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ORIGINAL RESEARCH

Neurobiological substrates of processing speed in childhood epilepsy

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Abstract
This study investigated the association between processing speed and cortical morphometry in children with idiopathic epilepsies ($n = 81$) versus healthy controls ($n = 57$), age 8–18. Participants underwent 1.5 T MRI scanning and cognitive testing including assessment of psychomotor speed (Digit Symbol) at or near the time of epilepsy diagnosis. Vertex analyses of cortical volume, thickness, surface area, and local gyrification index (LGI), as well as volume-based analyses of subcortical structures and cerebellum, were used to determine the morphometric correlates of Digit Symbol performance. Group comparisons revealed that the epilepsy and control groups exhibited different patterns of morphometric association with Digit Symbol performance - controls exhibited several areas of correlation between LGI and psychomotor speed, whereas participants with focal epilepsies exhibited different areas of correlation in different directions, and participants with generalized epilepsy exhibited no correlations. The other cortical morphometric measures showed no regions of significant correlation with Digit Symbol performance. In addition, cerebellum and brain stem volumes correlated with Digit Symbol performance in the control group, but not in epilepsy patients. These results suggest that LGI analysis is able to capture nuanced relationships between features of cortical and subcortical morphology with psychomotor speed, these relationships disrupted in different ways in children with epilepsy.

Keywords Epilepsy · Gyrification · Processing speed · Pediatric

Introduction

Of the potential cognitive impairments associated with epilepsy, the domains of memory, language and executive function are among the most studied, with several imaging investigations focused on the disrupted networks associated with these cognitive anomalies (c.f., Hermann et al. 2009; Addis et al. 2013). Psychomotor slowing is also a common though less investigated cognitive complication of the epilepsies. While psychomotor slowing is associated with many antiseizure medications, cognitive and/or psychomotor slowing is also evident in new onset adult and pediatric epilepsy patients prior to administration of AEDs (Oostrom et al. 2003; Baker et al. 2011), and has been shown to persist following remission of epilepsy (Berg et al. 2008; Aldenkamp et al. 1993).

The amount of neuroimaging research dedicated to understanding psychomotor slowing in epilepsy is modest. Dow et al. (2004) examined mental scanning speed in adults with temporal lobe epilepsy and found slower speeded performance related to reduced global cerebral white matter volume. Alexander et al. (2014) reported that increased fractional anisotropy (FA) of the left fornix was related to faster processing speed in temporal lobe epilepsy patients without hippocampal sclerosis. Van Veenendaal et al. (2017) examined the relationship between central information processing speed and rs-fMRI network efficiency and found no relationship between speed and network analysis in 55 patients with localization-related epilepsy.

In this limited literature there has been minimal investigation of whether processing speed is associated with the

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morphology of cortical and subcortical structures. Studies of brain structure often focus on dimensional morphometric measures such as surface area, thickness, and volume across the cortical mantle. Some studies have also included analysis of cortical folding, but this analysis is typically performed using a metric derived from local curvature and may be missing some of the more acute distinctions captured by an index of local gyrification (Shimony et al. 2016). This may result in barriers to the appreciation of the subtler effects of epilepsy on brain structure and warrants study to examine nuanced structural findings with cognitive function. Studies examining the cortical local gyrification index (LGI) and its correlates in regard to cognition have recently emerged, suggesting that cortical folding analysis has the capacity to reveal previously untapped relationships between brain structure and function (Green et al. 2017; Chung et al. 2017; Forde et al. 2017) in other clinical groups and healthy populations.

Cognitive and psychomotor slowing is not a unitary trait and in epilepsy research it has been assessed in a number of ways including simple and complex reaction time, finger tapping, mental scanning, and motor assembly tasks (for review see Grevers et al. 2016). A common approach across diverse disorders has been the use of digit substitution tests, with applications to examine speeded performance in disorders such as schizophrenia (Dickinson et al. 2007; Knowles et al. 2010; Morrens et al. 2007) and multiple sclerosis (Benedict et al. 2010) as well as normal aging (Salthouse 2000; Tucker-Drob and Salthouse 2008). The origin of generic digit substitution tests date to the early 1900s (Boake 2002) and were initially thought to represent a metric of incidental learning, but deconstructions of the task have shown that it is driven in considerable part by speed-dependent processes (graphomotor speed, perceptual speed) with secondary contributions of visual scanning efficiency, learning/memory and executive function (Joy et al. 2003; Ashendorf and Reynolds 2013). As such, it is an appropriate but not pure measure of processing speed, but one that has been used and investigated in multiple disorders as well as in normal and abnormal aging.

Here we examine the association of cortical volume, thickness, surface area, local gyrification index (LGI) and select subcortical and cerebellar volumes with Digit Symbol performance to characterize the relationships in normally developing children and how these associations may be altered in the context of new onset childhood epilepsy.

Methods

Participants

The study sample consisted of 81 children and adolescents with new onset epilepsy and 57 healthy first-degree cousin controls between the ages of 8 and 18 years. All participants gave informed consent and assent to participate in this study at University of Wisconsin-Madison and Marshfield Clinic (Marshfield, WI).

Entry criteria for epilepsy participants included a diagnosis of epilepsy within the past 12 months, no other neurological disorder, normal neurological examination, and normal clinical magnetic resonance imaging (MRI) scan. The control group consisted of first-degree cousins of the epilepsy patients that had no history of: (1) an initial precipitating event such as febrile seizures, (2) seizures or seizure-like events, (3) a diagnosed neurological disorder, (4) loss of consciousness for longer than 5 min, or (5) family history of a first-degree relative with epilepsy or febrile convulsions. None of the controls had a history of head injury. Use of first-cousin controls allowed for control over socioeconomic confounds while minimizing structural anomalies resulting from shared genetic factors.

Table 1 provides descriptive statistics for the demographic characteristics of the subjects. Neither age nor gender distributions differed significantly between groups, $t(136) = 1.299$, $p = 0.660$ for age and chi squared $(1, N = 138) = 0.086$, $p = 0.769$ for gender. Handedness did not differ between groups as well (Fischer exact test statistic, 0.098). Mean-centered age and gender were used as covariates in all analyses.

Neuropsychological assessment

Participants were administered a test battery that included the Wechsler Abbreviated Scale of Intelligence-2 subtest (WASI-II) Full Scale IQ (FSIQ) to assess general intelligence, and psychomotor processing speed was assessed using the Digit Symbol/Coding Test (Wechsler Intelligence Scale for Children, Third Edition). Digit Symbol performance was not considered in the derivation of FSIQ.

MRI acquisition

Imaging was conducted on a 1.5 T GE (Waukesha, Wisconsin) Signa scanner where T1-weighted 3-dimensional spoiled gradient recalled images were obtained (repetition time = 24 ms, echo time = 5 ms, flip angle = 40°, plane = coronal, slice thickness = 1.5 mm, matrix = 256 X 256 X 124, 0.78 X 0.78 X 1.5 mm voxels. Subjects were excluded if they possessed MR scanning contraindication due to metal braces or claustrophobia, or if scans were of poor quality due to movement artifacts. All images were inspected visually for possible motion-related artifacts or distortion. There were no such artifacts.

Cortical morphology

Freesurfer v5.3 image analysis suite was used for cortical reconstruction and segmentation of the T1-weighted volumetric MR images, which included removal of non-

Table 1 Demographic information and cognitive results

Group	Patient	Control	Statistic	*P* value
Age: M (SD) in years	12.9 (3.3)	13.2 (3.1)	$T = 1.3$	0.66
Gender: M / F	42 / 39	31 / 26	Chi Squared = 0.09	0.77
Handedness: R / L	69 / 12	54 / 3	Fischer exact	0.01
Digit Symbol Scaled Score: M (SD)	8.4 (2.5)	10.3 (3.3)	F = 9.96	0.002
WASI-2 Full Scale IQ: M (SD)	101.5 (15.8)	109 (10.1)	F = 6.00	0.003
(LRE) /(IGE) epilepsy	39 / 42			

M mean, *SD* standard deviation, *LRE* Localization related epilepsy, *IGE* Idiopathic generalized epilepsy

brain tissue, automated Taliarach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (e.G. *hippocampus*, amygdala, caudate, putamen, ventricles), intensity normalization, tessellation of the gray matter/white matter boundary, automated topology correction, and surface deformation following intensity gradients to effectively place the boundaries between brain tissue (cerebrospinal fluid, white matter, and gray matter). FreeSurfer's Desikan-Killiany atlas was used to identify cortical regions volumetrically (Fischl and Dale 2000; Fischl et al. 2004). The cross-sectional stream was used to analyze the structure-function associations within the epilepsy and control groups. Visual inspection was also used throughout the processing stream to maintain consistent quality of measurements. Pial and white matter surfaces were verified to follow the proper contours. Pial surface errors were corrected by editing the brain mask and control points were utilized for improper white matter contours. If edits were required, Freesurfer was restarted using the options appropriate for each edit. Final inspections were completed prior to data analysis. Any unrepairable subjects were not used in this analysis.

Computations for cortical volume (CV), cortical thickness (CT), and surface area (SA) were calculated across the cortical mantle. The Local Gyrification Index (LGI) was calculated as well to compare cortical complexity between groups. LGI is calculated as the ratio of the area of cortex buried within the sulcal folds of the pial surface to the area of cortex on the outer visible cortex of the smoothed surface. Volumes of left hemisphere and right hemisphere subcortical structures included the cerebellum, thalamus, hippocampus, caudate, putamen, pallidum, amygdala, and brainstem were also extracted for correlational analysis.

Statistical analysis

Digit Symbol scores were scaled using age adjustment based on test norms. These Digit Symbol scores were used to compare performance between groups using an analysis of covariance (ANCOVA) controlling for gender and IQ. The statistical analyses were performed using the IBM software package SPSS v23.

Analyses for CV, CT, SA, and LGI were conducted via FreeSurfer's statistical tool, Qdec. CV, CT, and SA measurements were smoothed with a 15-mm full-width half maximum (FWHM) smoothing kernel, whereas LGI measurements did not use the FWHM smoothing kernel due to the inherent smoothing present in the metric itself. All morphological tests involved mapping each subject's calculated measure at each vertex to a standard average brain surface. Covariates for group differences included age, gender, and IQ. Use of Qdec's Monte Carlo simulation allowed for corrections of multiple comparisons, with the cluster forming threshold set to $p < 0.05$.

Correlational analysis between the scaled Digit Symbol score and the cortical morphological measures (CV, CT, SA, and LGI) was conducted within Qdec using the Monte Carlo cluster correction, incorporating IQ as a covariate in order to correct for overall cognitive ability. Within-group tests for clusters of significant correlation as well as between-group tests for clusters of significant difference in correlation were performed for Digit Symbol score and each morphological measure.

Correlations between subcortical volumes and Digit Symbol score were conducted in SPSS controlling for age, gender, intracranial volume, and IQ, using a Sidak correction for multiple comparisons. A Fischer R-to-Z transformation was used to compare within and between group correlations in the patients and controls to determine significant differences.

Additionally, secondary analyses examined the role of epilepsy syndrome (localization-related epilepsy (LRE) or idiopathic generalized epilepsy (IGE)) to determine the effect of syndrome type on the associations between Digit Symbol and morphometric measures. Gender distributions did not differ between LRE/IGE/controls. However, the IGE group was slightly older than the LRE and control groups, $F(2, 137) = 5.998$, $p = 0.003$, due to older age of patients with juvenile myoclonic epilepsy, the other IGE syndromes with ages similar to the LRE and control groups.

Results

Table 1 provides descriptive characteristics of the epilepsy and control participants and information concerning test scores. Patients exhibited significantly lower scaled Digit Symbol performance than the control group when controlling for IQ and gender ($F = 9.96$, $p = 0.002$).

Regarding association of psychomotor speed with brain metrics, no clusters of significant correlation with Digit Symbol scores were found for morphological measures of cortical volume, thickness or surface area within the epilepsy or control groups, nor were clusters of significant difference found between group correlations for those metrics. Figure 1 shows that vertex-based cluster analysis within the control group found areas of negative correlation between adjusted Digit Symbol score and LGI in the left precentral gyrus, left insula, and right fusiform gyrus ($p < 0.001$) and clusters of positive correlation in the right posterior cingulate ($p < 0.05$) (See Supplemental Figure for scatterplots of representative findings). Regions of negative correlation represent regions in which controls with lower LGI in the region tended to have higher Digit Symbol scores, whereas regions of positive correlation represent regions where controls with higher LGI in the region tended to have higher Digit Symbol scores. No clusters of significant correlation between Digit Symbol and LGI were found in the epilepsy group. Comparison between groups found that patients exhibited less negative correlation between Digit Symbol scores and LGI than controls in the left precentral gyrus, left insula, and right fusiform gyrus (all $p < 0.001$), as well as a more positive correlation in the left superior parietal lobe ($p < 0.01$).

Subcortical volumetric correlational analysis found positive correlations with Digit Symbol scores in the left cerebellum ($r = 0.385$, $p = 0.008$), right cerebellum ($r = 0.348$, $p = 0.01$), and brain stem ($r = 0.438$, $p = 0.001$) in the controls. No subcortical correlations with Digit Symbol scores were found within the patient group. Comparisons of subcortical volume/ Digit Symbol correlations between groups found that each subcortical correlation in the control group was significantly higher than that of the patient group (left cerebellum $p = 0.003$, right cerebellum $p = 0.02$, and brain stem $p = 0.006$).

When accounting for syndrome type, clusters of positive correlation between LGI and Digit Symbol score manifest in the left postcentral gyrus, left lateral occipital gyrus, and right caudal middle frontal gyrus of the patient group, as seen in Fig. 2. These findings were driven by positive correlations found in the LRE group, as the IGE group demonstrated no clusters of significant correlation. Controlling for syndrome did not affect the results for any other morphometric measure, including the results for subcortical volume correlations.

Discussion

This study provides a novel perspective regarding the relationship between brain morphology and an important cognitive morbidity in pediatric epilepsy by examining associations between vertex-level gyrification and other measures of cortical morphology and subcortical volumes with a well-known and commonly used metric of processing speed (Digit Symbol). We found unique patterns of structure-function association not captured with commonly used metrics such as cortical thickness, volume, or surface area.

The cross-sectional analysis found an expected difference in Digit Symbol performance between participants with

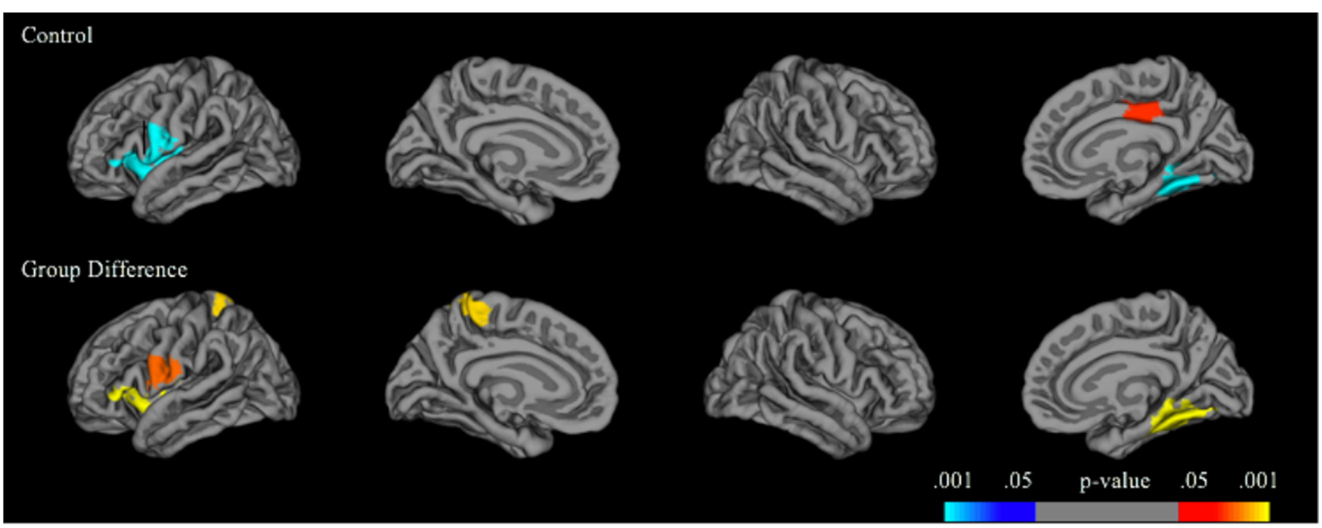

Fig. 1 Cross sectional vertex analysis results for correlations between LGI and digit symbol score. Red/yellow clusters for the Control row indicate clusters with positive correlations between LGI and digit symbol score. Red/yellow clusters for the Group Difference column indicate clusters where patients have a less negative correlation between LGI and digit symbol score than controls

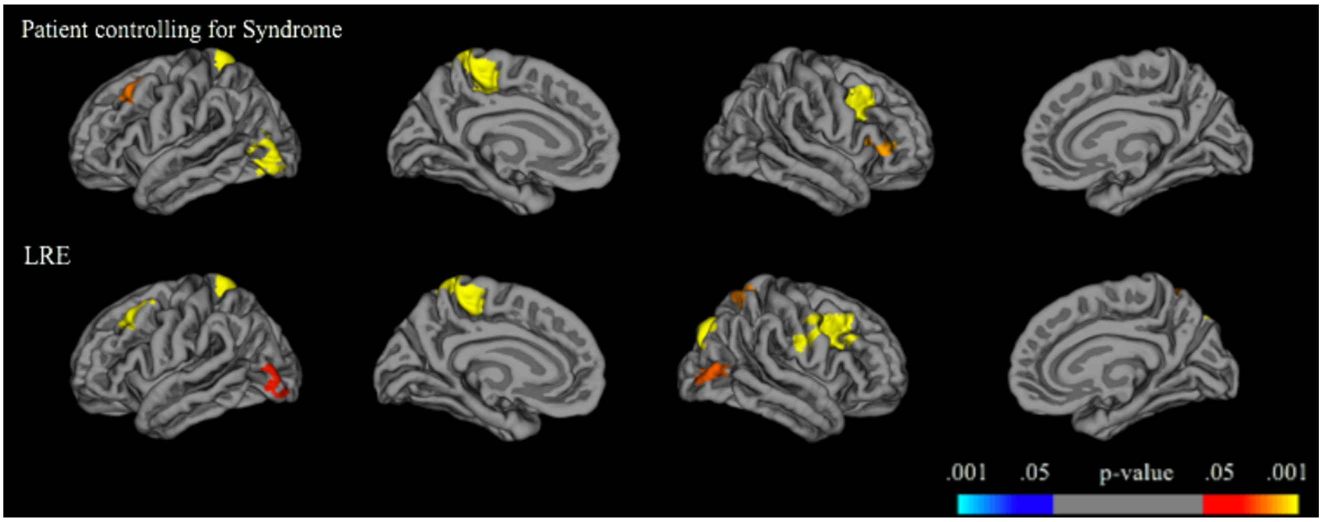

Fig. 2 Cross sectional vertex analysis results for correlations between LGI and Digit Symbol score when controlling for epilepsy syndrome. Red/yellow regions indicate clusters with positive correlation between LGI and Digit Symbol score

epilepsy and controls, with slower processing speed in the children with epilepsy, even after controlling for overall intellectual level. This finding is consistent with reports that cognitive abnormality in epilepsy is not solely attributable to the duration of epilepsy or years of intractable seizures and treatment as this difference was detected very early in the course of the children's epilepsy (Oostrom et al. 2003; Baker et al. 2011). We found an interesting difference in the pattern of associations between LGI and Digit Symbol performance across the cortical surface. Controls showed several regions of the cortical surface where only local gyrification was highly correlated with processing speed performance, while these relationships were absent in the epilepsy participants, suggesting that normal structure-function relationships were disrupted in that group. These results further suggest that the altered brain organization thought to be found in epilepsy participants could either alter gyrification patterns or alter the brain's reliance on gyrification in order to perform processing speed tasks (Scanlon et al. 2009; Alhusaini et al. 2012; Ronan et al. 2011, 2012).

Controls exhibited more numerous and stronger areas of correlation between LGI and Digit Symbol performance, suggesting that the presence of epilepsy disrupted these normal brain-behavior relationships. When examining the role of syndrome (localization related, idiopathic generalized), associations remain absent in children with IGE, or were altered in children with LRE compared to the controls, again consistent with the theory that structure-function relationships remain altered or negated regardless of syndrome, in addition to the observed psychomotor slowing. Although no other morphometric measure studied was found to have a significant correlation with Digit Symbol score across the cortical surface, the cerebellum and brain stem volumes were found to be positively correlated with Digit Symbol in controls, suggesting that "subcortical" structure volume may have a larger impact on processing speed than cortical volume in a particular region - again, a relationship that was not observed in the epilepsy group. The children with epilepsy exhibited significantly smaller cerebellar volume compared to controls, which is interesting in multiple respects as cerebellar atrophy has been classically attributed to chronic epilepsy and/or medication effects (phenytoin) (for review see Hermann et al. 2006), neither of which characterized the pediatric epilepsy sample examined here. Examination of speed-cerebellar relationships in epilepsy is rare, but Botez et al. (1989) examined the clinical and neuropsychological characteristics of 33 patients with epilepsy with normal CT scans compared to 31 patients with cerebellar and brain stem atrophy. The cerebellar/brainstem atrophy group performed significantly slower on Digit Symbol (as well as other cognitive measures) and, when examining composite cognitive domain scores, processing speed was significantly lower in the cerebellar/brainstem atrophy group compared to the normal CT scan patients. While no direct correlations were computed between cerebellar/brainstem volume and cognitive scores, this clearly indicated a relationship between cerebellar/brainstem atrophy and processing speed and symmetry between these investigations of pediatric and adult epilepsy samples. While the associations of Digit Symbol performance with diverse cortical regions (left precentral gyrus, left insula, right fusiform gyrus, posterior cingulate) are congruent with behavioral deconstructions of the task that suggest contributions of speeded motor, attention, perception and memory abilities, these findings await replication in an independent sample.

Several other studies have begun to examine the role of cortical gyrification in epilepsy in addition to volume, thickness, and surface area, but the application of these findings to cognitive performance has been infrequent, these types of studies focused primarily on healthy populations (e.g., Green et al. 2017; Chung et al. 2017). Further studies into the differences in functional connectivity associated with different levels of gyrification would provide greater explanatory power towards the relationship between gyrification and cognition, and would provide even greater support for the hypothesis that epilepsy results in functional reorganization with cognitive consequences. Future studies investigating the relationship between cortical gyrification and other cognitive measures such as executive function and language may serve to enhance understanding of the altered neurobiology associated with cognitive compromise in epilepsy. Lastly, it remains important to determine how slowed processing speed impacts the efficiency of other cognitive systems in children with epilepsy in order to characterize the broader significance of this cognitive anomaly.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the University of Wisconsin – Madison Institutional Review Board and with the 1964 Helsinki Declaration and its later amendments.

Informed consent Informed consent was obtained for all individual participants included in this study.

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