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Executive Dysfunction is Associated with an Altered Executive Control Network in Pediatric Temporal Lobe Epilepsy

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Abstract

Objectives—Children with temporal lobe epilepsy (TLE) exhibit executive dysfunction on traditional neuropsychological tests. However, there is limited evidence of neural network alterations associated with this clinical executive dysfunction. The objective of this study was to characterize working memory deficits in children with TLE via activation of the executive control network on fMRI and determine the relationships to fMRI behavioral findings and traditional neuropsychological tests.

Experimental Design—Functional magnetic resonance imaging was conducted on 17 children with TLE and 18 healthy control participants (age 8–16 years) while they performed the *N*-back task in order to assess activation of the executive control network. *N*-back accuracy, *N*-back reaction time, and traditional neuropsychological tests (Delis-Kaplan Executive Function [D-KEFS] color-word interference and card-sort test) were also assessed.

Principal Observations—Children with TLE exhibited executive dysfunction on D-KEFS testing, reduced *N*-back accuracy and increased *N*-back reaction time compared to healthy controls. D-KEFS and *N*-back behavioral findings were significantly correlated. Children with TLE also exhibited significant reduction in activation of the frontal lobe within the executive control network compared to healthy controls. These alterations were significantly correlated with *N*-back behavioral findings and D-KEFS testing.

Conclusions—Children with TLE exhibit executive dysfunction which correlates with executive control network alterations. This lends validity to the theory that the executive control network

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contributes to working memory function. The findings also indicate that children with TLE have network alterations in non-temporal brain regions.

Keywords

Temporal Lobe Epilepsy; Pediatric; Executive Control Network; N-back task; neuropsychological testing; Executive Dysfunction; focal impaired awareness seizures

Introduction

Chronic temporal lobe epilepsy (TLE) in adults is known to be associated with neuropsychological abnormalities that extend beyond the expected anomalies in memory to include other cognitive domains including executive function [1], [2]. Working memory (WM), which is a component of executive function (EF), is the ability to store temporarily and manipulate information [3] and is frequently impaired in patients with TLE [4], [5], [6], [7], [8]. WM is generally considered a frontal lobe function [4], [9] and is not traditionally associated with temporal lobe lesions, but increasing evidence indicates that medial temporal lobe dysfunction may directly or indirectly impair WM [1], [9]. The mechanisms underlying WM disruption in TLE remain unclear, however, alterations in distributed neural networks have been suggested to play a role [10], [11], [12], [13].

In addition to results from neuropsychological studies, a number of imaging studies have investigated and corroborated WM deficits in TLE patients, addressing the potential neurobiological correlates of cognitive dysfunction in TLE. Quantitative imaging studies have documented cortical thinning of the frontal lobe in TLE [14], [15] with reduced prefrontal cortex volume associated with compromised working memory function [16]. Tractography studies demonstrate reduced fractional anisotropy in the cingulate (verbal WM-related fiber bundles) [17] and altered frontostriatal tracts and caudate atrophy in TLE [18], [19]. PET studies reveal hypometabolism of the prefrontal cortex in TLE, which correlate with higher-order measures of working memory [20]. Numerous functional imaging studies in patients with TLE demonstrate altered connectivity and disrupted networks in the frontal lobe [12], [21], [22], [23], [24], with the dorsal attention and default mode networks exhibiting decreased connectivity related to neuropsychological findings [25], [26], [27]. In addition, fMRI activation studies reveal reduction in activation of the executive control network in TLE [9], [17].

The findings from the above studies are based on investigations within an adult TLE population. As a result, it is often presumed that the network deficits described above develop over the natural course of chronic epilepsy [28] as they frequently correlate with a longer duration of epilepsy or an earlier age of onset of epilepsy [1], [22], [29], [30]. As such, the effects from prolonged TLE as opposed to the origins of the disorder itself are yet to be distinguished. However, emerging evidence indicates that children with TLE including new-onset TLE exhibit EF (including WM) deficits [8], [31], [32]. Furthermore, fMRI studies in children with TLE reveal altered network connectivity in language and default mode networks [25], [33], [34], [35]. These and other findings suggest that cognitive deficits

may develop early in the course of TLE or even simultaneously with epilepsy onset. EF dysfunction has even been reported to precede the onset of clinical epilepsy [17].

Interestingly, less attention has been devoted to functional imaging investigations of EF (including WM) in children with TLE. A clear understanding of EF deficits is essential as primary impairment of EF in children with TLE may contribute to the development of other cognitive dysfunctions such as poor memory performance (e.g., Sepeta et al., 2017 [36]). Few studies evaluate extra temporal connection deficits in children with TLE using functional neuroimaging. Given the notion that this may be a more vulnerable group [17], [28], [37], further evaluation is warranted.

In functional imaging research, working memory is frequently investigated using the '*N*-back' task, which involves monitoring a series of letters or pictures and responding whenever the stimulus is presented *N* trials prior [38]. The '*N*' instruction regularly changes throughout the task requiring constant on-line monitoring and updating of information. This *N*-back paradigm is processed through the executive control network that includes both bilateral frontal and parietal cortical regions [39]. To the best of our knowledge, this task has not been examined in children with TLE. Furthermore, the relationship between this task which engages WM and neuropsychological tests which are traditionally used to assess EF is yet to be characterized. In the present study, we examine WM in children with TLE and its substrate using functional neuroimaging along with neuropsychological testing. We also aimed to characterize the relationships between behavioral performance on the *N*-back test, functional imaging findings on the *N*-back test, with performance on traditional neuropsychological tests of EF in children with TLE with the goal of characterizing the brain abnormalities underlying EF dysfunction in a pediatric TLE population.

Methods

Participants

Thirty-five children (17 participants with TLE, 18 controls, ages 8–16) served as the research participants. Healthy children and pediatric TLE patients were recruited from MedSTAR Georgetown University Hospital. Parents gave written informed consent while the children provided written assent according to the approved IRB protocol. Selection criteria for all participants included the following: native English speakers; capacity to fully cooperate and follow directions; absence of significant structural abnormalities such as stroke or tumor (mesial temporal sclerosis excepted for TLE patients) as assessed using clinical MRI; and no other neurological/sleep disorder which could affect cognition. Exclusion criteria included MRI safe metallic implants or devices that distort MRI signal including braces; non-MRI compatible implanted devices, and claustrophobia. For TLE patients, focal impaired awareness seizures of definite or probable temporal lobe origin were diagnosed by a pediatric epileptologist. The epileptologist reviewed patients' medical records including seizure characteristics and recent EEG and neuroimaging reports. Definite temporal lobe epilepsy was defined by continuous video-EEG monitoring of spontaneous seizures demonstrating temporal lobe seizure onset; probable temporal lobe epilepsy was determined by review of clinical characteristics with features reported to reliably identify focal seizures of temporal lobe origin versus onset in other origins (e.g., frontal lobe) in

conjunction with interictal EEG, neuroimaging findings, and developmental and clinical history. Only patients meeting criteria for definite and probable temporal lobe epilepsy proceeded to recruitment for study participation.

Selection criteria for healthy control participants also included no history of loss of consciousness for >5 minutes or developmental learning disorder diagnosed/suspected at school. Healthy control participants were matched for age and gender. A diagnosis of ADHD did not exclude epilepsy or control participants from the study [41].

Image Acquisition

Imaging data was acquired using a 3T Siemens magnet (Siemens Magnetom TIM Trio, Erlangen, Germany) equipped with 12-channel head coil. Participants viewed the stimuli via a mirror mounted on the coil that reflected the images projected onto a screen. Stimuli were displayed on screen at the back of the scanner using a projector located outside of the scanner room. Anatomical images of subjects were collected using a sagittal T₁ MPRAGE sequence with the following parameters: TR/TE=1900/2.52 ms, TI=900 ms, 176 slices, slice resolution= 1.0 mm³. This scan served to screen for anatomical abnormalities. Blood oxygen level-dependent (BOLD) changes were measured using functional images (122 acq/run) acquired using a T2*-sensitive gradient-echo EPI sequence with the following parameters: repetition time = 2500ms, echo time = 30ms, field of view = 192mm, and effective voxel size = 3.0 × 3.0 × 3.0mm³. The fMRI images were collected parallel to the anterior commissure-posterior commissure plane, which served as an origin reference. Whole-brain volumes consisted of 50 axial slices of 2.8mm thickness with a 0.2mm gap between slices.

Procedures

All participants were required to avoid stimulants 24 hours prior to testing. Participants began with administration of the Wechsler Abbreviated Scale of Intelligence-2 (WASI-2) (Matrix Design and Vocabulary subtests) [36], [40].

Imaging

Before scanning, the participant was familiarized with the scanner and *N*-back test using a mock scanner and each child completed a shortened version of the *N*-back test prior to scanning. Once pre-MRI evaluation was completed, scanning was performed. The *N*-back task consisted of presenting participants with a series of single consonant letters with the instruction to press a button with their dominant hand when the presented letter was the same as the one presented *N* letters ago. Participants were tested using three loads: a 0-back, 1-back, and 2-back. This represented no, low, and high working memory load fMRI runs each lasting 305 seconds. Each run consisted of 12 blocks of 9 *N*-back trials. The first run alternated between 0-back and 1-back blocks and the second run alternated 1-back and 2-back blocks. Each trial was presented on the screen for 2500ms with an instruction (rest) slide presented over 2500ms preceding each block. Responses and reaction times were recorded using a fiber-optic response box (MRA Inc, Washington, PA, USA). All tasks were programmed using E-PRIME software (version 1.1; Psychology Software Tools, Pittsburgh,

PA, USA) and generated by a PC. Stimuli were back-projected onto a computer screen that could be viewed through a mirror attached above the scanner's head coil. Errors were counted when the answer was not correct or participants failed to press the button.

Neuropsychological assessment

After scanning and a short break, the participants underwent neuropsychological testing. In addition to the WASI-2, patients and controls were administered a brief test battery that included executive function (Delis-Kaplan Executive Function (D-KEFS Color Word Interference and Card Sort tests) [42], [43], and speeded fine motor dexterity (Grooved Pegboard – dominant hand) [1].

Analysis

Analysis of fMRI behavioral data and neuropsychological measures

All behavioral data was analyzed using standard statistical software (SPSS, version 23; SPSS Inc., Chicago, Illinois, USA). The *N*-back accuracy and speed scores as well as cognitive scores were log-transformed and normality was checked. Univariate and Multivariate Analysis of Co-Variance (ANCOVA & MANCOVA) was used to evaluate differences between control and TLE participants. The independent variable was group (TLE versus control participants) and the dependent variables were the log-transformed fMRI behavioral data and neuropsychological test scores. A supplementary analysis using stepwise linear regression was performed using age, ADHD diagnosis, FSIQ, medications as covariates. Except for age, the effects of these potential confounding variables were minimal and non-contributory to the analyses, so were excluded as covariates. Age was included as a covariate to address potential confounding effects in all analyses. Alpha level was $p=0.05$, with a targeted minimum partial *eta* squared effect size of 0.1 (medium effect size). LSD post-hoc tests were used for individual comparisons. Partial correlations, controlling for age, were performed between fMRI behavioral data and neuropsychological tests to determine any relationships.

Analysis of imaging data

Statistical parametric mapping (SPM12) software package (Wellcome Department of Imaging Neuroscience, London, United Kingdom) was used for data analyses. The fMRI volumes were subjected to standard preprocessing procedures including realignment, ArtRepair (artifact detection and repair of bad slices for high-motion pediatric fMRI studies, 15% required repair of average of 3 slices each), spatial normalization to the EPI template and smoothing with a 6mm full-width-at-half-maximum isotropic Gaussian kernel. The smoothed images from each participant underwent a first-level analysis to determine the contrasts of interest. To remove residual variance from head movements during that image acquisition, the movement parameters (*x*-, *y*-, *z*-, pitch, roll and yaw directions) extracted in the realignment procedure were included in the model as covariates. (Head motion was monitored closely during the scanning with a threshold of 0.5 mm FD and participants with more than 20% of their volumes above this cutoff were excluded). Filtering of the data included the use of a high-pass filter of 128 seconds to remove signal drift. The model was then convolved with the canonical hemodynamic response function. Contrast images were

generated for each subject comparing 2-back minus 0-back. The contrast images were then included in a two-sample t-test in order to extract effects of group. This included validation of the task network by pooling the data from all subjects as well as comparison of the two groups. All contrasts were thresholded by applying a family wise error (FWE) cluster-level correction of $P < 0.05$; after using a cluster-defining threshold of $P < 0.001$ and a minimal cluster size of 40 voxels (magnitude of peak activation). Age was used as a covariate of interest. The bspmview software was used to determine the anatomic sites of the differences in activation (Montreal Neurological Institute coordinates), t-values, and number of voxels in the activated areas.

Analysis of relationships between imaging data, fMRI behavioral data and neuropsychological measures

Whole-brain multiple regression analyses were performed in SPM12 software to determine the correlations with fMRI behavioral data and neuropsychological tests. The regression analyses were performed separately for each neuropsychological and fMRI behavioral measure to determine any significant regions of interest associated with these measures. FWE cluster-level correction was utilized to avoid errors from multiple comparisons. Age was used as a covariate of interest.

Results

Demographics

Basic demographic and clinical characteristics are provided and compared in Table 1a&b. There were no patients with clear evidence of bilateral temporal lobe epilepsy on EEG. As expected, the TLE group had a lower mean Full Scale IQ score compared to healthy controls ($p = 0.02$, $\eta_p^2 = 0.274$). There were no significant group differences in age or gender. Both healthy control and TLE groups included individuals with ADHD. Treatment in the TLE participants included valproic acid ($N = 2$), leviteracetam ($N = 4$), lamotrigine ($N = 3$), carbamazepine ($N = 2$), oxcarbazepine ($N = 3$), perampanel ($N = 1$), lacosamide ($N = 1$), and medical marijuana ($N = 1$) (Table 1b). Four TLE patients (27%) were being treated with two antiepileptic medications. Head motion parameters did not differ significantly between the two groups ($F(1,28) = 0.17$, $p=0.68$).

Neuropsychological EF Data

In accordance with prior studies, children with TLE showed executive dysfunction on standardized EF testing compared to control participants. Children with TLE performed poorer on grooved pegboard speed (dominant hand) ($F(1,26) = 9.23$, $p=0.007$, $\eta_p^2 = 0.327$), D-KEFs Color Word Interference speed ($F(1,26) = 5.45$, $p=0.031$, $\eta_p^2 = 0.223$), D-KEFs Color Word Interference accuracy ($F(1,26) = 5.21$, $p=0.034$, $\eta_p^2 = 0.215$), and D-KEFs Card Sort correct sorts performance ($F(1,26) = 9.103$, $p=0.007$, $\eta_p^2 = 0.324$).

N-Back Behavioral Data

N-back reaction times were analyzed via one-way ANCOVA with group as the independent variable. Results showed slower reaction time among epilepsy patients compared to controls

in both the low working memory load ($F(1,26) = 8.98, p=0.008, \eta_p^2 = 0.346$) and high working memory load ($F(1,26) = 10.72, p=0.004, \eta_p^2 = 0.387$) tests (Figure 1).

In the next step, accuracy measures were compared between two groups. Results yielded no differences between epilepsy patients and controls in the low working memory task ($F(1,26) = 2.66, p=0.149, \eta_p^2 = 0.1$). However, in the high working memory task, epilepsy patients were less accurate compared to controls ($F(1,26) = 4.24, p=0.041, \eta_p^2 = 0.2$) (Figure 2).

N-Back Behavioral Data and Neuropsychological Tests

Low and high load working memory tasks were collapsed to examine whether accuracy and reaction time correlated with other behavioral variables. Using partial correlations, we found that *N*-back reaction time positively correlated grooved pegboard speed (dominant hand) ($R = 0.591, p = 0.006$) and negatively correlated with WASI-2 FSIQ ($R = -0.676, p = 0.006$), D-KEFs Color Word Interference speed ($R = -0.499, p = 0.050$), and D-KEFs Card Sort correct sorts performance ($R = -0.544, p = 0.036$) (see Table 2). *N*-back accuracy negatively correlated with grooved pegboard speed (dominant hand) ($R = -0.654, p = 0.002$) and positively correlated with WASI-2 FSIQ ($R = 0.449, p = 0.050$), D-KEFs Color Word Interference accuracy ($R = 0.588, p = 0.023$) and D-KEFs Card Sort correct sorts performance ($R = 0.515, p = 0.02$) (see Table 2).

Imaging Data

A total of four participants did not tolerate the fMRI scanner. Individuals analyzed displayed an activation pattern consistent with the executive control network, indicating that they had engaged the task correctly. A total of three participants did not display a pattern consistent with the network being analyzed.

In the *N*-back task, the 2-back minus 0-back data showed consistent activation patterns in the controls with the main activation located in the bilateral frontal and parietal regions. The pooled working memory task activated an extended area within the frontal and parietal lobes including left inferior parietal lobe ($p < 0.001$), left middle frontal gyrus ($p < 0.001$), left inferior frontal gyrus ($p = 0.001$), left lingual gyrus ($p = 0.002$), and right superior frontal gyrus ($p = 0.003$) were activated. This is the expected activation pattern from the working memory network (Table 3 & Figure 3).

Direct comparison of the groups showed a difference in the left middle frontal gyrus such that controls activate this region more than TLE participants during the task ($p = 0.033$, Table 3).

N-back Behavioral Data and Imaging Data

In a separate whole-brain analysis, a multiple regression was utilized to determine the relationship between *N*-back performance and fMRI BOLD activation. Significant negative correlations showed that individuals with longer reaction times (speed) and more errors (accuracy) exhibited less activation in the working memory network, specifically within the left inferior parietal lobe, right middle frontal gyrus, and left middle frontal gyrus ($p < 0.001$, Table 4). In addition, reaction times were also correlated less activation of the left inferior

frontal gyrus ($p = 0.001$), left inferior temporal gyrus ($p = 0.007$), left middle occipital gyrus ($p = 0.014$), and right cuneus ($p = 0.033$)

Neuropsychological Testing and Imaging Data

A multiple regression evaluating the relationship between the executive function neuropsychological testing and fMRI BOLD activation was conducted using a whole-brain analysis. D-KEFs Color-Word interference errors (accuracy), D-KEFs Color-Word interference reaction times (speed), and Pegboard speeded dexterity were correlated with fMRI activation. Significant negative correlations showed that individuals with more D-KEFs errors (accuracy) exhibited less activation in the working memory network, specifically within the left superior parietal lobe ($p < 0.001$), left inferior frontal gyrus ($p < 0.001$), and right superior frontal gyrus ($p = 0.003$, Table 4). Significant negative correlations showed that individuals with longer D-KEFs reaction times (speed) exhibited less activation of the left inferior parietal lobe ($p < 0.001$), left inferior frontal gyrus ($p < 0.001$), right superior frontal gyrus ($p = 0.001$), and left middle occipital gyrus ($p = 0.031$, Table 4). Significant negative correlations showed that individuals with longer Pegboard reaction times (speed) exhibited less activation of the left inferior parietal lobe ($p < 0.001$), left inferior frontal gyrus ($p < 0.001$), and right superior frontal gyrus ($p < 0.001$, Table 4).

Discussion

The goal of this investigation was to determine if children with TLE exhibit deficits in extra-temporal neural networks and to determine if these extra-temporal neural network abnormalities correlate with the extra-temporal cognitive deficits previously reported in pediatric TLE. There are four key findings. First, our results corroborate prior findings of EF dysfunction in children with TLE. Using standardized assessments of EF, we found that children with TLE performed significantly worse across measures of novel problem-solving and response inhibition. Children with TLE also demonstrated deficits in speeded fine motor dexterity. Second, using the *N*-back test as a behavioral measure of working memory, children with TLE exhibited deficits in working memory reaction time as well as accuracy. Third, children with TLE showed less activation of the executive control network compared to healthy controls during the fMRI *N*-back task and the activation correlated with reaction time of the *N*-back behavioral data. Fourth, the decreased fMRI activation and the poorer performance on fMRI working memory tasks correlated with EF neuropsychological tests.

It is evident that EF deficits in children with TLE is a reliable finding. Our results add to the mounting evidence of extra-temporal cognitive deficits in children with TLE [8], [32], [36], [44]. Specifically, children with TLE showed worse response inhibition and novel problem solving capacity (D-KEFs Color Word Interference and Card Sort). Furthermore, the deficits in Full-Scale IQ and visual motor speed suggest evidence of a wider network of dysfunction and not just disrupted frontotemporal networks as might be expected with EF deficits only. Specifically, this corroborates prior evidence indicating a more generalized global cognitive deficit in children with TLE.

The fMRI behavioral data indicate that children with TLE exhibit deficits in reaction time during the *N*-back task regardless of level of difficulty. Children with TLE were consistently

slower on all *N*-back task loads, while accuracy differences may only appear when demand increased. During the less challenging *N*-back run (low working memory load), children with TLE performed similarly to healthy controls. However during the more taxing *N*-back run (high working memory load), children with TLE may no longer be able to adequately compensate, that is, their accuracy waned and performance was poorer compared to healthy controls. Thus, manipulation of task difficulty may unmask impairments not evident in a less challenging task. These deficits in both reaction time and accuracy of the *N*-back testing provides further evidence of a global cognitive deficit affecting both frontotemporal networks as well as other non-temporal networks. Further investigation involving activation of specific fMRI networks in children with TLE is necessary to fully delineate the extent and magnitude of these global cognitive deficits. Most important, performance on these EF neuropsychological tests correlate with the *N*-back behavioral results, demonstrating that in-scanner performance has meaningful implications for traditional assessment of EF and also infers that EF overall is impaired regardless of testing situation.

Children with TLE also exhibited performance deficits during the *N*-back task that were accompanied by distinct activity reductions in the frontal lobe (right prefrontal cortex). These results suggest that WM impairment in pediatric TLE follows a pattern of neural dysfunction in the executive control network, which is not typically associated with temporal lobe dysfunction. This finding suggests that the neural networks in TLE participants are altered such that there may be an inability to increase frontal lobe activity to meet the higher demand as was seen amongst control participants. Further investigation into the relationship between neuropsychological deficits and fMRI in pediatric TLE is warranted to gain a better understanding of the clinical effects of these disrupted neural networks.

Specific regions of interest within the BOLD fMRI findings correlated with the *N*-back behavioral findings as well as the neuropsychological testing. To our knowledge, this is the first documentation of a clear relationship between fMRI behavioral findings, BOLD fMRI findings, and EF deficits characterized by traditional neuropsychological measures in children with TLE. Our findings, which accounted for age, medications, FSIQ, and ADHD, indicate that the fMRI findings may indeed be reflective of extended objective test performance, which provides evidence of ecological validity of functional imaging measures.

These novel findings indicate that children with TLE do indeed exhibit extra-temporal abnormalities as identified both on fMRI and neuropsychological testing with important relationships between the modes of assessment and activation strength on fMRI. In addition, given the relatively modest duration of TLE (mean= 3.8 years, as opposed to conventional adult studies of TLE where patients often have 20+ years of effects from this chronic disorder), the frontal abnormalities identified appear to be part of the origins of the disorder and not a consequence of multiple years of seizure activity.

These findings indicate that the EF deficits persist in spite of using IQ as a covariate suggests that the EF deficits are separate from general intellectual ability in pediatric TLE. Further studies would be necessary to verify these findings. In addition, the current findings

may be specific to TLE, however, similar EF deficits have been described in frontal lobe epilepsies [45] as well as primary generalized epilepsies [46].

Limitations and Future Directions

The limitations associated with this investigation should be noted. Our sample size was limited and it is possible that with a larger sample size, more extensive analyses would have been possible to determine the existence of interactions among these three modes of cognitive evaluation. In spite of our limited sample size, we were able to document these novel findings. Conceivably, children with TLE require recruitment of compensatory brain regions to complete the frontal lobe tasks successfully [17]. This network reorganization could possibly explain the consistently slower speed we found among children with TLE during the *N*-back task. Given our limited sample size, we were unable to evaluate this in detail. Relationships between imaging tasks and episodic memory/language would be of interest and should be evaluated in future studies. Future studies using larger sample sizes are necessary to characterize relationships between EF neuropsychological tests and neurobiological substrates of EF, which will in turn provide a further understanding of the effects of TLE on typical ‘frontal lobe’ measures in a pediatric population. With a larger sample size, the role of potential contributing variables such as laterality of temporal focus and the effect of medications can be delineated.

Conclusions

This study demonstrates the existence of EF deficits in children with TLE via neuropsychological tests, fMRI behavioral findings, and fMRI BOLD activation measures. Our data corroborates prior findings and establishes evidence of a relationship between these three modes of evaluation. Our findings indicate that the significant frontal lobe dysfunction exhibited in adults with TLE may indeed be a neurodevelopmental phenomenon that perhaps worsens over the course of the chronic epilepsy since these significant anomalies are evident in childhood early in the course of the epilepsy. Further investigation is warranted to begin to determine the etiology of these findings.

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Epilepsy Paper Highlights

1. Our goal was to determine if children with temporal lobe epilepsy (TLE) exhibit deficits in extra-temporal neural networks on fMRI
2. Children with TLE exhibit deficits in working memory - reaction time and accuracy
3. In addition, children with TLE showed less activation of the executive control network
4. The decreased fmri activation and the poorer performance on fmri working memory tasks correlat with neuropsychological testing of executive function.

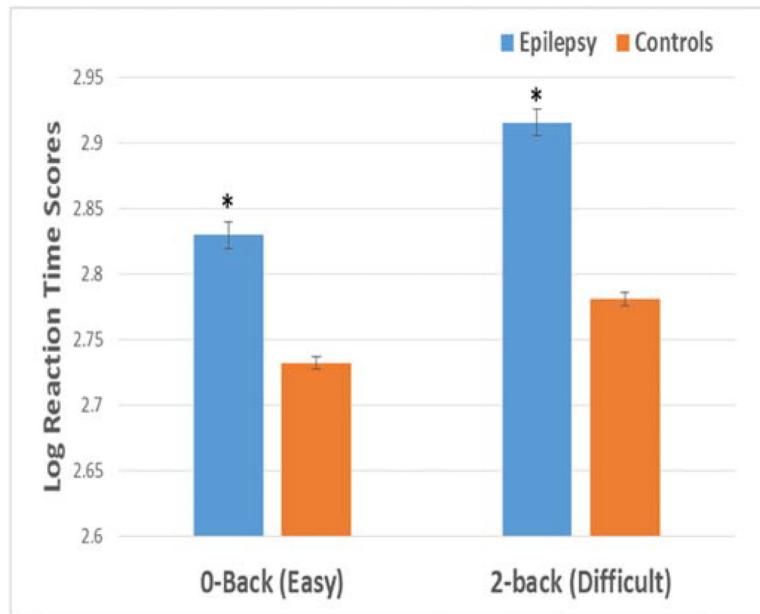


Figure 1:
TLE patients perform the 0-back and 2-back tests at a slower speed compared to controls.
* $p < 0.05$

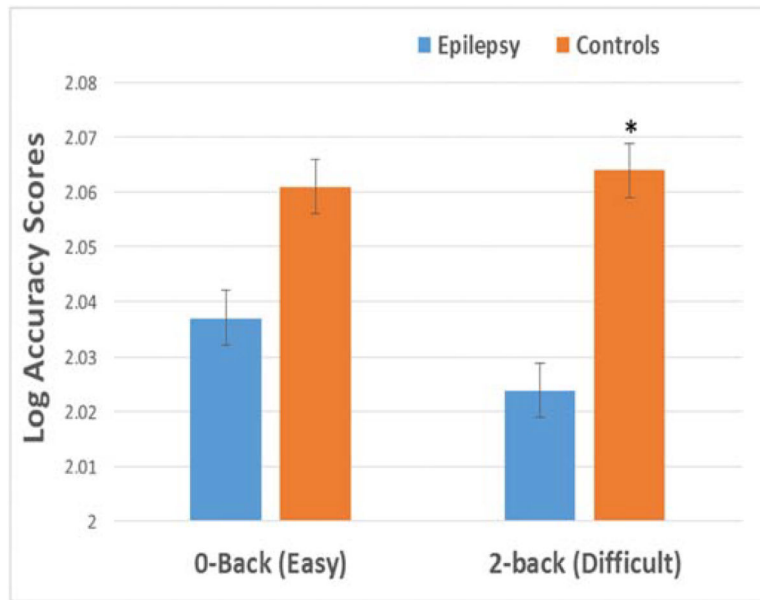


Figure 2: TLE patients perform poorer on the 2-back test, compared to controls. The 0-back test did not differ from controls. * $p < 0.05$

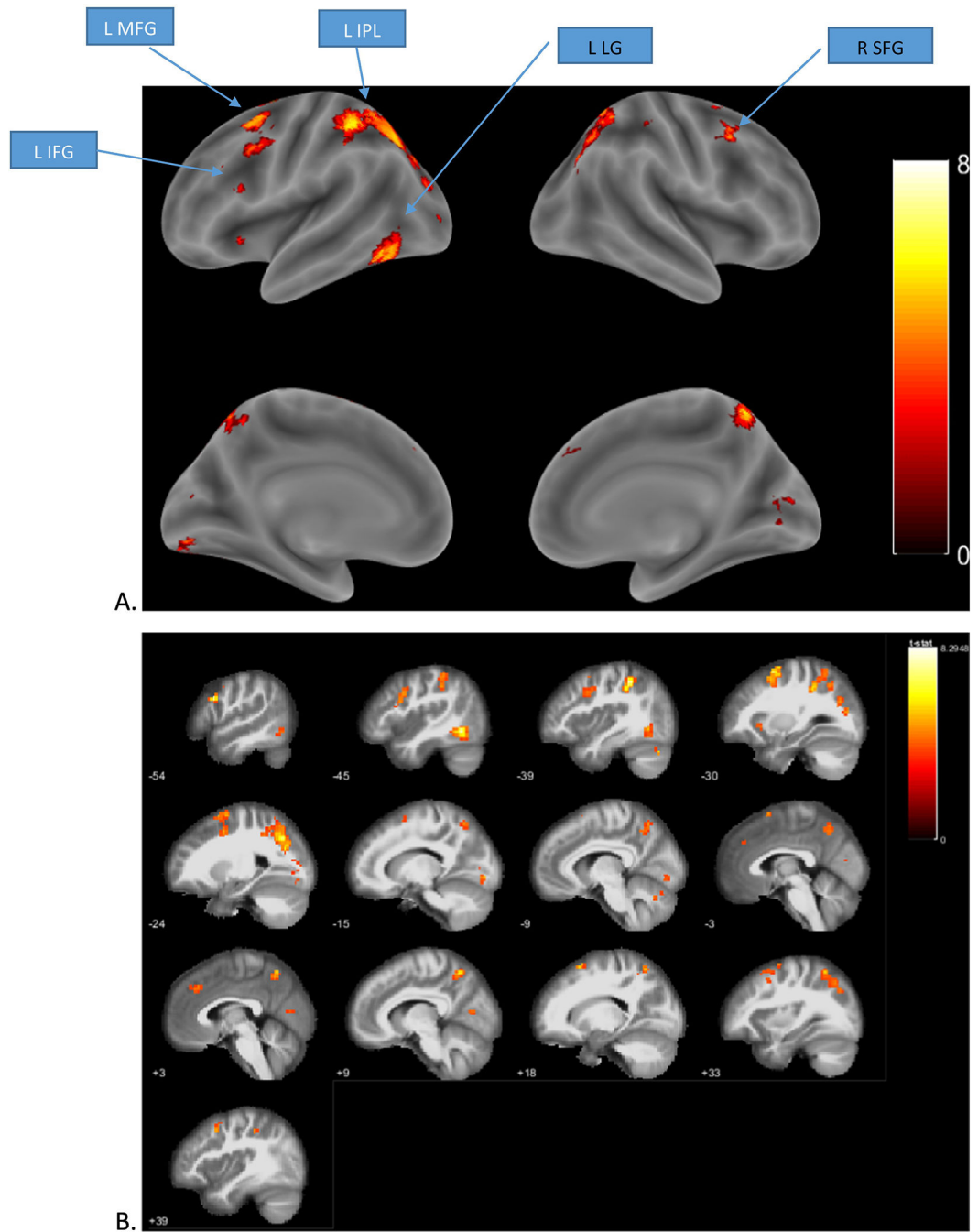


Figure 3: Activation maps for pooled N-Back task. Activation maps are FWE corrected ($p < 0.05$, cluster size > 40 voxels) in surface rendering view (A) and slice montage view (B). R = Right, L = Left, IPL = Inferior Parietal Lobe, MFG = Middle Frontal Gyrus, IFG = Inferior Frontal Gyrus, LG = Lingual Gyrus, SFG = Superior Frontal Gyrus

Table 1a.

Demographics Table

	TLE N=15	Controls N=15
Age, y (SD)	11.2 (0.8)	10.7 (0.6)
Gender, %F	46%	53%
Grade (SD)	5.1 (0.7)	5.4 (0.8)
Race, %Caucasian	42%	33%
Full Scale IQ (SD)	86 [*] (6.3)	108 (6.0)
Duration of epilepsy, y	3.9 (0.7)	--
Hippocampal Sclerosis	6%	--
Laterality of TLE	40%L	--
ADHD Diagnosis	20%	20%
ADHD medication	7%	20%
Handedness	93%R	100%R
Framewise Displacement (# of slices > 0.5mm)	15.13 (14.3)	15.0 (18.3)

*p<0.05. SD = Standard Deviation

Table 1b.

Specific Demographics for TLE participants.

	Age	Gender	Handedness	Age of Onset	Side of Focus	MRI Findings	Epilepsy Medications
Pt #1	11	M	R	9	L	Hippocampal Sclerosis	Lamotrigine
Pt #2	9	F	R	5	R	Normal	Valproic Acid
Pt #3	9	M	R	9	L	Normal	Leviteracetam
Pt #4	11	F	R	7	R	Normal	Carbamezapine
Pt #5	11	F	R	6	L	Normal	Lamotrigine
Pt #6	12	M	R	5	R	Normal	Valproic Acid Leviteracetam
Pt #7	10	M	R	8	R	Normal	Oxcarbazine Leviteracetam
Pt #8	10	F	R	8	L	Normal	Carbamezapine
Pt #9	9	M	R	7	L	Normal	None
Pt #10	9	M	R	3	R	Normal	None
Pt #11	15	M	R	10	L	Normal	Perampanel Lacosamide
Pt #12	12	M	R	6	R	Normal	Oxcarbazine
Pt #13	8	F	L	2	R	Normal	Leviteracetam Medical Marijuana
Pt #14	9	F	R	7	R	Normal	Lamotrigine
Pt #15	12	F	R	8	R	Normal	Oxcarbazine

Pt = Participant, R = Right, L = Left

Table 2.

Partial correlations controlling for age and gender.

	N-Back Accuracy	N-Back Reaction time
Pegboard dominant hand (speed)	-0.654 **	0.591 **
WASI	0.449 *	-0.676 **
D-KEFs Color Word Interference speed		-0.499 *
D-KEFs Color Word Interference accuracy	0.588 *	
D-KEFs Card Sort	0.515 *	-0.544 *

*
p<0.05,

**
p<0.01

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Table 3.

Activation in pooled N-Back task, activation of controls compared to TLE, and activation of TLE compared to healthy controls in the 2-back minus 0-back task.

Region	Peak t-value	Peak MNI coordinate	Cluster volume (voxels)	Cluster p-value (FWE)
Pooled (Controls &TLE)				
L Inferior Parietal Lobe	7.61	-39, -40, 50	678	<0.001
L Middle Frontal Gyrus	7.07	-30, 5, 62	169	<0.001
L Inferior Frontal Gyrus	8.29	-54, 14, 32	118	0.001
L Lingual Gyrus	7.60	-45, -61, -10	113	0.002
R Superior Frontal Gyrus	5.97	18, 14, 68	105	0.003
Controls > TLE				
L Middle Frontal Gyrus	4.34	-30, 8, 56	43	0.033
TLE > Controls				
N/A				

MNI, Montreal Neurological Institute;

R, right;

L left.

Table 4.

Multiple regression comparing activation in the 2-back minus 0-back task to N-back behavioral data and neuropsychological testing.

Region	Peak t-value	Peak MNI coordinate	Cluster volume (voxels)	Cluster p-value
<i>N Back behavioral data & imaging data</i>				
<i>N Back accuracy</i>				
L Inferior Parietal Lobe	9.86	-36, -37, 44	578	<0.001
R Middle Frontal Gyrus	8.76	36, 11, 50	158	<0.001
L Middle Frontal Gyrus	6.81	-30, 8, 56	149	<0.001
<i>N Back speed</i>				
L Inferior Parietal Lobe	9.66	-36, -37, 44	533	<0.001
L Middle Frontal Gyrus	6.81	-30, 8, 56	159	<0.001
R Middle Frontal Gyrus	9.31	36, 11, 50	147	<0.001
L Inferior Frontal Gyrus	7.87	-54, 14, 32	118	0.001
L Inferior Temporal Gyrus	7.00	-42, -61, -7	76	0.007
L Middle Occipital Gyrus	5.04	-12, -88, -7	65	0.014
R Cuneus	4.84	3, -79, 11	53	0.033
Neuropsychological testing & imaging data				
<i>D-KEFs Color-Word Interference Inhibition Accuracy</i>				
L Superior Parietal Lobe	5.94	-27, -64, 56	352	<0.001
L Inferior Frontal Gyrus	6.06	-51, 14, 32	301	<0.001
R Superior Frontal Gyrus	5.39	21, 11, 65	119	0.003
<i>D-KEFs Color-Word Interference Inhibition Speed</i>				
L Inferior Parietal Lobe	6.62	-24, -67, 41	444	<0.001
L Inferior Frontal Gyrus	5.99	-51, 14, 32	309	<0.001
R Superior Frontal Gyrus	5.38	21, 11, 65	130	0.001
L Middle Occipital Gyrus	5.01	-45, -64, -7	58	0.031
<i>Pegboard (Speeded Dexterity)</i>				
L Inferior Parietal Lobe	5.96	-24, -67, 41	366	<0.001
L Inferior Frontal Gyrus	6.17	-51, 14, 32	358	<0.001
R Superior Frontal Gyrus	5.41	21, 11, 65	134	<0.001
L Inferior Temporal Gyrus	4.98	-42, -64, -4	48	0.065

MNI, Montreal Neurological Institute;

R, right;

L left.