Structural neuroimaging provides a non-invasive method to understand hippocampal pathology, but traditionally only at a whole-hippocampal level. However, recent methodological advances have enabled the non-invasive quantification of subfield pathology in patients, enabling potential integration into clinical workflow. In this study, we characterize patterns of hippocampal subfield atrophy in patients with TLE and examine the associations between subfield atrophy and clinical characteristics.
Participants and Methods: High-resolution T2 and T1-weighted MRI were collected from 31 participants (14 left TLE; 6 right TLE; 11 healthy controls [HC], aged 18-61 years). Reconstructions of hippocampal subfields and estimates of their volumes were derived using the Automated Segmentation of Hippocampal Subfields (ASHS) pipeline. Total hippocampal volume was calculated by combining estimates of the subfields CA1-3, DG, and subiculum. To control for variations in head size, all volume estimates were divided by estimates of total brain volume. To assess disease effects on hippocampal atrophy, hippocampi were recoded as either ipsilateral or contralateral to the side of seizure focus. Two sample t-tests at a whole-hippocampus level were used to test for ipsilateral and contralateral volume loss in patients relative to HC. To assess whether we replicated the selective histopathological patterns of subfield atrophy, we carried out mixed-effects ANOVA, coding for an interaction between diagnostic group and hippocampal subfield. Finally, to assess effects of disease load, non-parametric correlations were performed between subfield volume and age of first seizure and duration of illness.
Results: Patients had significantly smaller total ipsilateral hippocampal volume compared with HC ($d=1.23$, $p<.005$). Contralateral hippocampus did not significantly differ between TLE and HC. Examining individual subfields for the ipsilateral hemisphere revealed significant main-effects for group ($F(1, 29)=8.2$, $p<0.01$), subfields ($F(4, 115)=550.5$, $p<0.005$), and their interaction ($F(4, 115)=8.1$, $p<0.001$). Post-hoc tests revealed that TLE had significantly smaller volume in the ipsilateral CA1 ($d=-2.0$, $p<0.001$) and DG ($d = -1.4$, $p<0.005$). Longer duration of illness was associated with smaller volume of ipsilateral CA2 ($\rho=-0.492$, $p<0.05$) and larger volume of contralateral whole-hippocampus ($\rho=0.689$, $p<0.001$), CA1 ($\rho=0.614$, $p < 0.005$), and DG ($\rho=0.450$, $p<0.05$).
Conclusions: Histopathological characterization after surgery has revealed important associations between hippocampal subfield cell loss and memory impairments in patients with TLE. Here we demonstrate that non-invasive neuroimaging can detect a pattern of subfield atrophy in TLE (i.e., CA1/DG) that matches the most common form of histopathologically-observed hippocampal sclerosis in TLE (HS Type 1) and has been linked directly to both verbal and visuospatial memory impairment. Finally, we found evidence that longer disease duration is associated with larger contralateral hippocampal volume, driven by increases in CA1 and DG. This may reflect subfield-specific functional reorganization to the unaffected brain tissue, a compensatory effect which may have important implications for patient function and successful treatment outcomes.

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26 The Importance of Executive Functioning for Academic Achievement Among a National Sample of Children with Epilepsy

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Objective: Children with epilepsy are at greater risk of lower academic achievement than their typically developing peers (Reilly and Neville, 2015). Demographic, social, and neuropsychological factors, such as executive functioning (EF), mediate this relation. While research emphasizes the importance of EF skills for academic achievement among typically developing children (e.g., Best et al., 2011; Spiegel et al., 2021) less is known among children with epilepsy (Ng et al., 2020). The purpose of this study is to examine the influence of EF skills on academic achievement in a nationwide sample of children with epilepsy.
Participants and Methods: Participants included 427 children with epilepsy (52% male; M_{Age}= 10.71), enrolled in the Pediatric Epilepsy Research Consortium (PERC) Epilepsy Surgery Database who had been referred for surgery and underwent neuropsychological testing. Academic achievement was assessed by performance measures (word reading, reading comprehension, spelling, and calculation and word-based mathematics) and parent-rating measures (Adaptive Behavior Assessment System (ABAS) *Functional Academics* and Child Behavior Checklist (CBCL) *School Performance*). EF was assessed by verbal fluency measures, sequencing, and planning measures from the Delis Kaplan Executive Function System (DKEFS), NEPSY, and Tower of London test. Rating-based measures of EF included the 'Attention Problems' subscale from the CBCL and 'Cognitive Regulation' index from the Behavior Rating Inventory of Executive Function (BRIEF-2). Partial correlations assessed associations between EF predictors and academic achievement, controlling for full-scale IQ (FSIQ; A composite across intelligence tests). Significant predictors of each academic skill or rating were entered into a two-step regression that included FSIQ, demographics, and seizure variables (age of onset, current medications) in the first step with EF predictors in the second step.
Results: Although zero-order correlations were significant between EF predictors and academic achievement (.29 < *r's* < .63 for performance; -.63 < *r's* < -.50 for rating measures), partial correlations controlling for FSIQ showed fewer significant relations. For performance-based EF, only letter fluency (DKEFS Letter Fluency) and cognitive flexibility (DKEFS Trails Condition 4) demonstrated significant associations with performance-based academic achievement (*r's* > .29). Regression models for performance-based academic achievement indicated that letter fluency (β = .22, *p* = .017) and CBCL attention problems (β = -.21, *p* =.002) were significant predictors of sight-word reading. Only letter fluency (β = .23, *p* =.006) was significant for math calculation. CBCL Attention Problems were a significant predictor of spelling performance (β = -.21, *p* = .009) and reading comprehension (β = -.18, *p* =.039). CBCL Attention Problems (β = -.38, *p* <.001 for ABAS; β = -.34, *p* =.002 for CBCL School) and BRIEF-2 Cognitive Regulation difficulties (β = -.46, *p* < .001 for ABAS; β = -.46, *p* =.013 for CBCL School) were significant predictors of parent-rated ABAS *Functional Academics* and CBCL *School Performance*.
Conclusions: Among a national pediatric epilepsy dataset, performance-based and ratings-based measures of EF predicted performance academic achievement, whereas only ratings-based EF predicted parent-rated academic achievement, due at least in part to shared method variance. These findings suggest that interventions that increase cognitive regulation, reduce symptoms of attention dysfunction, and promote self-generative, flexible thinking, may promote academic achievement among children with epilepsy.

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