



Default mode network deactivation in pediatric temporal lobe epilepsy: Relationship to a working memory task and executive function tests

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ABSTRACT

Objectives: Children with temporal lobe epilepsy (TLE) exhibit executive dysfunction on traditional neuropsychological tests. There is limited evidence of different functional network alterations associated with this clinical executive dysfunction. This study investigates working memory deficits in children with TLE by assessing deactivation of the default mode network (DMN) on functional Magnetic Resonance Imaging (fMRI) and the relationship of DMN deactivation with fMRI behavioral findings and neuropsychological test performance.

Experimental design: fMRI was conducted on 15 children with TLE and 15 healthy controls (age: 8–16 years) while performing the N-back task in order to assess deactivation of the DMN. N-back accuracy, N-back reaction time, and neuropsychological tests of executive function (Delis–Kaplan Executive Function System [D-KEFS] Color-Word Interference and Card Sort tests) were also assessed.

Principal observations: During the N-back task, children with TLE exhibited significantly less deactivation of the DMN, primarily in the precuneus/posterior cingulate cortex compared with controls. These alterations significantly correlated with N-back behavioral findings and D-KEFS results.

Conclusions: Children with TLE exhibit executive dysfunction which correlates with DMN alterations. These findings suggest that the level of deactivation of specific functional networks may contribute to cognitive impairment in children with TLE. The findings also indicate that children with TLE have network alterations in extratemporal lobe brain regions.

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1. Introduction

The default mode network (DMN) is a consistent, robust, and well-studied network that is traditionally considered to be a functional network in which activation is attenuated during a wide range of active cognitive tasks [1]. During the execution of specific complex cognitive tasks, pertinent task-positive brain networks are activated while other networks such as the DMN are simultaneously deactivated [2]. The DMN is thought to be engaged during the maintenance of baseline processes associated with self-awareness, consciousness, strength of cognitive reserve, episodic memory, and modulation of internal (mental) tasks [3]. Brain regions involved in the DMN include the medial prefrontal cortex, posterior cingulate cortex, lateral and medial temporal lobes, and posterior inferior parietal lobule [1,2].

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The exact function of the DMN remains unclear, however, it is evident that the DMN plays an alternating but complementary role with pertinent functional networks as activation of the DMN is significantly higher than that of task-positive networks during rest periods and is deactivated during cognitive tasks when the activity level of pertinent task-positive networks increases. These direct relationships have been well established in healthy populations [1] and are dysfunctional in adults with neurological disorders [4], including Alzheimer's disease and epilepsy [5–7]. The level of DMN dysfunction has also been correlated to differences in cognitive performance [8] in healthy controls.

Working memory (WM) is the ability to temporarily store and manipulate information while performing a range of cognitive tasks [9] and is frequently impaired in patients with temporal lobe epilepsy (TLE) [10–12]. Working memory, which is a component of executive function (EF), is generally considered a frontal lobe function and is not traditionally associated with temporal lobe lesions, but increasing evidence indicates that medial temporal lobe dysfunction may directly or indirectly impair WM [13–15].

A widely used paradigm to evaluate WM is the 'N-back' task, which involves monitoring a series of letters or pictures and responding whenever

the stimulus is presented N trials prior [16]. 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 (ECN) that includes both bilateral frontal and parietal cortical regions [17]. The unique nature of the N -back paradigm allows for studies to be designed to examine the effects of variations of WM load on cognitive performance [18]. A previous study from our lab documented that children with TLE exhibit alterations in the ECN during the N -back task, which correlated with the pertinent neuropsychological test results [15]. During the N -back task, healthy individuals show significant deactivation of the DMN [2]. The degree of anticorrelation between the DMN and WM network is maximal as the N -back task complexity increases [2]. Furthermore, if the strength of the negative correlation between the WM network and the DMN is high, individuals show better performance on the N -back task [2]. Interestingly, even though the DMN involves multiple regions of the brain, only the regions of the posterior cingulate/parietal lobe (ventral DMN) predict WM performance [2]. It is unknown if these findings would be similar in a pediatric TLE, a common neurological disorder.

In the adult TLE literature, there is evidence that atypical language laterality and impaired language function are associated with reduced suppression and poor integration of the DMN in functional connectivity studies [7]. Few studies have assessed the status of the DMN in children with TLE, and the limited available literature has focused primarily on functional connectivity data [19]. In addition, only a small number of studies have assessed DMN alterations in children with epilepsy during tasks, and the few existing studies focused primarily on language tasks [20].

It is now well established that children with TLE may have cognitive deficits that extend outside of the temporal lobe and language dysfunction [12,15,21]. Our lab recently demonstrated that children with TLE exhibited deficits in EF which correlated with neural network alterations, specifically in the ECN [15]. During the N -back task, children with TLE showed less recruitment of specific regions of the ECN leading to less activation of the network overall. The reasons for this poor activation of the ECN remain to be determined, however, the results do indicate that other networks may also be altered during this specific task. The current study seeks to determine if DMN is altered during the N -back task performed by children with TLE.

To the best of our knowledge, characterization of the level of deactivation of the DMN during task performance has not yet been examined in children with TLE. The N -back task is an ideal probe test in this regard. Furthermore, the relationship between level of DMN deactivation and performance on the N -back task and neuropsychological tests examining EF remains to be characterized. The goal of this study was to determine if the DMN is altered in children with TLE during the N -back task compared with controls and to determine if this finding correlates with N -back task performance and neuropsychological status. We hypothesized that children with TLE would show less deactivation of the DMN and that these alterations would be significantly correlated with N -back behavioral findings and neuropsychological testing (executive dysfunction) results.

2. Methods

2.1. Participants

The data for this observational study included 30 children (15 participants with TLE, 15 controls, ages 8–16) who served as the research participants. Healthy children and patients with pediatric TLE were recruited from MedSTAR Georgetown University Hospital and clinics between August 2015 and December 2016. Parents gave written informed consent while the children provided written assent according to the approved Institutional Review Board (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 patients with TLE) as assessed using clinical magnetic resonance imaging (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, history of stroke or tumor, and claustrophobia. For patients with TLE, complex partial seizures (i.e., focal seizures with alteration of consciousness with or without motor activity) of definite or probable temporal lobe origin were diagnosed by an epileptologist with expertise in pediatric electroencephalography (EEG). The epileptologist reviewed patients’ medical records including seizure characteristics and recent 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 diagnosis/suspected at school. Healthy control participants were matched for age and gender. A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) did not exclude epilepsy or control participants from the study [22].

2.2. Image acquisition

Imaging data were acquired using a 3 T 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 the scanner room. Anatomical images of subjects were collected using a sagittal T₁ Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence with the following parameters: repetition time (TR)/echo time (TE) = 1900/2.52 ms, inversion time (TI) = 900 ms, 176 slices, and 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 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 mm³. 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.

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) [21] to characterize overall intellectual ability.

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 in N letters ago. Participants were tested using the following 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 personal computer (PC). Stimuli were back-projected onto a 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.

3.2. Neuropsychological assessment

After scanning and a short break, the participants underwent neuropsychological testing. Patients and controls were administered a brief test battery that included tests of EF including Delis–Kaplan Executive Function System (D-KEFS) Color-Word Interference and Card Sort tests [23].

4. Analysis

4.1. Analysis of fMRI behavioral data and neuropsychological measures

All behavioral data were analyzed using standard statistical software (Statistical Package for the Social Sciences (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 confirmed. Univariate and multivariate analyses of covariance (ANCOVA and MANCOVA) were used to evaluate differences between control and participants with TLE. The independent variable was grouped (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, Full Scale Intelligence Quotient (FSIQ), and medications (mono- vs polytherapy) as covariates. Except for age, the effects of these potential confounding variables were minimal and noncontributory 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). Least Significant Difference (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.

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 [24] (artifact detection and repair of bad slices for high-motion pediatric fMRI studies, 15% required repair of an average of 3 slices), 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 extracted in the realignment procedure were included in the model as covariates. 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 the deactivation (negative contrast images) (0-back > 2-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. A comparison of the two groups (controls > TLE and TLE > controls contrasts) was performed to determine which regions the controls deactivate less compared to rest (0-back) and which regions the patients deactivate less compared to rest (0-back) during the *N*-back task. All contrasts were thresholded by applying a family-wise error (FWE) cluster-level correction after using a cluster-defining threshold of $p < 0.001$ and a minimal cluster size of 25 voxels. Age was used as a covariate of no interest. Whole brain multiple regression analyses were performed to determine the correlations with fMRI behavioral data and neuropsychological tests. 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.

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. Family-wise error cluster-level correction was utilized to avoid errors from multiple comparisons. Age was used as a covariate of interest.

5. Results

5.1. Demographics

Basic demographic and clinical characteristics are provided and compared in Tables 1 and 2. There were no patients with clear evidence of bilateral TLE on EEG. Both drug-resistant and well-controlled patients were included in the study. As expected, the group with TLE had a lower mean Full Scale Intelligence Quotient (IQ) score compared with healthy controls ($p = 0.02$, $\eta_p^2 = 0.274$) [11,12,24]. There were no significant group differences in age or gender. Both healthy control and groups with TLE included individuals with ADHD. Patients and controls were matched for ADHD to result in an equal distribution of individuals with ADHD in both groups, which may be less likely to bias the results. Treatment in the participants with TLE included valproic acid ($N = 2$), levetiracetam ($N = 4$), lamotrigine ($N = 3$), carbamazepine ($N = 2$), oxcarbazepine ($N = 3$), perampanel ($N = 1$), lacosamide ($N = 1$), and cannabidiol (clinical trial) ($N = 1$) (Table 2). Four patients with TLE (27%) were being treated with two antiepileptic medications. Behavioral and imaging data for the individual on cannabidiol did not fall outside the range of other individuals on traditional antiepileptic

Table 1
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%
Duration of epilepsy, y	3.9 (0.7)	–
Hippocampal sclerosis	6%	–
Laterality of TLE	40%L	–
Handedness	93%R	100%R
ADHD diagnosis	20%	20%
Full Scale IQ (SD)	86* (18.4)	108 (15.1)
Full Scale IQ range	58–148	76–160
Full Scale IQ median	81	119
Full Scale interquartile range	28.7	18.2

* $p < 0.05$.

Table 2

Specific demographics for participants with TLE. Pt = Participant, R = Right-handed, L = Left-handed, bid = twice daily, tid = three times daily, mg/kg/d = milligrams per kilogram per day.

	Age	Gender	L/R	Age of onset	Side of focus	MRI findings	Epilepsy medications	Seizure frequency
Pt #1	11	M	R	9	L	Hippocampal sclerosis	Lamotrigine 75 mg bid (8 mg/kg/d)	Quarterly
Pt #2	9	F	R	5	R	Normal	Valproic acid 250 mg tid (22 mg/kg/d)	Yearly
Pt #3	9	M	R	9	L	Normal	Levetiracetam 250 mg bid (18 mg/kg/d)	Monthly
Pt #4	11	F	R	7	R	Normal	Carbamazepine 400 mg bid (18 mg/kg/d)	Quarterly
Pt #5	11	F	R	6	L	Normal	Lamotrigine 300 mg bid (13 mg/kg/d)	Quarterly
Pt #6	12	M	R	5	R	Normal	Valproic acid 1000 mg bid (20 mg/kg/d) Levetiracetam 2250 mg bid (44 mg/kg/d)	3–4 per day
Pt #7	10	M	R	8	R	Normal	Oxcarbazine 300 mg bid (8 mg/kg/d) Levetiracetam 750 mg bid (20 mg/kg/d)	Weekly
Pt #8	10	F	R	8	L	Normal	Carbamazepine 550 mg bid (39 mg/kg/d w/low plasma level of 4.7)	Monthly
Pt #9	9	M	R	7	L	Normal	None	Yearly
Pt #10	9	M	R	3	R	Normal	None	Yearly
Pt #11	15	M	R	10	L	Normal	Perampanel 8 mg daily Lacosamide 200 mg bid (7.5 mg/kg/d) Oxcarbazine 300 mg bid (8 mg/kg/d)	2–3 per week
Pt #12	12	M	R	6	R	Normal	Levetiracetam 200 mg bid (18 mg/kg/d)	Quarterly
Pt #13	8	F	L	2	R	Normal	Cannabidiol	Monthly
Pt #14	9	F	R	7	R	Normal	Lamotrigine 75 mg bid (6 mg/kg/d)	Quarterly
Pt #15	12	F	R	8	R	Normal	Oxcarbazine 600 mg bid (27 mg/kg/d)	Biannually

medications. Furthermore, this individual abstained from cannabidiol three days prior to testing.

5.2. N-back behavioral data and neuropsychological testing

N-back accuracy and reaction times were compared between two groups. On average, children with epilepsy showed slower N-back reaction times compared with controls ($F(1,26) = 11.08, p = 0.003$, Fig. 1). There was a trend towards a significant difference on N-back accuracy scores ($F(1,26) = 3.41, p = 0.077$, Fig. 1) (see further details in previously published findings [15]). Children with TLE performed poorer on D-KEFS Color-Word Interference speed, D-KEFS Color-Word Interference accuracy, and D-KEFS Card Sort correct sorts performance (Fig. 2, see further details in previously published findings [15]). These significant findings remained when our data were analyzed with FSIQ as a covariate.

5.3. Imaging data

An activation pattern consistent with the ECN was required, indicating that they had engaged the task correctly. Details on the ECN activation pattern have been previously reported [15]. Three participants (2 with TLE, 1 control) displayed a non-ECN pattern, and five participants (1 with TLE, 4 controls) did not tolerate the scanner. Of the 30

participants, fMRI findings and fMRI behavioral data were excluded for eight participants total. For those eight participants, their neuropsychological data were retained for analysis.

During task performance, the DMN was deactivated both in the controls and patients with TLE. A summary of regions showing group differences is represented in the Table 3 and Fig. 3. These regions were confirmed with a previously published a priori mask of the DMN map to confirm the following results (see [REF] in Fig. 3) [25]. The data showed consistent deactivation patterns with the main deactivation in the bilateral precuneus, bilateral posterior cingulate gyri, and medial frontal gyri. The DMN was less deactivated in patients with epilepsy during the task compared with controls (Fig. 3). This was reflected in the significant cluster volumes as well (Table 3). Controls showed only one significant region, the right precuneus ($p < 0.001$), while the patients with epilepsy had five significant regions that were less deactivated during the N-back task [right precuneus ($p < 0.001$), left posterior inferior parietal lobe ($p < 0.001$), right posterior cingulate cortex ($p < 0.001$), right occipital lobe ($p = 0.022$), left medial frontal gyrus ($p = 0.007$) (Table 3)]. Upon direct comparison using a 2-sample *t*-test, the DMN demonstrated reduced deactivation in the patients with epilepsy compared with controls, specifically in the left parietal lobe ($p = 0.041$) and the right precuneus region ($p = 0.026$) (Table 3). This finding was most evident as the task became more challenging (during the 2-back task).

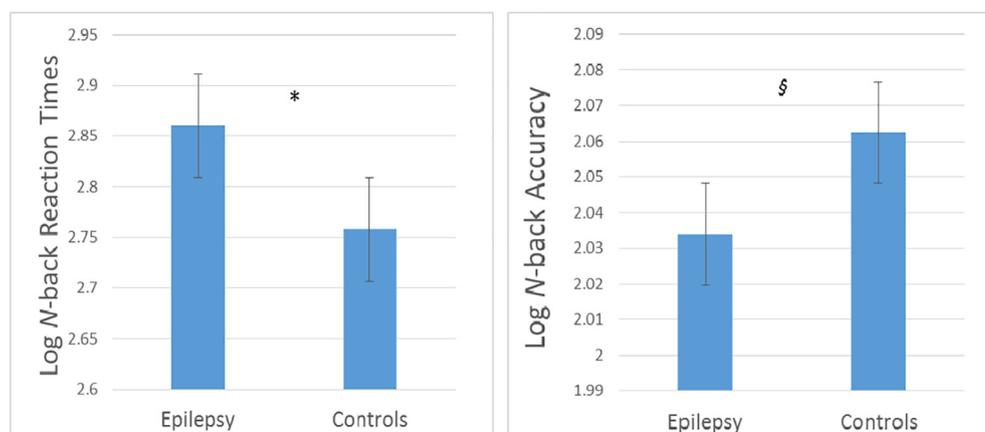


Fig. 1. Patients with epilepsy show slower N-back reaction times compared with healthy controls with a trend towards lower N-back accuracy scores. * $p < 0.05$, § $p < 0.1$.

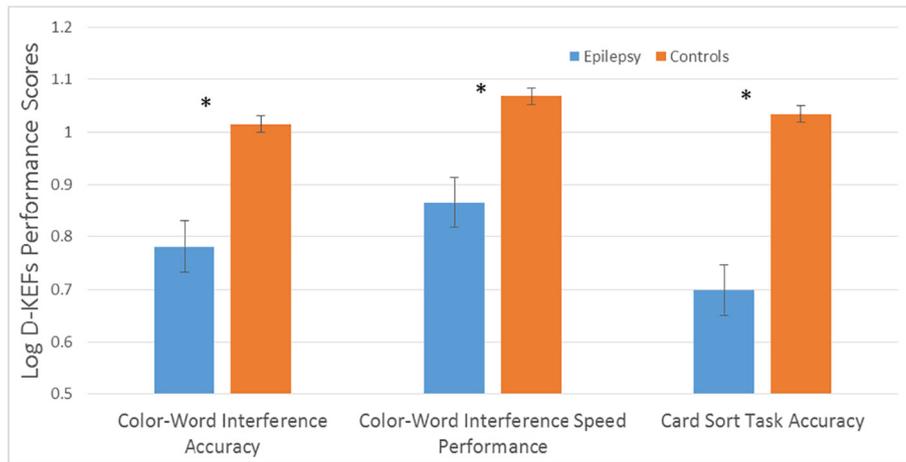


Fig. 2. Children with epilepsy perform poorer on D-KEFS Color-Word Interference accuracy, D-KEFS Color-Word Interference speed performance, and D-KEFS Card Sort task accuracy compared with healthy controls, * $p < 0.05$.

5.4. 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 collapsing across groups. A significant negative correlation showed that individuals with lower accuracy scores on the *N*-back task exhibited less deactivation of the DMN, specifically within the left posterior inferior parietal lobe ($p < 0.001$), right medial prefrontal cortex ($p = 0.049$), posterior cingulate cortex ($p < 0.001$), and the medial frontal gyrus ($p = 0.005$, Table 4). Furthermore, a significant negative correlation showed that individuals with longer reaction times on the *N*-back task exhibited less deactivation of the DMN, specifically within the left posterior parietal lobe ($p < 0.001$), posterior cingulate cortex ($p < 0.001$), right medial prefrontal cortex ($p = 0.013$), and left parietal lobe ($p < 0.001$, Table 4).

5.5. Neuropsychological testing and imaging data

To examine the clinical significance of DMN findings, a multiple regression evaluating the relationship between EF assessed outside the scanner and fMRI BOLD activation was conducted using a whole brain

Table 3

Activated DMN regions during the *N*-back task (0-back > 2-back) in controls (A) and patients with TLE (B). (C) and (D) represent direct comparisons of DMN regions between controls and patients with TLE. (C) shows the difference regions (controls > TLE contrast) indicating which regions the controls deactivate less during the *N*-back task (none). (D) shows the difference regions (TLE > controls contrast) indicating which regions the patients with TLE deactivate less during the *N*-back task. MNI, Montreal Neurological Institute; R, right; L left.

Region	Peak t-value	Peak MNI coordinate	Cluster volume (voxels)	Cluster p-value (FWE)
A. Controls				
R precuneus	7.44	3, -49, 62	281	<0.001
B. TLE				
R precuneus	7.82	0, -49, 53	454	<0.001
L posterior inferior parietal lobe	7.01	-27, -88, -1	325	<0.001
R posterior cingulate cortex	6.49	0, -31, 29	68	0.001
R occipital lobe	5.69	27, -85, -13	32	0.022
L medial frontal gyrus	5.1	3, 62, 29	40	0.007
C. Controls > TLE				
N/A				
D. TLE > controls				
L parietal lobe	6.96	-15, -13, 41	28	0.041
R precuneus	4.89	15, -25, 44	31	0.026

analysis collapsing across groups. Participants with more errors on the D-KEFS Color-Word Interference test (response inhibition) showed less deactivation on the DMN in the left posterior parietal lobe ($p = 0.038$) and posterior cingulate cortex ($p < 0.002$, Table 4). Participants who took a longer time completing the D-KEFS Color-Word Interference showed less deactivation on the DMN in the medial prefrontal cortex ($p = 0.002$) and posterior cingulate cortex ($p < 0.001$). Finally, on the D-KEFS Card Sort task, participants who identified fewer correct categories on this concept formation task showed less deactivation in the DMN in the medial frontal gyrus ($p < 0.001$), medial prefrontal cortex ($p = 0.01$), left parietal lobe ($p = 0.003$), and right precuneus ($p < 0.001$, Table 4).

6. Discussion

This investigation sought to further previous findings [15] by determining if children with TLE exhibit deficits in the DMN during a complex cognitive task and sought to characterize relationships with in-scanner *N*-back task performance and extra-scanner neuropsychological status. Our previous findings showed that children with TLE exhibit executive dysfunction on D-KEFS testing and significant reduction in activation of the frontal lobe within the ECN compared with healthy controls [15]. Our current study provided three key findings. First, using the *N*-back task to test WM, we demonstrated that children with TLE show less deactivation of the DMN compared with controls. Second, the level of DMN deactivation is correlated with accuracy and reaction time of *N*-back task. Finally, this reduced DMN deactivation is correlated with neuropsychological tests of EF, specifically, measures of inhibition and problem solving abilities.

Executive dysfunction in children with TLE is a reliable finding [10, 12, 15, 21]. Our study corroborates this executive dysfunction on both neuropsychological testing (D-KEFS) and fMRI behavioral testing (*N*-back accuracy and reaction time). We recently demonstrated that children with TLE also display deficits in the ECN during the *N*-back task [15]. Less has been documented regarding the DMN in children with TLE, especially during a specific task. Our data show that there are indeed deficits in DMN deactivation during the *N*-back task. Children with TLE exhibit less deactivation of the DMN while performing a cognitive task compared with typically-developing controls and perform less accurately compared with typically-developing controls.

The dysfunction of the DMN in children with TLE correlated with *N*-back accuracy and reaction time, as well as D-KEFS speed and accuracy. This suggests that children with TLE may be less capable of adequately performing the task as they are unable to sufficiently suppress functional networks which are not directly involved in the task and unable to effectively activate the network involved in the task. The evidence

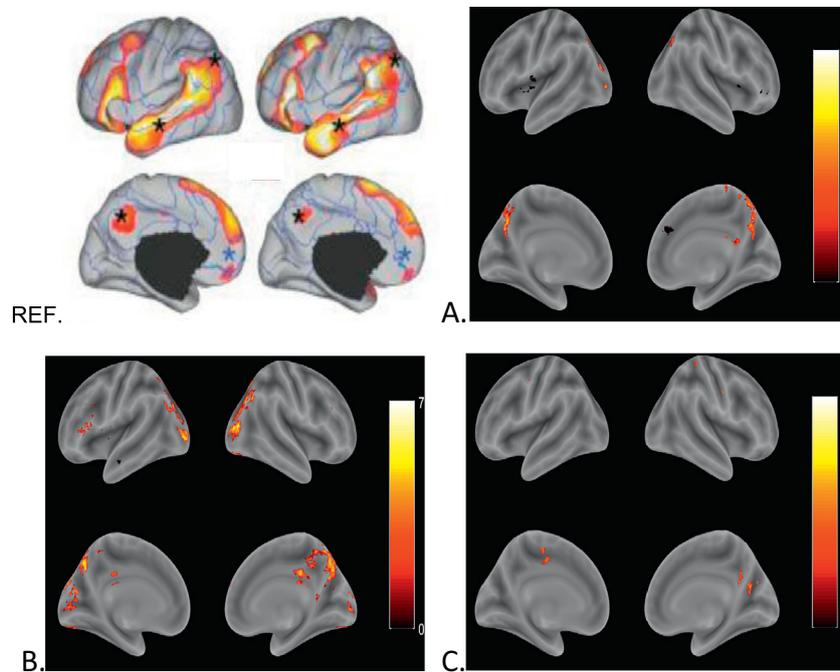


Fig. 3. Using bspmview software, this panel indicates the deactivation (negative contrast images, 0-back > 2-back). FWE cluster-level correction, cluster defining threshold $p < 0.001$, cluster size > 25 voxels. A - shows the controls only, the clusters of activation of the DMN are smaller and less intense compared to B during the *N*-back task. B - shows the patients with TLE only, the clusters of activation of the DMN are larger and more intense compared to A during the *N*-back task. C - shows the difference graph (TLE > controls contrast) indicating the regions that patients with TLE deactivate less during the *N*-back task. These significantly different regions are the left parietal lobe and the right precuneus, which are included in the DMN. The fMRI maps (in color) superimposed on anatomical images (gray scale). The red-yellow scale indicates intensity of activation of region. REF - results were confirmed using an a priori mask of the DMN map.

corroborates findings that the DMN plays a competitive role with task-positive networks such as the ECN [1]. Our data indicate that children with TLE have more difficulty suppressing the DMN as complexity of

the task increases compared with healthy controls. As a result, they may be less capable of engaging the ECN appropriately and therefore are unable to complete the task as accurately and swiftly as their typically-developing peers [1,2].

Table 4

Multiple regression shows the relationship between regions of the DMN with *N*-back performance and with neuropsychological tests of executive function.

Region	Peak t-value	Peak MNI coordinate	Cluster volume (voxels)	Cluster p-value
<i>N</i>-back accuracy				
L posterior inferior parietal lobe	6.21	−9, −70, 32	76	0.001
R medial prefrontal cortex	5.64	−3, 50, −16	29	0.049
Posterior cingulate cortex	5.49	0, −31, 26	113	<0.001
Medial frontal gyrus	5.41	0, 22, 41	48	0.005
<i>N</i>-back reaction time				
L posterior parietal lobe	5.6	−9, −70, 32	93	<0.001
R occipital lobe	5.53	9, −40, −1	34	0.022
Posterior cingulate cortex	5.43	0, −31, 26	103	<0.001
R medial prefrontal cortex	5.32	−3, 50, −16	38	0.013
L precuneus	5.22	0, −22, 41	81	<0.001
D-KEFS Color-Word Interference accuracy				
L posterior parietal lobe	5.19	−9, −70, 32	31	0.038
R precuneus	5.16	0, −19, 41	56	0.002
Posterior cingulate cortex	5.16	0, −37, 26	86	<0.001
Medial prefrontal cortex	5.03	−3, 50, −16	25	0.084
D-KEFS Color-Word Interference speed performance				
Medial prefrontal cortex	5.76	0, 50, −16	53	0.002
R occipital lobe	5.70	9, −40, −1	32	0.027
R precuneus	5.33	0, −19, 41	74	0.001
L posterior parietal lobe	5.28	−9, −70, 32	26	0.063
Posterior cingulate cortex	5.23	0, −37, 26	107	<0.001
D-KEFS Card Sort task accuracy				
Medial frontal gyrus	6.73	0, −22, 41	320	<0.001
Medial prefrontal cortex	6.13	−3, 50, −16	38	0.01
L posterior parietal lobe	5.86	−9, −70, 32	48	0.003
R precuneus	5.36	9, −61, 23	65	0.001

The data also indicated that the posterior cingulate/parietal lobe (ventral DMN) more frequently predicted WM performance, which corroborates prior findings [2] and differed significantly between controls and participants with TLE. Our data also suggest some predictive patterns involving the dorsal DMN, suggesting that perhaps this region of the DMN may be more predictive of performance on higher level concept formation assessed outside the scanner (D-KEF Card Sort). This lends credence to the fact that abnormalities on fMRI have direct relevance and clinical correlation to the widespread cognitive deficits that are frequently noted in children with TLE. It is important to note that the DMN deactivation regions did not directly overlap with the regions activated by the ECN. Specifically within the parietal lobe, the DMN deactivation occurred mainly in regions of the medial lower parietal lobe while the ECN activated regions of the superior lateral parietal lobe [15]. While within the frontal lobe, the DMN deactivation occurred primarily in regions of the medial frontal lobe, the ECN activated regions of the lateral frontal lobes primarily. A direct interaction was not evaluated given the limited sample size and multiple analyses, however, a direct comparison in future studies is warranted. Furthermore, future studies would determine whether the regional task activation (ECN) or the simultaneous regional deactivation (DMN) is more essential to successfully complete a task.

To our knowledge, there is no prior literature documenting DMN abnormalities in pediatric TLE during a task-based fMRI. Furthermore, our unique findings show a direct correlation of the DMN abnormalities in pediatric TLE to clinical cognitive findings. These findings also indicate that children with TLE not only exhibit widespread cognitive deficits, but also exhibit widespread neural network abnormalities. The DMN is a network that has not been strongly linked to the anterior mesial temporal lobe, however, it is clear here that pediatric TLE affects this relatively unrelated network either directly or indirectly. Our findings,

which accounted for age, medications, FSIQ, and ADHD, indicate that fMRI findings may indeed be reflective of traditional objective neuropsychological tests, which provides evidence of ecological validity of functional imaging measures.

7. Limitations and future directions

In spite of our limited sample size, we were able to document these novel findings. Because we had to ensure that our subjects could follow instructions, we had to inevitably exclude some individuals who have more severe disease. As a result, we may have ended up with a more 'benign' group. We expect that the differences would be even more notable if we were able to include a more severe group in our analysis. Ictal onsets were not captured for all the patients, which is the gold standard. With a larger wider-range sample size, the effects of TLE on typical 'frontal lobe' measures and the role of potential confounders such as laterality of temporal focus and medication effects can be delineated.

8. Conclusions

This study demonstrates dysfunction in the DMN in children with TLE, which correlates with EF on traditional neuropsychological tests and fMRI behavioral performance. Future studies addressing potential interactions between the ECN and DMN during task activation would elucidate the alternating and complementary, albeit dysfunctional collaboration between these two neural networks in pediatric TLE.

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Conflicts of interest

We have no conflicts of interest to report.

Disclosure statement

None of the authors has any conflict of interest to disclose.

Ethical publication statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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