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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 functional magnetic resonance imaging (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 System [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 with 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 contributes to working memory function. The findings also indicate that children with TLE have network alterations in nontemporal brain regions.

1. Introduction

Chronic temporal lobe epilepsy (TLE) in adults is known to be associated with neuropsychological abnormalities than 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 [4–8]. Working memory 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 [10–13].

In addition to results from neuropsychological studies, a number of imaging studies have investigated and corroborated WM deficits in patients with TLE, 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 WM function [16]. Tractographic 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]. Positron emission tomographic studies reveal hypometabolism of the prefrontal cortex in TLE, which correlate with higher-order measures of WM [20]. Numerous functional imaging studies in patients with TLE demonstrate altered connectivity and disrupted networks in the frontal lobe [12, 21–24], with the dorsal attention and default mode networks exhibiting

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decreased connectivity related to neuropsychological findings [25–27]. In addition, functional magnetic resonance imaging (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 population with TLE. 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 [25,33–35]. These and other findings suggest that cognitive deficits may develop early in the course of TLE or even simultaneously with epilepsy onset. The 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. [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, WM 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 online 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 and 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 population with TLE.

2. Methods

2.1. Participants

Thirty-five children (17 participants with TLE, 18 controls, ages 8–16) served as the research participants. Healthy children and pediatric patients with TLE were recruited from MedSTAR Georgetown University Hospital. Parents gave written informed consent while the children provided written assent according to the approved institutional review board 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 patients with TLE) as assessed using clinical MRI, and no other neurological/sleep disorder that 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 patients with TLE, 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 electroencephalogram (EEG) and neuroimaging reports. Definite TLE was defined by continuous video-EEG monitoring of spontaneous seizures demonstrating temporal lobe seizure onset; probable TLE 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 TLE proceeded to recruitment for study participation.

Selection criteria for healthy control participants also included no history of loss of consciousness for >5 min or developmental learning disorder diagnosed/suspected at school. Healthy control participants were matched for age and gender. A diagnosis of attention-deficit hyperactivity disorder (ADHD) did not exclude the controls or participants with epilepsy from the study [40].

2.2. Image acquisition

Imaging data were acquired using a 3-T Siemens magnet (Siemens Magnetom TIM Trio, Erlangen, Germany) equipped with a 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 T_1 Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence with the following parameters: Repetiition Time/Echo Time (TR/TE) = 1900/2.52 ms, Inversion Time (TI) = 900 ms, 176 slices, slice resolution = 1.0 mm^3. 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 Echo Planar Imaging (EPI) sequence with the following parameters: repetition time = 2500 ms, echo time = 30 ms, field of view = 192 mm, and effective voxel size = 3.0 × 3.0 × 3.0 mm^3. 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 2.8-mm thickness with a 0.2-mm gap between slices.

2.3. Procedures

All participants were required to avoid stimulants 24 h prior to testing. Participants began with administration of the Wechsler Abbreviated Scale of Intelligence-2 (WASI-2) (matrix design and vocabulary subtests) [36,41].

2.3.1. 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 WM load fMRI runs each lasting 305 s. 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 between 1-back and 2-back blocks. Each trial was presented on the screen for 2500 ms with an instruction (rest) slide presented over 2500 ms 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.

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2.3.2. 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 System [D-KEFS Color Word Interference and Card Sort tests]) [42,43] and speeded fine motor dexterity (Grooved Pegboard — dominant hand) [1].

2.4. Analysis

2.4.1. Analysis of fMRI behavioral data and neuropsychological measures

All behavioral data were 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 covariance (ANCOVA and MANCOVA) were used to evaluate differences between control and participants with TLE. The independent variable was group (participants with TLE versus controls), 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, full scale intelligence quotient (FSIQ), and medications as covariates. Except for age, the effects of these potential confounding variables were minimal and noncontributory to the analyses, so they 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). Least significant difference 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.

2.4.2. 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 6-mm 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 s 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 the 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.

2.4.3. 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. The FWE cluster-level correction was utilized to avoid errors from multiple comparisons. Age was used as a covariate of interest.

3. Results

3.1. Demographics

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

3.2. 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 ($F(1,26) = 9.103$, $p = 0.007$, $\eta_p^2 = 0.324$).

3.3. 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 patients with epilepsy compared to controls in both the low WM load ($F(1,26) = 8.98$, $p = 0.008$, $\eta_p^2 = 0.346$) and high WM load ($F(1,26) = 10.72$, $p = 0.004$, $\eta_p^2 = 0.387$) tests (Fig. 1).

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

Table 1a
Demographics table. SD = Standard Deviation.

	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 > 0.5 mm)	15.13 (14.3)	15.0 (18.3)

* $p < 0.05$.

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Table 1b
Specific demographics for TLE participants. Pt = Participant, R = Right, L = Left.

	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	Levetiracetam
Pt #4	11	F	R	7	R	Normal	Carbamazepine
Pt #5	11	F	R	6	L	Normal	Lamotrigine
Pt #6	12	M	R	5	R	Normal	Valproic acid Levetiracetam
Pt #7	10	M	R	8	R	Normal	Oxcarbazepine Levetiracetam
Pt #8	10	F	R	8	L	Normal	Carbamazepine
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	Oxcarbazepine
Pt #13	8	F	L	2	R	Normal	Levetiracetam Medical marijuana
Pt #14	9	F	R	7	R	Normal	Lamotrigine
Pt #15	12	F	R	8	R	Normal	Oxcarbazepine

3.4. N-back behavioral data and neuropsychological tests

Low and high load WM 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).

3.5. 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 WM 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 WM network (Table 3 & Fig. 3).

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

3.6. 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 WM network, specifically within the left inferior parietal lobe, right middle frontal gyrus, and left middle frontal

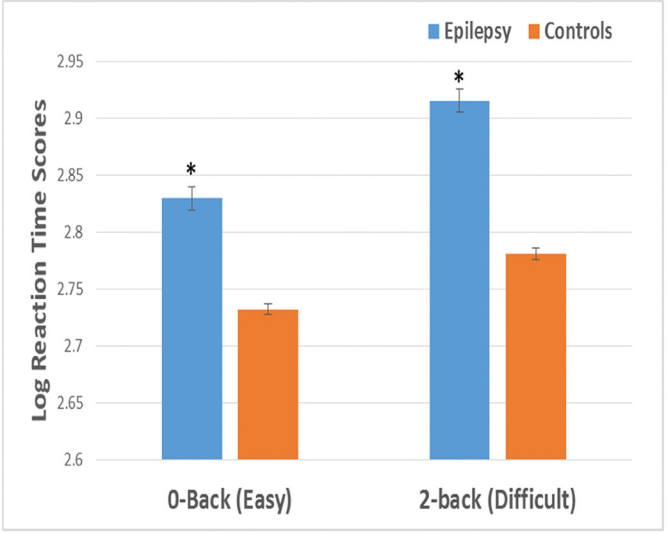

Fig. 1. Patients with TLE perform the 0-back and 2-back tests at a slower speed compared to controls. *$p < 0.05$.

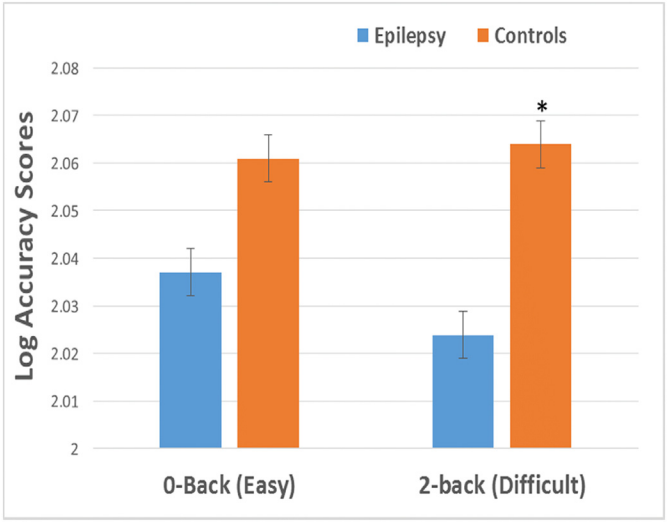

Fig. 2. Patients with TLE perform poorer on the 2-back test, compared to controls. The 0-back test did not differ from controls. *$p < 0.05$.

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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*

* $p < 0.05$.
** $p < 0.01$.

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 ($p = 0.033$).

3.7. 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. The 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 WM 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).

4. Discussion

The goal of this investigation was to determine if children with TLE exhibit deficits in extratemporal neural networks and to determine if these extratemporal neural network abnormalities correlate with the extratemporal 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 WM, children with TLE exhibited deficits in WM 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 WM tasks correlated with EF neuropsychological tests.

It is evident that the EF deficits in children with TLE translate as a reliable finding. Our results add to the mounting evidence of extratemporal 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 FSIQ 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 increase. During the less challenging *N*-back run (low WM load), children with TLE performed similarly to healthy controls. However, during the more taxing *N*-back run (high WM 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 nontemporal 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 correlates 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 participants with TLE are altered such that there may be an inability to increase frontal lobe activity to meet the higher demand as was seen among 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

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. MNI, Montreal Neurological Institute; R, right; L, left.

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				

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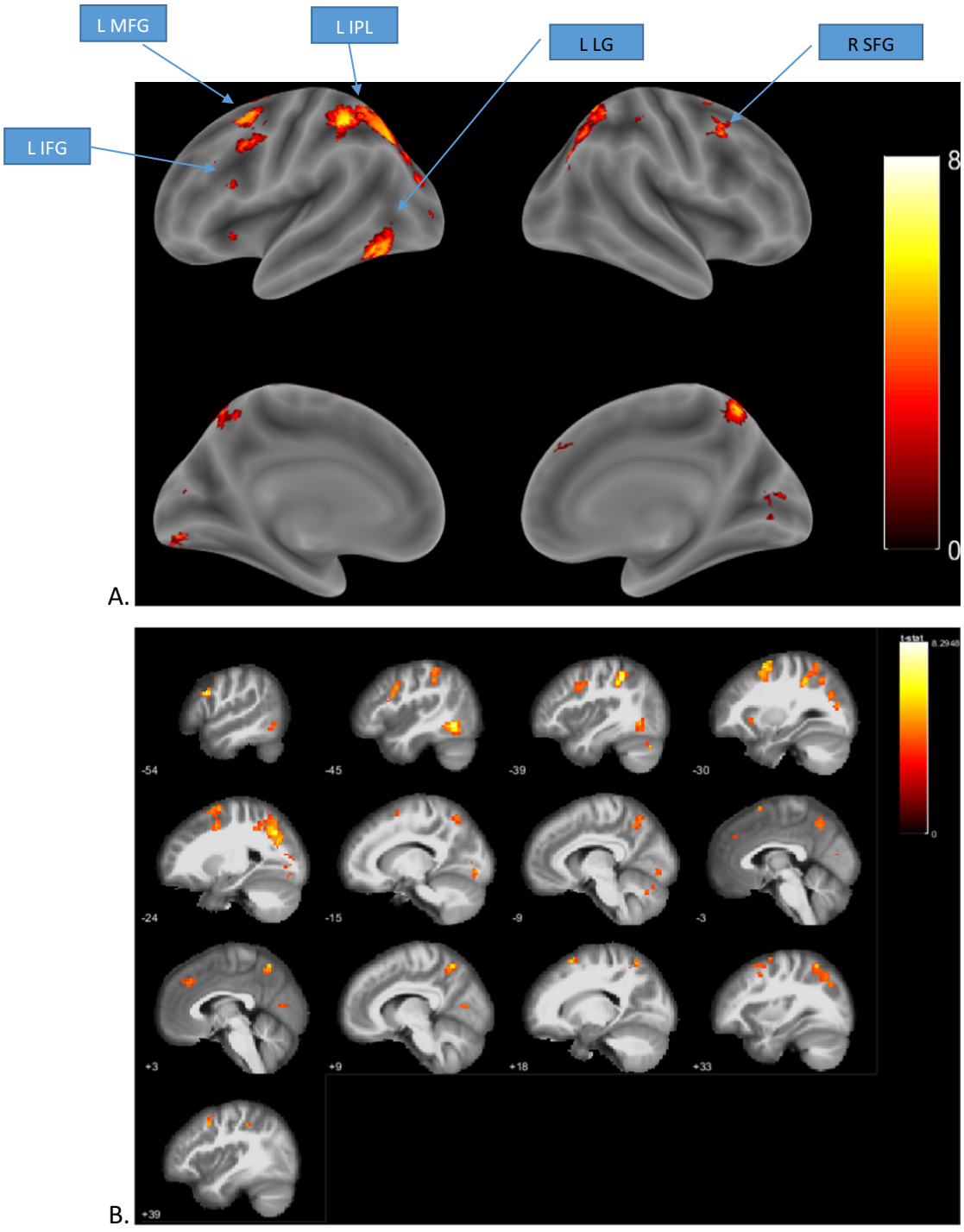

Fig. 3. Activation maps for pooled *N*-back task. Activation maps are FWE corrected ($p < 0.05$, cluster size > 40 voxels) in surface rendering view (A) and slice montage view (B). R = Right, L = Left, IPL = Inferior Parietal Lobe, MFG = Middle Frontal Gyrus, IFG = Inferior Frontal Gyrus, LG = Lingual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

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 extratemporal 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].

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Table 4
Multiple regression comparing activation in the 2-back minus 0-back task to *N*-back behavioral data and neuropsychological testing. MNI, Montreal Neurological Institute; R, right; L, left.

Region	Peak *t*-value	Peak MNI coordinate	Cluster volume (voxels)	Cluster p-value
N-back behavioral data & imaging data				
N-back accuracy				
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
N-back speed				
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				
D-KEFS Color–Word Interference inhibition accuracy				
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
D-KEFS Color–Word Interference inhibition speed				
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
Pegboard (speeded dexterity)				
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

5. 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.

6. 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 corroborate 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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Conflicts of interest

We have no conflicts of interest to report.

References

[1] Oyegbile TO, Dow C, Jones J, Bell B, Rutecki P, Sheth R, et al. The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. Neurology 2004; 62:1736–42.
[2] Hermann BP, Wyler AR, Richey ET. Wisconsin Card Sorting Test performance in patients with complex partial seizures of temporal-lobe origin. J Clin Exp Neuropsychol 1988;10:467–76.
[3] Baddeley A. The episodic buffer: a new component of working memory? Trends Cogn Sci 2000;4:417–23.
[4] Agah E, Asgari-Rad N, Ahmadi M, Tafakhori A, Aghamollaii V. Evaluating executive function in patients with temporal lobe epilepsy using the frontal assessment battery. Epilepsy Res 2017;133:22–7.
[5] Wang WH, Liou HH, Chen CC, Chiu MJ, Chen TF, Cheng TW, et al. Neuropsychological performance and seizure-related risk factors in patients with temporal lobe epilepsy: a restrospective cross-sectional study. Epilepsy Behav 2011;22: 728–34.
[6] Baxendale S, Thompson P. Beyond localization: the role of traditional neuropsychological tests in an age of imaging. Epilepsia 2010;51:2225–30.
[7] Glosser G, Cole LC, French JA, Saykin AJ, Sperling MR. Predictors of intellectual performance in adults with intractable temporal lobe epilepsy. J Int Neuropsychol Soc 1997;3:252–9.
[8] Guimaraes CA, Li LM, Rzezak P, Fuentes D, Franzon RC, Augusta Montenegro M, et al. Temporal lobe epilepsy in childhood: comprehensive neuropsychological assessment. J Child Neurol 2007;22:836–40.
[9] Stretton J, Thompson PJ. Frontal lobe function in temporal lobe epilepsy. Epilepsy Res 2012;98:1–13.
[10] Cashdollar N, Duncan JS, Duzel E. Challenging the classical distinction between long-term and short-term memory: reconsidering the role of the hippocampus. Future Neurol 2011;6:351–62.

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[11] Tracy JI, Osipowicz K, Spechler P, Sharan A, Skidmore C, Doucet G, et al. Functional connectivity evidence of cortico-cortico inhibition in temporal lobe epilepsy. Hum Brain Mapp 2014;35:353–66.
[12] Vlooswijk MC, Vaessen MJ, Jansen JF, de Krom MC, Majoie HJ, Hofman PA, et al. Loss of network efficiency associated with cognitive decline in chronic epilepsy. Neurology 2011;77:938–44.
[13] Pereira FR, Alessio A, Sercheli MS, Pedro T, Bilevicius E, Rondina JM, et al. Asymmetrical hippocampal connectivity in mesial temporal lobe epilepsy: evidence from resting state fMRI. BMC Neurosci 2010;11:66.
[14] Mueller SG, Laxer KD, Barakos J, Cheong I, Garcia P, Weiner MW. Widespread neocortical abnormalities in temporal lobe epilepsy with and without mesial sclerosis. NeuroImage 2009;46:353–9.
[15] McDonald CR, Hagler Jr DJ, Ahmadi ME, Tecoma E, Iragui V, Gharapetian L, et al. Regional neocortical thinning in mesial temporal lobe epilepsy. Epilepsia 2008;49:794–803.
[16] Keller SS, Baker G, Downes JJ, Roberts N. Quantitative MRI of the prefrontal cortex and executive function in patients with temporal lobe epilepsy. Epilepsy Behav 2009;15:186–95.
[17] Huang D, Lu F, Chen Z, Zheng J. Functional magnetic resonance and diffusion tensor imaging analysis of verbal working memory in patients with temporal lobe epilepsy. Int J Clin Exp Med 2015;8:18275–83.
[18] Wang XQ, Lang SY, Hong LU, Lin MA, Yan-ling MA, Yang F. Changes in extratemporal integrity and cognition in temporal lobe epilepsy: a diffusion tensor imaging study. Neurol India 2010;58:891–9.
[19] Riley JD, Moore S, Cramer SC, Lin JJ. Caudate atrophy and impaired frontostriatal connections are linked to executive dysfunction in temporal lobe epilepsy. Epilepsy Behav 2011;21:80–7.
[20] Jokeit H, Seitz RJ, Markowitsch HJ, Neumann N, Witte OW, Ebner A. Prefrontal asymmetric interictal glucose hypometabolism and cognitive impairment in patients with temporal lobe epilepsy. Brain 1997;120:2283–94.
[21] Riederer F, Lanzenberger R, Kaya M, Prayer D, Serles W, Baumgartner C. Network atrophy in temporal lobe epilepsy: a voxel-based morphometry study. Neurology 2008;71:419–25.
[22] Lin JJ, Riley JD, Juranek J, Cramer SC. Vulnerability of the frontal-temporal connections in temporal lobe epilepsy. Epilepsy Res 2008;82:162–70.
[23] Waites AB, Briellmann RS, Saling MM, Abbott DF, Jackson GD. Functional connectivity networks are disrupted in left temporal lobe epilepsy. Ann Neurol 2006;59:335–43.
[24] Liao W, Zhang Z, Pan Z, Mantini D, Ding J, Duan X, et al. Altered functional connectivity and small-world in mesial temporal lobe epilepsy. PLoS One 2010;5:c8525.
[25] Widjaja E, Zamyadi M, Raybaud C, Snead OC, Smith ML. Impaired default mode network on resting-state fMRI in children with medically refractory epilepsy. Am J Neuroradiol 2013;34:552–7.
[26] Zhang Z, Lu G, Zhong Y, Tan Q, Liao W, Wang Z, et al. Altered spontaneous neuronal activity of the default-mode network in mesial temporal lobe epilepsy. Brain Res 2010;1323:152–60.
[27] Zhang Z, Lu G, Zhong Y, Tan Q, Yang Z, Liao W, et al. Impaired attention network in temporal lobe epilepsy: a resting FMRI study. Neurosci Lett 2009;458:97–101.
[28] Helmstaedter C, Elger CE. Chronic temporal lobe epilepsy: a neurodevelopmental or progressively dementing disease. Brain 2009;132:2822–30.
[29] Oyegbile TO, Bhattacharya A, Seidenberg M, Hermann BP. Quantitative MRI biomarkers of cognitive morbidity in temporal lobe epilepsy. Epilepsia 2006;47:143–52.
[30] Oyegbile T, Hansen R, Magnotta V, O'leary D, Bell B, Seidenberg M, et al. Quantitative measurement of cortical surface features in localization-related temporal lobe epilepsy. Neuropsychology 2004;18:729–37.
[31] Hermann B, Jones J, Sheth R, Dow C, Koehn M, Seidenberg M. Children with new-onset epilepsy: neuropsychological status and brain structure. Brain 2006;129:2609–19.
[32] Rzezak P, Valente KD, Duchowny MS. Temporal lobe epilepsy in children: executive and mnestic impairments. Epilepsy Behav 2014;31:117–22.
[33] Cataldi M, Avoli M, de Villers-Sidani E. Resting state networks in temporal lobe epilepsy. Epilepsia 2013;54:2048–59.
[34] Croft LJ, Baldeweg T, Sepeta L, Zimmaro L, Berl MM, Gaillard WD. Vulnerability of the ventral language network in children with focal epilepsy. Brain 2014;137:2245–57.
[35] Appel S, Duke ES, Martinez AR, Khan OI, Dustin IM, Reeves-Tyer P, et al. Cerebral blood flow and fMRI BOLD auditory language activation in temporal lobe epilepsy. Epilepsia 2012;53:631–8.
[36] Sepeta LN, Casaletto KB, Terwilliger V, Facella-Ervolini J, Sady M, Mayo J, et al. The role of executive functioning in memory performance in pediatric focal epilepsy. Epilepsia 2017;58:300–10.
[37] Hermann BP, Seidenberg M, Bell B. The neurodevelopmental impact of childhood onset temporal lobe epilepsy on brain structure and function and the risk of progressive cognitive effects. Prog Brain Res 2002;135:429–38 (Review).
[38] Gevins A, Cutillo B. Spatiotemporal dynamics of component processes in human working memory. Electroencephalogr Clin Neurophysiol 1993;87:128–43.
[39] Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 2005;25:46–59.
[40] Becker SP, Langberg JM, Vaughn AJ, Epstein JN. Clinical utility of the Vanderbilt ADHD diagnostic parent rating scale comorbidity screening. J Dev Behav Pediatr 2012;33:221–8.
[41] Walker NM, Jackson DC, Dabbs K, Jones JE, Hsu DA, Stafstrom CE, et al. Is lower IQ in children with epilepsy due to lower parental IQ? A controlled comparison study. Dev Med Child Neurol 2013;55:278–82.
[42] Vega C, Brenner LA, Madsen J, Bourgeois B, Waber DP, Boyer K. Lexical retrieval pre- and posttemporal lobe epilepsy surgery in a pediatric sample. Epilepsy Behav 2015;42:61–5.
[43] Parrish J, Geary E, Jones J, Seth R, Hermann B, Seidenberg M. Executive functioning in childhood epilepsy: parent-report and cognitive assessment. Dev Med Child Neurol 2007;49:412–6.
[44] Hermann BP, Jones JE, Jackson DC, Seidenberg M. Starting at the beginning: the neuropsychological status of children with new-onset epilepsies. Epileptic Disord 2012;14:12–21.
[45] Braakman HM, Vaessen MJ, Jansen JF, Debeij-van Hamm MH, de Louw A, Hofman PA, et al. Frontal lobe connectivity and cognitive impairment in pediatric frontal lobe epilepsy. Epilepsia 2013;54:446–54.
[46] Raud T, Kaldoja ML, Kolk A. Relationship between social competence and neurocognitive performance in children with epilepsy. Epilepsy Behav 2015;52:93–101.

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