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RESEARCH ARTICLE

# Cognitive and brain health in juvenile myoclonic epilepsy: Role of social determinants of health

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## Abstract

**Objective:** Juvenile myoclonic epilepsy (JME) is a prevalent genetic generalized epilepsy with linked abnormalities in cognition, behavior, and brain structure. Well recognized is the potential for advancing understanding of the epigenetic contributions to the neurobehavioral complications of JME, but to date there has been no examination of the role of socioeconomic disadvantage in regard to the cognitive and brain health of JME, which is the focus of this investigation.

**Methods:** Seventy-seven patients with JME and 44 unrelated controls underwent neuropsychological assessment, structural neuroimaging, and clinical interview to delineate epilepsy history and aspects of family status. The Area Deprivation Index characterized the presence and degree of neighborhood disadvantage, which was examined in relation to cognitive factor scores underlying a comprehensive neuropsychological test battery, academic metrics, integrity of brain structure, and family characteristics.

**Results:** JME participants resided in neighborhoods associated with significantly more socioeconomic disadvantage, which was associated with significantly poorer performance across all three cognitive factor scores and reading fluency. JME was associated with significant reduction of total subcortical gray matter (GM) but not total cortical gray or white matter volumes. Among controls, participants residing in more advantaged areas exhibited increased volumes of total subcortical GM and diverse subcortical structures as well as areas of increased cortical thickness and volume in frontal/prefrontal regions, findings that were compromised or not evident in JME, raising the possibility of disease-related attenuation of socioeconomic advantage.

**Significance:** Socioeconomic disadvantage in JME is associated with adverse effects on cognitive and academic status, whereas socioeconomic advantage in controls is associated with increased brain volumes and thickness, markers of brain health that were largely attenuated or absent in JME. The associations detected here argue for the need to better integrate the social determinants of health with

genetic and epigenetic factors in advancing understanding of cognitive and brain health in JME.

**KEYWORDS**

juvenile myoclonic epilepsy, neighborhood deprivation, neuroimaging, neuropsychology

## 1 | INTRODUCTION

Social determinants of health (SDOH) have been associated with epilepsy incidence and prevalence, as well as access to and quality of diverse treatments and their medical, surgical, social, and quality of life outcomes.[1–4] Recently, the potential contributions of SDOH have been extended to the cognitive and behavioral complications of the epilepsies, which historically have centered on their relationships with clinical features of the disorder (e.g., syndrome, etiology, chronicity, intractability),[5,6] and diverse neuroimaging and electrographic markers (e.g., brain structure, connectivity) that have advanced understanding of the disordered neurobiology underlying these neurobehavioral comorbidities and their course.[7–9]

A more recent stream of research has examined neighborhood and personal markers of socioeconomic disadvantage, demonstrating their associations with cognition and behavior in adults with pharmacoresistant temporal lobe epilepsy,[10,11] mixed adult focal epilepsies,[12] youth with new and recent onset epilepsies,[13,14] and older adults with focal epilepsies.[15] Far less attention has been directed to the relevance of socioeconomic disadvantage for the cognitive and brain health of patients with idiopathic (genetic) generalized epilepsies, among which juvenile myoclonic epilepsy (JME) is prevalent, typically with onset in childhood/adolescence,[16–18] with its own cognitive complications[19,20] for which potential epigenetic contributions have been of interest, reflected in the search for familial aggregation of cognitive, behavioral, and even imaging-based abnormalities in the unaffected siblings of JME patients.[18,19] Also underinvestigated in epilepsy generally, and JME in particular, are the potential neuroanatomical correlates of socioeconomic inequity. To date, we are aware of only one such investigation demonstrating an association between disadvantage and abnormalities in the white matter connectome of adults with temporal lobe epilepsy.[21]

To address these issues, our overall objective was to examine the relationship of socioeconomic status (SES) to cognitive and brain health in JME using the Area Deprivation Index (ADI). The ADI incorporates 17 data elements derived from US Census and American Community Survey data (e.g., education, employment, housing, and poverty) to quantify neighborhood-level socioeconomic position.[22,23] Our specific aims were to (1) compare the ADI in participants with JME to unrelated controls; (2) examine the relationship between the ADI and metrics of cognition and academic performance in JME and control participants; (3) determine the relationship of ADI to both global (total intracranial volume, total cerebral and subcortical volumes) and specific (vertex based) measures of cortical thickness, volume, and curvature; and (4) characterize the association of ADI with aspects of family structure (parental education, employment marital status) and clinical epilepsy history (age at onset, duration, number of medications, seizure density).

**Key points**

- Social determinants of health, including socioeconomic disadvantage, have been underinvestigated in JME, a prevalent genetic generalized epilepsy.
- Neighborhood disadvantage in JME was associated with significantly poorer neuropsychological ($p \leq .025$) and academic status (reading fluency; $p < .001$).
- Neighborhood advantage in controls was linked with increased volumes of subcortical structures ($p \leq .045$) and increased thickness/volume in frontal regions.
- Advantaged-associated benefits observed in controls were not evident in JME, suggesting disease-related attenuation of socioeconomic advantage.
- More research is needed to clarify the interactive effects of socioeconomic status and epilepsy on cognitive and brain health in genetic generalized epilepsies.

## 2 | MATERIALS AND METHODS

### 2.1 | Participants

Inclusion criteria for JME participants were (1) chronological age between 12 and 25 years; (2) English

speaking; and (3) a diagnosis of JME supported by at least two of the three following criteria: (a) clinical description or directly observed early morning myoclonic jerks, (b) clinical description or directly observed generalized tonic–clonic (GTC) seizures, and (c) an electroencephalogram (EEG) with bursts of 3.5–5-Hz generalized spike–wave and/or polyspike wave discharges. Exclusion criteria included (1) inability to provide informed consent, (2) reported or directly observed semiological or EEG features suggestive of focal epilepsy, (3) presence of any lesions other than nonspecific white matter abnormalities on 3-T magnetic resonance imaging (MRI) with a dedicated epilepsy protocol that included high-resolution axial T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence, (4) an active infectious etiology for seizures, and (5) diagnosis of autistic spectrum disorder (ASD). The control group was composed of participants unrelated to the JME patients ($n = 44$) recruited from control participants in other local epilepsy investigations and from widely community-placed recruitment posters and email blasts. Exclusion criteria for controls included (1) history of any initial precipitating insult (e.g., simple or complex febrile seizures, cerebral infection, or perinatal stroke), (2) any seizure or seizurelike episode, (3) diagnosed neurological disease, (4) loss of consciousness for >5 minutes, and (5) diagnosis of ASD.

## 2.2 | Area Deprivation Index

The ADI is a composite measure of neighborhood socioeconomic disadvantage for the United States[22] based on similar measures used internationally for resource planning and health policy development. As noted, this factor-based index incorporates 17 US Census poverty, education, housing, and employment indicators to characterize neighborhood disadvantage and risk in specific census-based regions through a ZIP code-linked process, which has the added advantage of not requiring a lengthy and intrusive discussion with patients and families.[24] The ADI from the 2015 American Community Survey used here is a validated and widely used measure of neighborhood-level disadvantage.[23]

To calculate ADI in our sample, family addresses were entered into the University of Wisconsin-Madison's Neighborhood Atlas (www.neighborhoodatlas.medicine.wisc.edu) to geocode each family to its census block group and its assigned ADI value (i.e., state decile and national percentile), where higher values indicate greater levels of disadvantage. The home address was obtained from the participating family/participant at the time of the baseline study visit so that the correct residence was not confounded by any inaccuracies that may have been inherent in the electronic medical records. As an aside, the obtained addresses were used for remittance of the institutional review board-approved study participation renumeration, and no mailing was returned undelivered, so we are confident of the addresses.

Because ADI quintiles are predominantly used along with national percentiles in the literature, state deciles were converted from deciles (1–10) to quintiles (1–5), with 1 representing the least disadvantaged and 5 the most disadvantaged. Targeted sensitivity analyses dichotomized participants into the lowest two quintiles (1 + 2 = low disadvantage) and the highest two quintiles (4 + 5 = high disadvantage), an approach we have used in our prior ADI research in epilepsy.[13,21,25,26]

## 2.3 | Clinical data

Electronic forms were used for recording demographic, medical, neuropsychological, neurologic examination, quality of life, and electrophysiological data based on the National Institutes of Health Common Data Elements (https://www.commondataelements.ninds.nih.gov/). These data were captured through chart review, questionnaires completed by the patient, and a structured interview covering details of seizure history, seizure types, seizure frequency, family structure, parental education, work history, marital status, participant educational history, and general medical status.

## 2.4 | Cognitive assessment

All participants were administered a comprehensive neuropsychological test battery assessing diverse cognitive domains including language, visuoperception/construction, verbal and visual learning and memory, executive function, and processing speed. Table S1 overviews the administered cognitive tests, their representative domains, and the specific abilities targeted. All listed measures met criteria for inclusion in a factor analysis that reduced the battery to three underlying factors[27] that are depicted in Table 2. In addition, three measures assessing aspects of academic performance used in epilepsy research[32] were assessed, including Reading Fluency, Math Fluency, and Word Attack.

## 2.5 | Statistical analyses

Analyses (SPSS v28.0) of categorial data used the chi-squared test, whereas continuous data used appropriate

parametric or nonparametric analytics based on the distributional characteristics of the data.

## 2.6 | MRI acquisition protocol

MRI images were acquired on 3-T MR750 scanners (General Electric) using a Nova 48-channel head coil. T1-weighted structural images were acquired using a three-dimensional gradient-echo pulse (MPRAGE) sequence (repetition time = 2075 ms, echo time = 2.96 ms, inversion time = 1060 ms, flip angle = 8°, field of view = 25.6 cm, 1-$mm^3$ isotropic spatial resolution).

## 2.7 | Image analytics

T1-weighted volumetric images were corrected for B1 bias using the N4 algorithm[33] implemented in ANTs.[34] The bias-corrected images were then preprocessed with the FreeSurfer 7.4.1 image analysis suite (http://freesurfer.net) using the recon-all pipeline[35] (motion correction, nonuniform intensity normalization, Talairach transform computation, intensity normalization, and skull stripping).[36–38] Visual inspection of the processed images was undertaken to maintain consistent quality throughout. Computations for cortical volume, cortical thickness, and mean curvature were calculated across the entire cortical mantle, based on the Desikan–Killiany[39] probabilistic atlas. All images were visually inspected for possible motion-related artifacts or distortion.

The FreeSurfer script *mris_preproc* was used to compare cortical measures between groups. It allows one to concatenate all the subjects' maps that will be used for group analyses for each measure and hemisphere, and smoothing kernels (to improve intersubject variability). Afterward, *mri_glmfit* was applied to configure the model and establish the contrasts (it creates uncorrected contrast maps for the different measures). Then, multiple comparison cluster correction was performed using *mri_glmfit-sim* with a cluster-forming threshold set to $p \leq .05$. Group comparisons in this article are all presented at a smoothing kernel of 10 mm full width at half maximum.

# 3 | RESULTS

Table 1 provides a summary of the participant groups. There were no group differences in the distribution of gender, handedness, or age (all $p > .39$). The mothers of the unrelated controls had a significantly higher proportion with a college degree compared to the mothers of JME participants. There was no difference in the distribution of participants across the various academic achievement categories, but there was a trend of higher academic achievement in controls. For pre-high school participants, their current grade levels were equivalent (9.5 in controls and 9.9 in JME, $p = .368$).

Table 2 presents the three cognitive factors underlying the administered neuropsychological test battery and the associated test metrics. Details regarding the derivation of these factor scores are provided in a separate paper,[27] but essential details are contained in Supporting Information S1.

## 3.1 | Aim 1: ADI in JME and control participants

JME participants resided in neighborhoods associated with less advantage compared to the controls. This relationship was reflected in analyses of both ADI national percentile (Mann–Whitney $U = 833.5$, $z = -4.14$, $p < .001$) and state quintile ($\chi^2 = 13.355$, $df = 4$, $p < .01$), with overrepresentation of controls in the less disadvantaged areas (Figure 1).

Sensitivity analysis revealed that, of the JME participants, 29% resided in the least disadvantaged (quintiles 1 + 2) and 71% in disadvantaged neighborhoods (quintiles 4 + 5), whereas among controls 8% resided in disadvantaged and 92% in advantaged neighborhoods ($\chi^2 = 13.35$, $df = 4$, $p = .01$).

## 3.2 | Aim 2: ADI and cognitive performance

There were no significant relationships between disadvantage and performance across the cognitive factor scores in the control group (Spearman correlations of $r = -.167$, $p = .297$ for Factor 1; $r = -.264$, $p = .095$ for Factor 2; and $r = -.030$, $p = .85$ for Factor 3). In contrast, significant associations with deprivation were observed for the JME participants across all factor scores ($r = -.501$, $p < .001$ for Factor 1; $r = -.331$, $p = .004$ for Factor 2; and $r = .235$, $p = .04$ for Factor 3). In all cases, poorer cognitive performance in the JME participants was associated with increasing disadvantage (Figure 2).

Examining relationships between deprivation and measures of academic performance, no significant associations (Spearman correlation) were observed for controls (Reading Fluency, Math Fluency, Word Attack $r$'s of $-.214$, $p = .196$; $r = -.026$, $p = .87$; $r = -31$, $p = .052$) but with significant relationships observed for JME participants for Reading Fluency ($r = -.396$, $p < .001$) but not Math Fluency ($r = -.144$, $p = .216$) or Word Attack ($r = -.097$, $p = .409$).

**TABLE 1** Participant characteristics.

| Characteristic | Unrelated controls, $n=44$ | JME, $n=77$ | Statistic |
|---|---|---|---|
| Age, years (SD) | 20.3 (3.2) | 19.7 (3.7) | $F=.73$, $df=1119$, $p=.395$ |
| Gender, % male | 45% | 33% | $\chi^2=2.2.2$, $df=1$, $p=.155$ |
| Education, % | | | $\chi^2=9.92$, $df=5$, $p=.08$ |
| In HS | 3.3% | 3.8% | |
| HS degree | 6.7% | 26.9% | |
| Associate's degree | 0% | 7.7% | |
| Some college | 46.7% | 38.5% | |
| College degree | 30% | 19.2% | |
| Masters+ | 13.3% | 3.8% | |
| Handedness, % right handed | 97.5% | 93.4% | $\chi^2=1.47$, $df=1$, $p=.225$ |
| Mother education, % college | 70.5% | 42.1% | $\chi^2=9.13$, $df=2$, $p=.01$ |
| Father education, % college | 54.5% | 43.7% | $\chi^2=1.49$, $df=2$, $p=.473$ |
| Onset, years (SD) | | 13.6 (3.7) | |
| Duration, years (SD) | | 6.46 (5.4) | |
| ASMs, *n* (SD) | | 1.49 (.62) | |
| Most recent seizure, days | | 15.8 days | |

Abbreviations: ASM, antiseizure medication; HS, high school; JME, juvenile myoclonic epilepsy.

### 3.3 | Aim 3: ADI and brain structure

Analysis of covariance (age, gender) did not reveal a group (control vs. JME participants) difference in total intracranial volume (TIV; $F=2.813$, $df=1.99$, $p=.097$). Multivariate analysis of covariance (age, TIV) examining group differences in total subcortical gray matter, total cortical gray matter, and total cerebral white matter volumes was significant (Hotelling $T=.242$, $F=7.83$, $p<.001$). Univariate effects demonstrated significantly lower subcortical gray matter volume in JME ($F=7.143$, $p=.009$) but no group differences in cerebral gray ($F=1.36$, $p=.247$) or cerebral white matter ($F=.559$, $p=.457$) volumes.

The relationship between ADI (national percentile) and adjusted TIV (age, gender) was not significant for controls ($r=.211$, $p=.21$), whereas for JME participants increasing deprivation was associated with smaller total intracranial volume ($r=-.383$, $p=.003$; Figure 3).

In control participants, nonparametric partial (age, TIV) correlations revealed no association of ADI (national percentile) with total cortical gray ($r=-.045$, $p=.793$) or white matter ($r=.226$, $p=.179$) but a significant association with total subcortical gray matter ($r=.488$, $p=.002$), with increasing advantage linked to larger volume. All associations were statistically nonsignificant in the JME participants ($p>.061$).

In controls, nonparametric partial (age, TIV) correlations examined associations of ADI (national percentile) with specific left and right hemisphere subcortical structures (thalamus, caudate, putamen, pallidum, hippocampus, amygdala) and cerebellum (Table 3). Significant correlations indicating increasing adjusted volumes with less disadvantage (i.e., increasing advantage) was evident for the left caudate and pallidum as well as right putamen, hippocampus, and amygdala. In contrast, comparable analyses for JME participants revealed an attenuated number and scope of such associations, limited to left cerebellar gray matter and left amygdala.

Figure 4 provides the results of cortical vertex analyses for thickness and volume, where again less disadvantage/more advantage in controls was associated with areas of increased thickness and volume in frontal and prefrontal regions, findings not evident in JME.

**TABLE 2** Cognitive factors and their components.

| General mental ability (Factor 1) | | Speed/response inhibition (Factor 2) | | Verbal learn/memory (Factor 3) | |
|---|---|---|---|---|---|
| **Ability** | **Test** | **Ability** | **Test** | **Ability** | **Test** |
| Word naming | EVT-III | Speeded word reading | D-KEFS Color-Word | Verbal list learning | WRAML-II List Learning |
| Word knowledge | WASI-II Vocabulary | Speeded color naming | D-KEFS Color-Word | Delayed verbal recall | WRAML-II List Learning |
| Visual object naming | BNT | Response inhibition | D-KEFS Color-Word | | |
| Problem solving | D-KEFS Card Sort | Number alternation | D-KEFS Trail Making | | |
| Verbal reasoning | WASI-II Similarities | Number–letter alternation | D-KEFS Trail Making | | |
| Category switching | D-KEFS Verbal Fluency | Phonemic fluency | D-KEFS Verbal Fluency | | |
| Visuoconstruction | WASI-II Block Design | | | | |
| Semantic fluency | D-KEFS Verbal Fluency | | | | |
| Nonverbal reasoning | WASI-II Matrix Reasoning | | | | |
| Visual learning | WRAML-II Total Picture Memory | | | | |

Abbreviations: BNT, Boston Naming Test[28]; D-KEFS, Delis-Kaplan Executive Function System[29]; EVT-III, Expressive Vocabulary Test, Third Edition[30]; WASI-II, Wechsler Abbreviated Scale of Intelligence, Second Edition[29]; WRAML-II, Wide Range Assessment of Memory and Learning, Second Edition.[31]

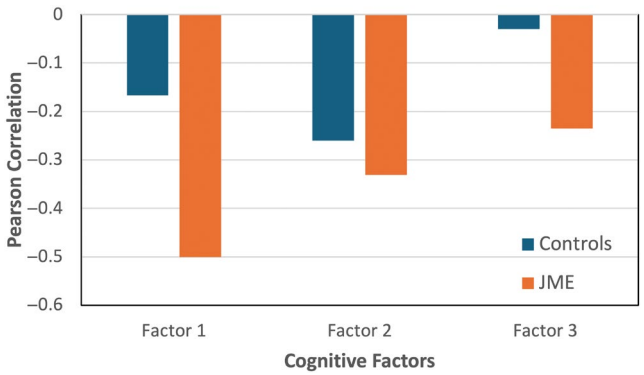


**FIGURE 1** Area Deprivation Index state quintile distribution across groups. Neighborhood disadvantage increases from quintile 1 (low) to 5 (high). JME, juvenile myoclonic epilepsy.

## 3.4 | Aim 4: ADI, and sociodemographic and epilepsy characteristics

### 3.4.1 | Marital status

There was no relationship between neighborhood deprivation (state quintiles) and marital status (single vs. two-parent home) for the controls ($\chi^2 = 5.01$, $df = 4$, $p = .287$) or JME participants ($\chi^2 = 2.538$, $df = 4$, $p = .67$).

### 3.4.2 | Parental education

For both controls ($\chi^2 = 13.47$, $df = 8$, $p = .097$) and JME participants ($\chi^2 = 13.598$, $df = 8$, $p = .093$), there was a trend for deprivation to be associated with lower maternal education. For both controls ($\chi^2 = 7.37$, $df = 8$, $p = .497$) and JME participants ($\chi^2 = 9.53$, $df = 8$, $p = .299$) there were no associations between paternal education and deprivation.

### 3.4.3 | Parental employment

For both controls ($\chi^2 = 1.9$, $df = 3$, $p = .59$) and JME participants ($\chi^2 = 3.11$, $df = 4$, $p = .539$), there were no relationships between deprivation and maternal work status or paternal work status ($\chi^2 = 4.039$, $df = 4$, $p = .401$).

### 3.4.4 | Association of parental factors with cognition in the JME and control groups

As noted previously, the control group had a higher proportion of mothers with a college education compared to the JME group. Examining the relevance of maternal education to participant cognitive performance, in the JME group increasing

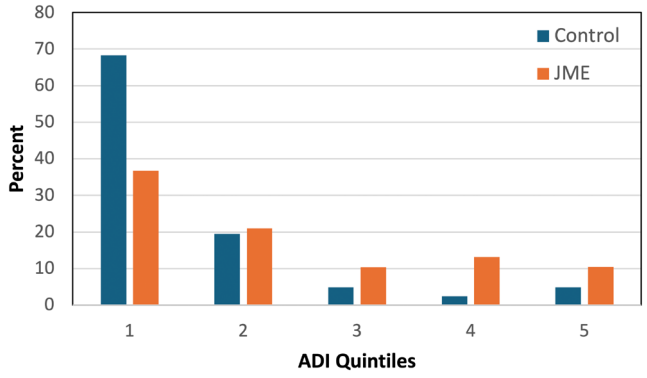


**FIGURE 2** Correlation of Area Deprivation Index (ADI) national percentile with cognitive factor scores. Greater deprivation is significantly associated with poorer performance in juvenile myoclonic epilepsy (JME) but not control participants.

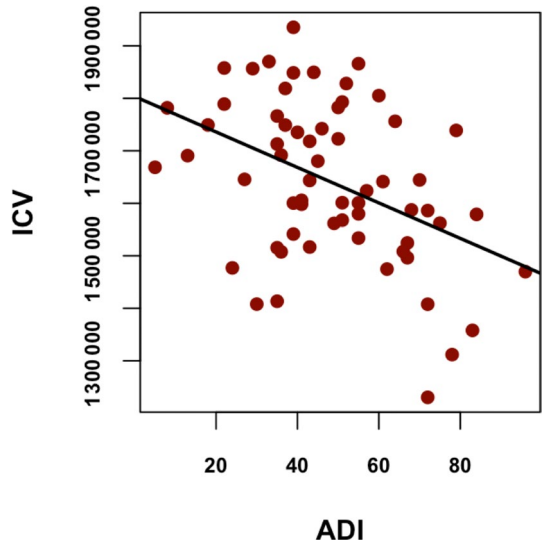


**FIGURE 3** Relationship between total intracranial volume (ICV) and Area Deprivation Index (ADI) national percentile in juvenile myoclonic epilepsy (JME). ICV decreases with increasing deprivation in the JME group.

maternal education was associated (Pearson correlation) with better participant performance on Factor 1 ($r=.257$, $p=.025$). Extending this analysis, within the JME group, paternal education was associated with better participant performance on Factor 1 (general mental ability, $r=.323$, $p=.006$) and Factor 2 (speed/executive function, $r=.244$, $p=.04$). Among controls, a significant relationship was limited to father work status with Factor 2 ($r=.550$, $p<.001$).

### 3.4.5 | Association of ADI with clinical seizure factors

There was no relationship between ADI (national percentile) and age at onset ($r=.016$, $p=.514$), duration of epilepsy ($r=.016$, $p=.897$), number of ASMs ($r=.55$, $p=.635$), or time to most recent seizure in days ($r=-.050$, $p=.665$).

**TABLE 3** Partial correlations of Area Deprivation Index (total intracranial volume, age) with subcortical structures.

| Structure | Controls | *p* | JME | *p* |
|---|---|---|---|---|
| Left caudate | $r=.331$ | .045 | | ns |
| Left pallidum | $r=.479$ | .003 | | ns |
| Right putamen | $r=.406$ | .013 | | ns |
| Right hippocampus | $r=.386$ | .018 | | ns |
| Right amygdala | $r=.462$ | .004 | | ns |
| Left cerebellum | | ns | $r=.277$ | .032 |
| Left amygdala | | ns | $r=.369$ | .004 |

Abbreviations: JME, juvenile myoclonic epilepsy; ns, not significant.

### 3.4.6 | Clinical seizure features and cognition

As we have noted previously,[27] among the JME participants there were no differences across cognitive cluster group participants in the number of antiseizure medications (ASMs; $p=.299$), age at onset ($p=.917$), duration of epilepsy ($p=.062$), or time since most recent seizure ($p=.44$). Additional analyses were undertaken aimed to identify other potential relationships between the cognitive factor scores and clinical considerations including time since most recent seizure and the presence and time since most recent GTC or myoclonic seizure. The time from neuropsychological assessment to the most recent myoclonic seizure was mean = 12 days and median = 4 days. The time from neuropsychological assessment to most recent GTC seizure was mean = 22.1 days and median = 11 days. There were no significant relationships between any of the three cognitive factor scores and time to most recent GTC (Spearman *r*'s from .19 to −.023, all *p*'s > .12) or most recent myoclonic seizure (Spearman *r*'s from .198 to .25, all *p*'s > .15). The presence/absence of a history of GTC seizures was not related to cognitive factor scores (all *p*'s > .145).

## 4 | DISCUSSION

To our knowledge, this report represents the first investigation of the relevance of social determinants of health, specifically neighborhood disadvantage as indexed by the ADI, to dimensions of cognitive and brain health in JME. The salient results are presented below as a function of our specific aims.

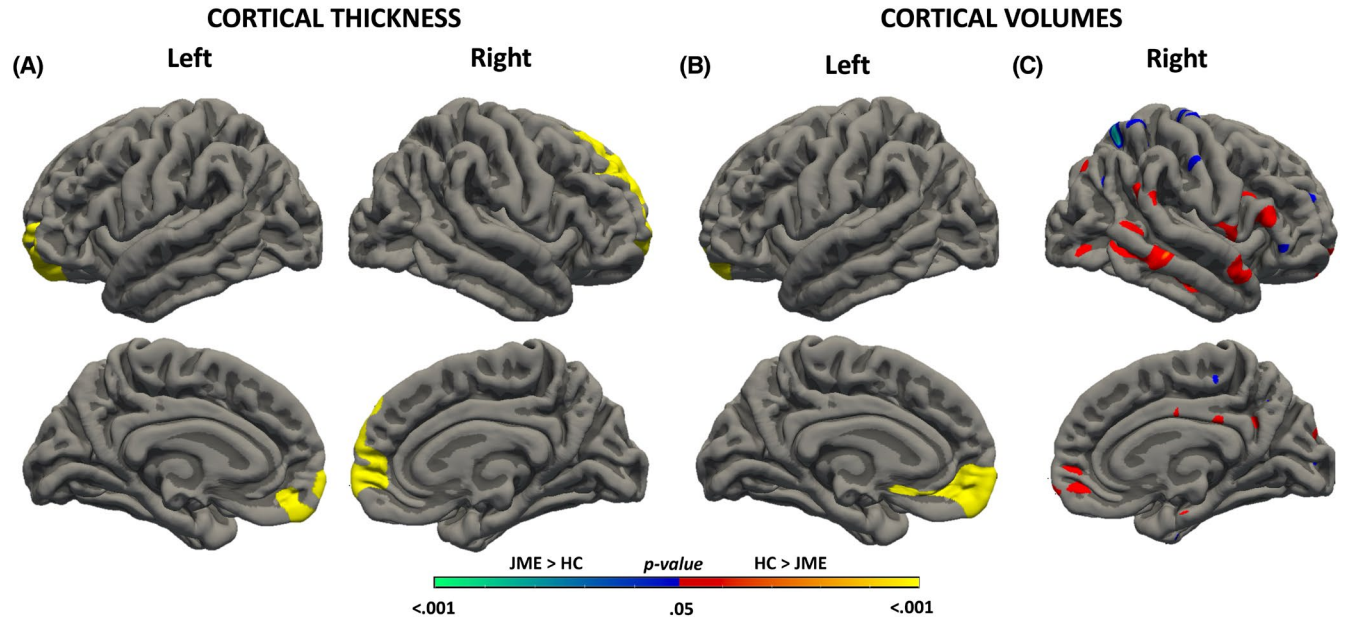


**FIGURE 4** Vertex analyses of Area Deprivation Index (ADI) with cortical thickness and volume. There was a significant interaction between healthy control (HC) and juvenile myoclonic epilepsy (JME) participants in regard to cortical thickness in bilateral frontal regions (A), where HC but not JME participants exhibited increased thickness with increasing advantage, and a comparable significant interaction for cortical volume in left lateral orbitofrontal areas (B). The right hemisphere did not present significant clusters; therefore uncorrected maps at $p < .05$ are presented (C). ADI scores were reversed to ease interpretation of the interactions (higher = less deprivation). Panels A and B were clusterwise corrected at a cluster-forming threshold at $p = .05$. Red–yellow = higher interaction in HC, blue–cyan = higher interaction in JME.

## 4.1 | Aim 1: Compare ADI in participants with JME to unrelated controls

Compared to a group of normally developing unrelated controls, participants with JME carried a higher (worse) overall neighborhood deprivation index, with underrepresentation in the least disadvantaged quintiles and overrepresentation in the more disadvantaged quintiles (Figure 1). When SES/social outcomes are examined in adults with epilepsy, one critical question is whether greater disadvantage is linked to the consequences of the many potential complications of the epilepsies (e.g., education, employment, income, marriage, health, lifestyle factors[40,41]) that may operate to adversely impact life course. In essence, the question becomes whether lower observed SES in such individuals is due to "social drift" over time versus a primary impact of disadvantage independent of such potential drift.[2,42] Here, the JME sample is young (19.7 years on average), with a short duration of epilepsy (6.5 years on average), arguing against progressive social drift that might be possible in considerably older adults experiencing decades of chronic epilepsy. Rather, there appears to be an earlier life exposure to greater disadvantage, and the question arises as to the consequences of this exposure for the longer term problematic life outcomes of JME that have been frequently[43,44] but not invariably[45] reported, including its implications for long-term cognitive and brain health.

## 4.2 | Aim 2: Examine metrics of general and specific aspects of cognition and academic performance with ADI in the JME and control groups

Examining cognition, there was a clear impact of disadvantage, as it was associated with significantly poorer performance across three specific cognitive factor scores underlying a comprehensive neuropsychological battery (general mental ability, speed/executive function, and verbal learning and memory) as well as a measure of reading ability. These effects were seen in the JME but not the control group and extend prior research in temporal lobe epilepsy, where increasing deprivation[11] has been linked to less adequate cognition and behavior, this relationship now extended to youth with idiopathic generalized epilepsy.

### 4.3 | Aim 3: Determine the relationship of ADI to both global (total intracranial volume, total cerebral and subcortical volumes) and specific (vertex-based) measures of cortical thickness, volume, and curvature

Two salient findings resulted. First, there was a significant association of reduced (adjusted) TIV with increasing deprivation in the JME participants, representing a potential SES-related adverse neurodevelopmental impact. TIV, or cranial capacity, is a known indicator of maximal brain size,[46] reaching 90% of ultimate volume by age 5 years, with slow subsequent residual development[47] into late adolescence/early adulthood. In the age-matched control and JME groups examined here, there was no relationship between chronological age and TIV, suggesting that TIV is a stable metric across the developmental epoch examined here. Regarding vulnerable regions potentially related to the TIV finding, the control and JME groups did not differ in total cerebral gray or white matter volumes, but there was a significantly smaller total subcortical gray matter volume in the JME group, arguably consistent with the known volumetric reductions across diverse subcortical structures in JME.[48,49]

Second, and relatedly, examining the association of advantage with brain structure in the control participants, there were numerous significant associations with increased volumes of diverse subcortical regions including total subcortical gray matter volume (but not total cerebral gray or white matter volumes), relationships that were largely absent or attenuated in the JME participants, suggesting that the advantages afforded to brain structure by higher SES are muted by the developmental effects of JME. But particularly notable was the relationship of advantage with regions of increased bilateral frontal/prefrontal thickness and volume, consistent with advantage/frontal lobe associations reported in the Adolescent Brain Cognitive Development study cohort,[50] raising the question of the relevance of these findings for the frequently reported dysexecutive function in JME.[19]

### 4.4 | Aim 4: Characterize the association of ADI with aspects of family structure (parental marital status, education, employment)

For both the control and JME groups, there were no significant relationships with marital status (single- vs. two-parent homes), paternal education (college educated), or parental employment (none, part, full time). For both groups, greater maternal educational attainment was seen in families in low deprivation (i.e., advantaged) areas. But also relevant is the relationship of paternal education with cognition. In JME participants, higher general mental ability was associated with higher maternal education, whereas better general mental ability and speed/response inhibition (executive function) was associated with higher father education. These findings are conceptually in line with prior research demonstrating the beneficial effects of family integrity on the cognitive status of youth with epilepsy.[32]

### 4.5 | Limitations and future directions

A greater range of factors reflective of the social determinants of health would be helpful in the future to link outcomes of interest to more specific SDOH factors. That said, in this investigation we used a major indicator of SDOH, and the relationships found should encourage future research in this area. The controls were a strength of this investigation, but their distribution of disadvantage was skewed to the positive (less disadvantage), which may have contributed to the lack of associations with deprivation in this group. The association of the ADI with the JME group was of most interest, but the distribution of the ADI in the controls allowed investigation of the ways in which the JME group did not benefit from socioeconomic advantage, representing novel findings.

As we reported previously,[27] among the JME participants there were no differences across cognitive cluster group participants in diverse clinical characteristics including the number of ASMs, age at onset, duration of epilepsy, or time since most recent seizure in general, or the presence and time since most recent GTC or myoclonic seizure in particular. But in this context it should be remembered that this is a young cohort by design, and it is certainly possible that clinical seizure characteristics may become more relevant and exert more harmful influences on cognition with longer durations of disorder. It is our intent to follow this cohort prospectively and track diverse clinical seizure features and their cognitive impact.

## 5 | CONCLUSIONS

The totality of findings suggests two underlying effects mediating relationships between SES as reflected by the ADI and cognitive and brain health in JME. The first is an association of greater disadvantage linked with poorer cognition in JME. These SDOH effects are not seen in the controls, which is arguably a more advantaged group compared to the JME group. Findings such as these are consistent with existing ADI research in adults and youth

with other epilepsy syndromes.[11,25] The second and more unexpected effect involves the relationships between increasing advantage and metrics of brain health including increasing volumes of subcortical structures and areas of cortical thickness and volume in frontal regions in the control participants, relationships that are absent in the JME participants. The inability to benefit from relative socioeconomic advantage may represent an adverse influence of epilepsy on brain structure that compromises the ability to benefit from advantage. Carrying this logic further, it could be hypothesized that in the case of JME the best-case scenario may be to minimize exposure to the influences of disadvantage, and here the most important operative factors that are embedded in the ADI need to be investigated. But more generally, the role of socioeconomic disadvantage needs to be considered in the cognitive and brain status of youth with this genetic generalized epilepsy.

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## CONFLICT OF INTEREST STATEMENT

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

## DATA AVAILABILITY STATEMENT

Datasets analyzed in this study are not publicly available, but further information about the datasets is available from the corresponding author on reasonable request.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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