31645315.
- 419 25. McCormick C, Quraan M, Cohn M, Valiante TA, McAndrews MP. Default mode  
420 network connectivity indicates episodic memory capacity in mesial temporal lobe epilepsy.  
421 *Epilepsia.* 2013;54(5):809-18. Epub 2013/01/31. doi: 10.1111/epi.12098. PubMed PMID:  
422 23360362.
- 423 26. Svoboda E, McKinnon MC, Levine B. The functional neuroanatomy of  
424 autobiographical memory: a meta-analysis. *Neuropsychologia.* 2006;44(12):2189-208. Epub  
425 2006/06/30. doi: 10.1016/j.neuropsychologia.2006.05.023. PubMed PMID: 16806314;  
426 PubMed Central PMCID: PMCPMC1995661.

- 427 27. Spreng RN, Grady CL. Patterns of brain activity supporting autobiographical  
428 memory, prospection, and theory of mind, and their relationship to the default mode network.  
429 *J Cogn Neurosci*. 2010;22(6):1112-23. Epub 2009/07/08. doi: 10.1162/jocn.2009.21282.  
430 PubMed PMID: 19580387.
- 431 28. Laufs H, Hamandi K, Salek-Haddadi A, Kleinschmidt AK, Duncan JS, Lemieux L.  
432 Temporal lobe interictal epileptic discharges affect cerebral activity in "default mode" brain  
433 regions. *Hum Brain Mapp*. 2007;28(10):1023-32. Epub 2006/11/30. doi: 10.1002/hbm.20323.  
434 PubMed PMID: 17133385; PubMed Central PMCID: PMC2948427.
- 435 29. Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD. Decoding subject-  
436 driven cognitive states with whole-brain connectivity patterns. *Cereb Cortex*.  
437 2012;22(1):158-65. Epub 2011/05/28. doi: 10.1093/cercor/bhr099. PubMed PMID:  
438 21616982; PubMed Central PMCID: PMC3236795.
- 439 30. Doucet GE, Skidmore C, Evans J, Sharan A, Sperling MR, Pustina D, et al. Temporal  
440 lobe epilepsy and surgery selectively alter the dorsal, not the ventral, default-mode network.  
441 *Front Neurol*. 2014;5:23. Epub 2014/03/22. doi: 10.3389/fneur.2014.00023. PubMed PMID:  
442 24653713; PubMed Central PMCID: PMC3948047.
- 443 31. Lezak MD, Howieson D. *Neuropsychological assessment* (5th ed.). References. 2012.
- 444 32. Marks WJ, Jr., Laxer KD. Semiology of temporal lobe seizures: value in lateralizing  
445 the seizure focus. *Epilepsia*. 1998;39(7):721-6. Epub 1998/07/22. doi: 10.1111/j.1528-  
446 1157.1998.tb01157.x. PubMed PMID: 9670900.
- 447 33. Bonini F, McGonigal A, Trebuchon A, Gavaret M, Bartolomei F, Giusiano B, et al.  
448 Frontal lobe seizures: from clinical semiology to localization. *Epilepsia*. 2014;55(2):264-77.  
449 Epub 2014/01/01. doi: 10.1111/epi.12490. PubMed PMID: 24372328.

Ventral DMN



Dorsal DMN



Combined

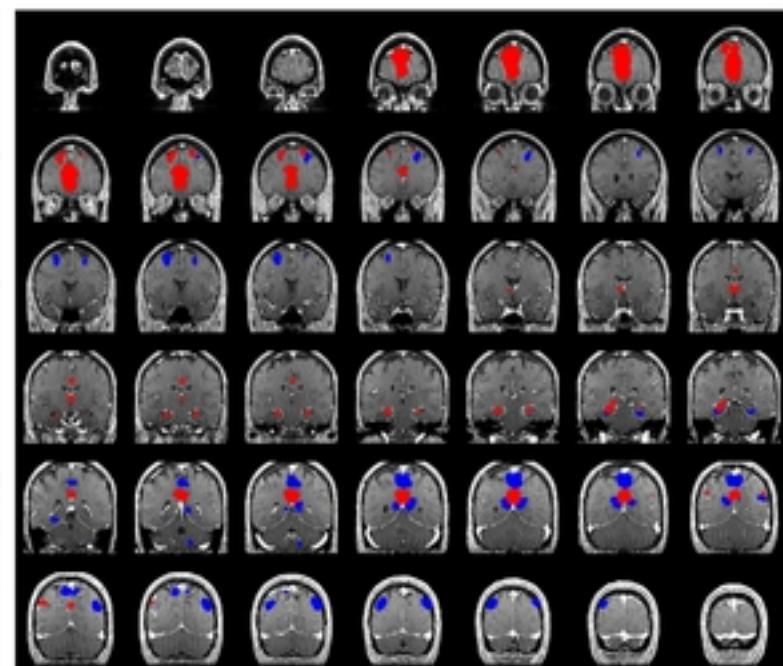


Figure 1

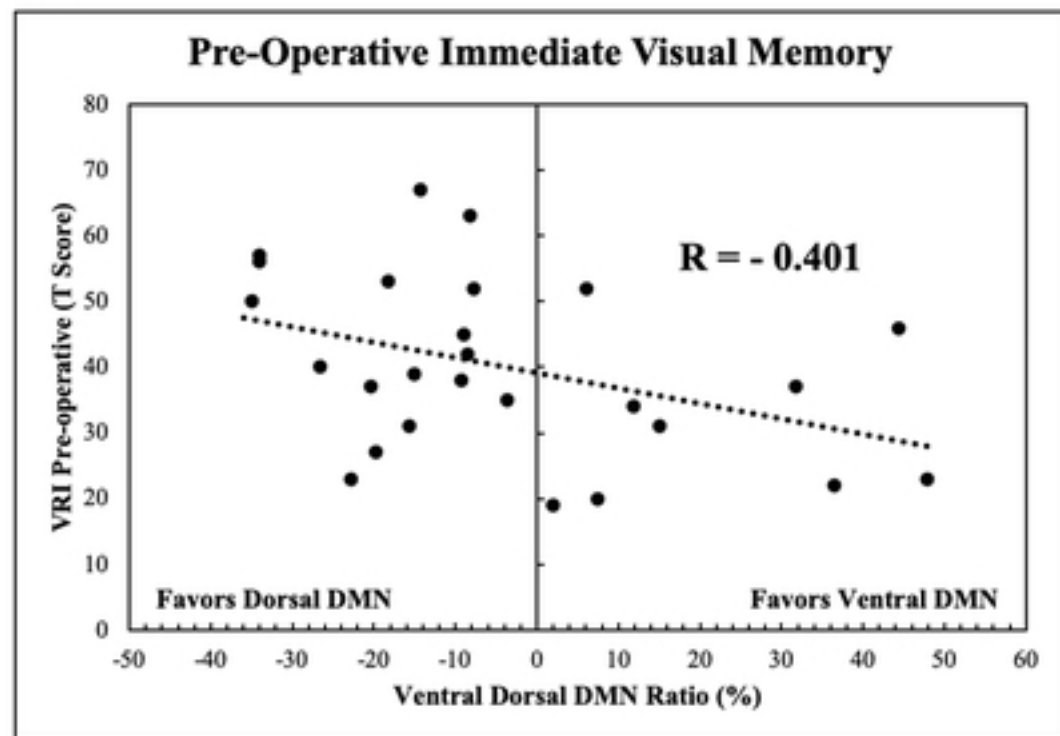
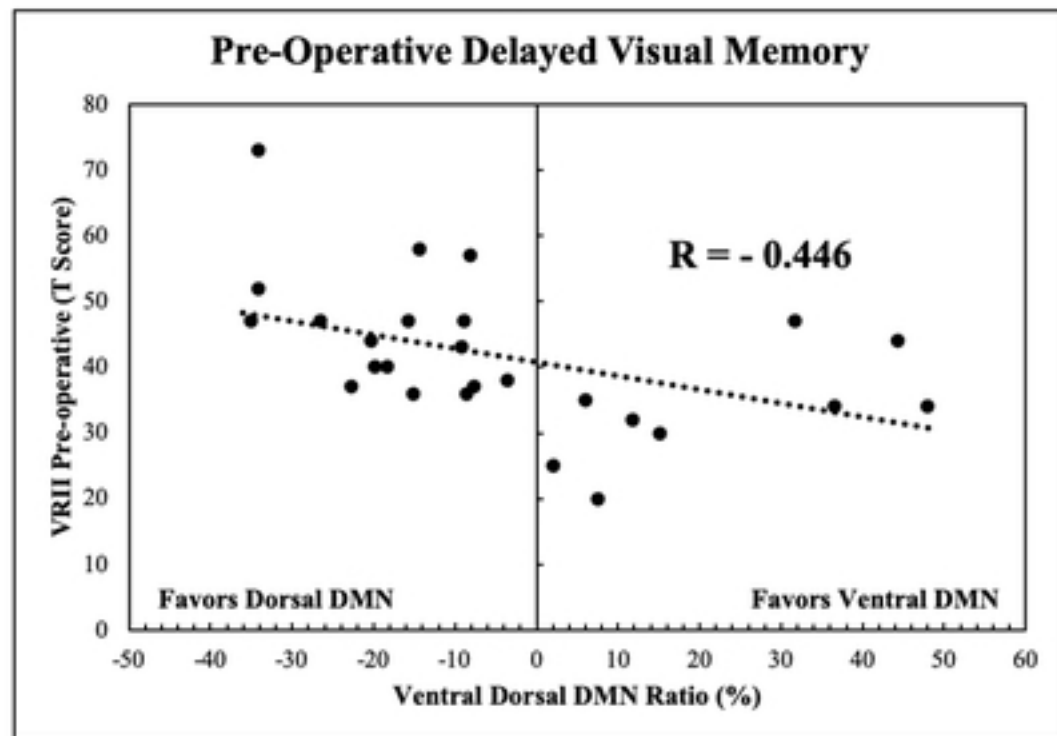
**A.****B.**

Figure 2

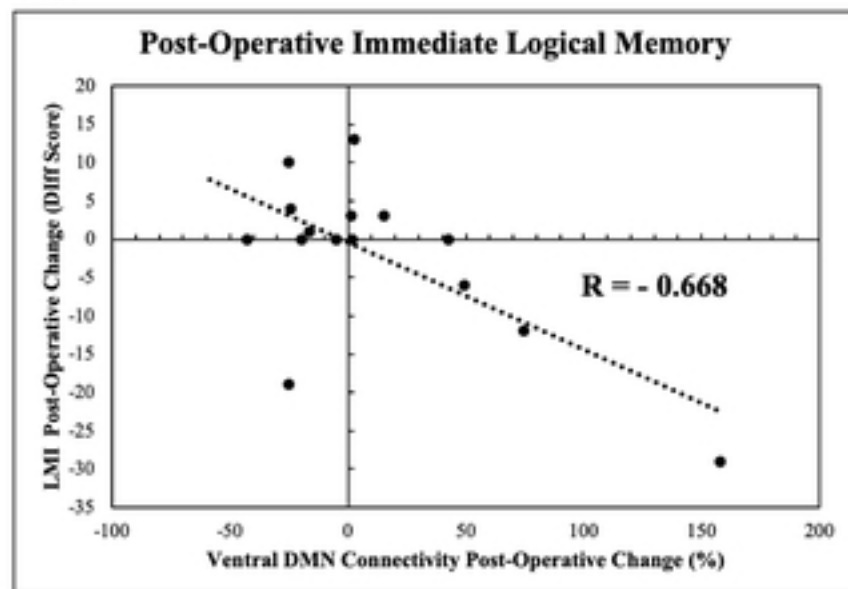
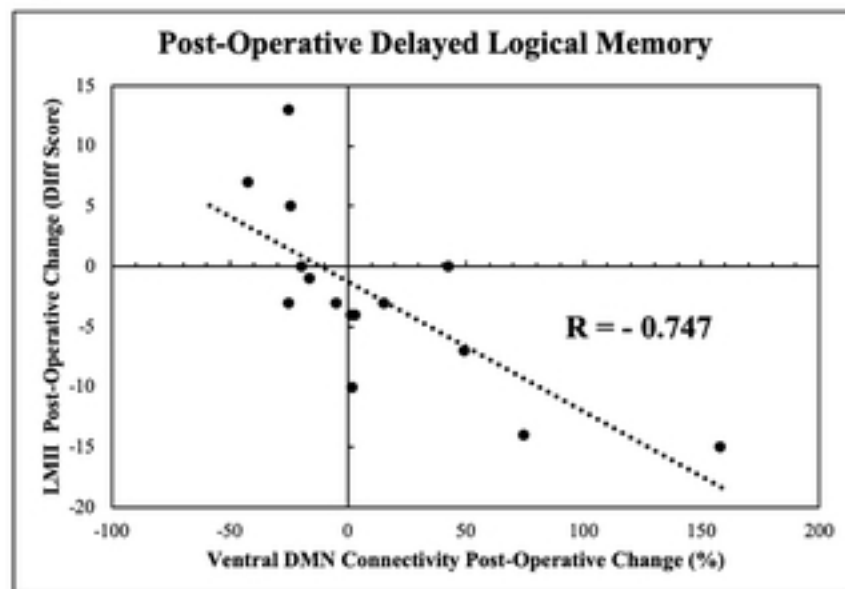
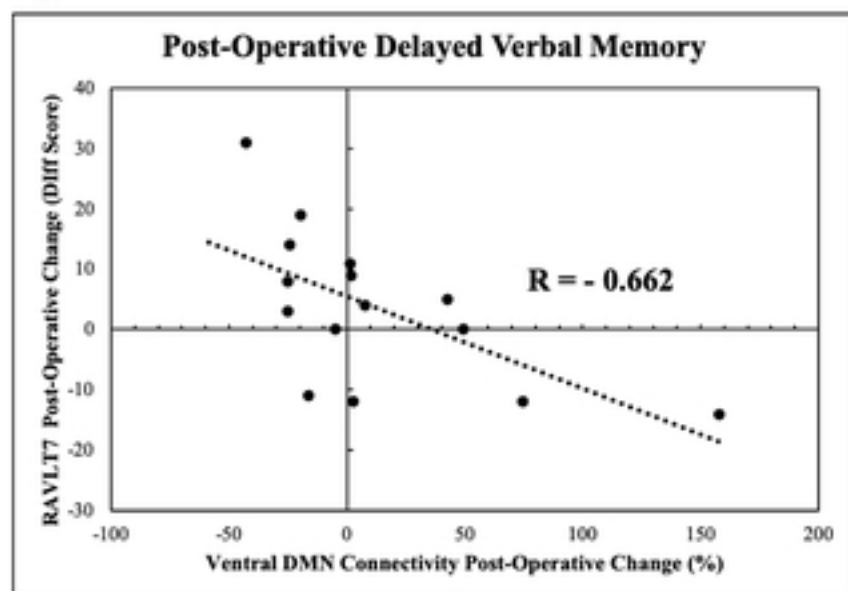
**A.****B.****C.**

Figure 3