

## GRAY MATTERS

# Invitation to participate in a prospective case–control study of sudden unexpected death in epilepsy

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The EpiNet study group is undertaking a case–control study of sudden unexpected death in epilepsy (SUDEP) and is inviting physicians looking after people with epilepsy to participate.

The study is being performed prospectively. We hope to identify 200 cases of SUDEP. Because SUDEP is not very common, we will need to get multiple centers involved. Relatives of cases will be interviewed, and medical records will be reviewed to learn as much as possible about the circumstances of death, the individual's epilepsy, its treatment, and lifestyle issues. For each case, we will also identify three age- and sex-matched controls from the same center, who will also be interviewed. Finally, we will interview one proxy control, who will be a relative of one of the control subjects with epilepsy.

SUDEP cases are going to be collected prospectively. At the outset, each center will need to identify a cohort from which cases and controls will be identified. The

nature of the cohort may vary from center to center, but it needs to be defined at the outset, and cases and controls must come from this cohort. New people with epilepsy can join the cohort during the course of the study, and only people who are alive at the time the study starts can be included.

The study is being funded by the Health Research Council in New Zealand.

If you would like to participate in the study, or find out more about it, please contact us at [epinetadmin@adhb.govt.nz](mailto:epinetadmin@adhb.govt.nz).

## CONFLICT OF INTEREST

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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**LETTER****The unclear interhemispheric modulation of mood: A response to Doherty et al. on predicting mood decline following temporal lobe surgery in adults**

To the Editors:

The preoperative and postoperative lateralization of mood in focal epilepsy has been controversial. Doherty et al.<sup>1</sup> added a valuable contribution with the statistical modeling of postoperative depression in more than 500 patients who underwent temporal lobe surgery. They found that the risk of postoperative depression measured by the Beck Depression Inventory (BDI)—second edition was greater in those who underwent surgery of the dominant side.

Doherty et al. failed to include studies, however, that evaluated longitudinal changes. Devinsky et al.<sup>2</sup> acquired a prospective cohort ( $N = 358$ ) studied before and after resective surgery; side had no effect on the presence of depression pre- or postoperatively measured with the BDI (first edition). These findings were supported by an earlier retrospective study that used the Diagnostic and Statistical Manual of Mental Disorders—third edition revised.<sup>3</sup>

A study that tracked mood with the same instrument, in contrast, found that right-sided resections were at higher risk for major postoperative psychiatric complications.<sup>4</sup> Our own group evaluated a cohort ( $N = 108$ ) of patients with mesial temporal lobe epilepsy who underwent anterior temporal lobectomy.<sup>5</sup> We created a summary score of psychiatric consequences of depression (self-reported depression, physician intervention for depression, or attempted or completed suicide) obtained during preoperative screening and assessed 1 year after surgery. Worse preoperative symptoms predicted severity of postoperative symptoms. Right-sided epilepsy surgery patients experienced more postsurgical psychiatric morbidity or mortality than did left-sided patients, accounting for verbal intelligence quotient in the statistical model.

We conclude that the interhemispheric modulation of mood remains unclear. One implication is that self-reported inventories such as the BDI may differ from behavioral markers (psychiatric treatment, suicide attempts or completion) of psychiatric morbidity or mortality in patients with epilepsy. We recommend that preoperative counseling and

postoperative monitoring remain high priorities of an epilepsy surgery program regardless of epilepsy syndrome or lateralization.

**CONFLICT OF INTEREST**

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

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## LETTER

## Response: Predicting mood decline following temporal lobe epilepsy surgery in adults

We thank Drs. Quigg, Broshek, and Bertram for raising an important issue in prediction modeling that we elaborate on here—the interpretation of individual predictor variables within a multivariable model.

Statistical modeling can be used for explanatory or predictive purposes; although the two uses are often conflated, they have very different goals.<sup>1–3</sup> Explanatory modeling aims to understand the relationship between individual predictors and an outcome variable. Here, a hypothesis is formed regarding the relationship, which is then tested via statistical inference, allowing for a clear conclusion to be reached. For example, Quigg et al. hypothesized that the incidence of pre and post-surgical depression in epilepsy may vary by seizure laterality.<sup>4</sup> To test this hypothesis, they developed explanatory regression models with side of epilepsy surgery and preoperative depression scores as the predictors and postoperative depression score as the outcome of interest. Based on their results, they concluded that right-sided resections were marginally associated with worse postoperative depression scores.

Conversely, the aim of predictive modeling is to identify a model that will accurately predict new observations, and not to study the correlations of individual variables with the outcome. In fact, because of complex relationships across predictor variables, it is often impossible to understand direct relationships between individual predictor variables and the outcome. Variables that are not significantly associated with the outcome in explanatory analyses may even be included in a predictive model when they enhance model performance.<sup>1</sup> In Doherty et al., our goal is to create a model that predicts an individual patient's risk of mood decline following temporal lobe epilepsy surgery, integrating multiple easily accessible patient-specific risk factors.<sup>5</sup> We are not studying any specific potential predictor.

The performance metrics differ for explanatory and predictive models as well. Explanatory models are evaluated with metrics focusing on explained variation (eg,  $R^2$ , root mean square error or Akaike information criterion). Predictive models are evaluated based on their discrimination (measured by the concordance index) and calibration capabilities.

We agree with Drs. Quigg, Broshek, and Bertram that the relationship between surgical side and postoperative

depression is controversial. As they mentioned, smaller studies found trends toward more psychiatric complications among patients who underwent right-sided resections,<sup>4,6</sup> whereas a large prospective study found no relationship between seizure laterality and postoperative depression.<sup>7</sup> All these studies examined surgery side (right vs left) without taking language dominance into account (dominant vs non-dominant resection). In our study, both surgical side and dominance of the resection were included as candidate predictor variables during model development. Surgical side was not significantly associated with postoperative mood decline in univariate analyses, nor was it selected for inclusion in our final model. Dominance of resection was selected for inclusion because it improved model performance. Dominant-sided resections are known to impart a higher risk for naming and verbal memory decline, potentially furthering postoperative depression.<sup>8</sup> Indeed, in our study, mood decline mirrored cognitive declines.<sup>5</sup>

In essence, our goal is to create an innovative tool that serves the clinical purpose of counseling patients, rather than to add to the literature of hypothesized individual drivers of outcome.

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## LETTER

## Echocardiography in epilepsy: A tool to be explored

To the Editors:

We read with great interest the article of Schreiber et al.,<sup>1</sup> “Children with refractory epilepsy demonstrate alterations in myocardial strain” in the October issue of *Epilepsia*. The authors found decreased left ventricle (LV) strain despite similar ejection fraction in children with refractory epilepsy compared to controls.

Echocardiography has become an important tool in cardiology and in general medical evaluation. It has the ability to analyze heart structure and function, including markers of sudden cardiac and all-cause death.<sup>2,3</sup> Myocardial strain is an additional echocardiographic tool. *Strain* relates to deformation produced by a force, and myocardial strain is the “stretching” of the heart myocytes during contraction, which can occur in longitudinal, radial, and circumferential directions.<sup>4</sup> It has additional prognostic value over left ventricle ejection fraction in many situations, such as heart failure with preserved or reduced ejection fraction, valvular heart disease, and even in asymptomatic individuals.<sup>4</sup>

Patients with epilepsy (PWE) represent, as a group, a high-risk population for sudden death. Sudden unexpected death in epilepsy is considered the most important cause of death in PWE, and their risk for sudden death is 24–27 times greater than individuals without epilepsy.<sup>5,6</sup> Therefore, the search for biomarkers of sudden death in PWE is of utmost importance.

We believe that the work of Schreiber et al.<sup>1</sup> is of high importance. However, some issues should be analyzed with caution. They used only apical four-chamber view to measure longitudinal strain (LS) and not apical two-, three-, and four-chamber view, as would be more appropriate.<sup>4,7</sup> Only a small difference (0.9%) in LS was found, still within the normal range, with unknown clinical relevance (at this point), between PWE and controls. LS is the most studied deformation index and has greater evidence of risk stratification.<sup>4</sup>

They also found a reduced mitral E wave and tissue Doppler E', but this alone cannot establish an impaired diastolic function as suggested. The E/E' relation would be more appropriate for this, because it reflects left ventricle filling pressures.<sup>8</sup> E/E' was 6.1 and 5.6 in cases and controls, respectively, which was similar to previous work in adult patients with temporal lobe epilepsy (6.2 × 5.4).<sup>2</sup> Left atrial volume, referred to as the “barometer of the heart,” because it reflects

chronic exposure to LV filling pressure, and pulmonary artery systolic pressure are also important in diastolic function analyses.<sup>2,8</sup>

Mitral E wave, tissue Doppler E' wave, and even strain are influenced by preload and afterload, which were not reported. Wheelchair-bound patients comprised 31.7% of cases, which could have some influence on hemodynamics.<sup>8</sup> LV pressure-volume curve evaluation is a form of correcting for hemodynamic state. Using this tool, we found higher left ventricle stiffness in PWE, and this was related to autonomic dysfunction, carbamazepine treatment, and polytherapy with antiseizure medications.<sup>9</sup> However, the other end of the curve showed similar left ventricular end-systolic elastance, arterial effective elastance, and ventricular–arterial coupling between PWE and controls.<sup>10</sup>

We congratulate the authors on their work and believe that, although not suggesting changes (yet) in clinical practice as the authors stated, we will be hearing more about echocardiography in PWE.

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## KEYWORDS

biomarker, cardiac, refractory epilepsy, strain

## CONFLICT OF INTEREST

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

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## LETTER

## Response: Let us not miss the forest for the trees. Reply to "Echocardiography in epilepsy: A tool to be explored"

To the Editors:

We appreciate the commentary by Fialho and colleagues and recognize their earlier work examining cardiac physiologic changes in patients with epilepsy.<sup>1,2</sup> They state that our results<sup>3</sup> should be viewed “with caution,” and we could not agree more. We acknowledged the limitations they mentioned in our article, including a significant proportion of nonambulatory subjects, changes that were statistically significantly different but within the accepted normal range (including deformation parameters), and the use of contemporaneous but not prospectively enrolled controls.

Our use of a single apical four-chamber view for longitudinal strain rather than a two- and three-chamber view as well was necessitated by our control population. However, this does not mean that the approach lacks merit, as there is ample literature that uses a single apical view for assessment of longitudinal strain. Furthermore, it has been suggested that a single apical strain assessment has outstanding correlation with a multiview approach in terms of both measurement concordance and prognostic value.<sup>4,5</sup> Lastly, we should not forget the pediatric axiom that “children are not little adults,” and the regional wall motion abnormalities that may be relevant to older patients are unlikely to be a factor in the evaluation of young children without coronary artery disease. Similarly, it should be noted that the works cited by Fialho et al. are based on patients 25 years older than our cohort, with nearly three times the length of epilepsy, making a comparison challenging.

With regard to diastolic parameters, two-chamber views are not universally obtained in our echocardiography laboratory, nor are they standard in pediatric echocardiograms,<sup>6</sup> precluding the use of left atrial volume as a diastolic variable. This is unfortunate, as the writers’ own work shows the most significant alteration in this particular parameter.<sup>7</sup> The writers are correct that decreased mitral inflow E-wave velocity and tissue Doppler E’ velocities alone cannot diagnose diastolic dysfunction, but neither can the suggested E/E’ ratio in isolation. We are gratified that their calculation of the E/E’ ratio from our data demonstrates remarkable concordance with their work, which also falls into the category of statistically significant but within the accepted normal range.

Recognizing that the audience for this correspondence is almost exclusively not cardiologists, this all may seem to be deep in the weeds. We concur. Our goal is not to promote one esoteric echocardiographic parameter over another, nor is it to propose multiple parameters that together will be a Rosetta Stone for perfectly identifying at-risk patients. Rather, our study adds to the small but growing body of literature recognizing mechanical cardiac alterations that exist in patients with epilepsy. Importantly, it determines that these alterations are present in childhood, suggesting that age and length of disease are not critical factors in these mechanical findings. Although it is important to be measured in our language—terms like “abnormalities” and “dysfunction” perhaps overstate the differences observed—these findings raise important questions. Autonomic dysfunction, sympathetic stimulation, myocardial fibrosis, myocyte ion handling, or other as-yet-unsuspected mechanisms may all play a role: the forest to the echocardiographic trees.

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

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## LETTER

# Usefulness of the postkainate spontaneous recurrent seizure model for screening for antiseizure and neuroprotective effects

To the Editors:

We read with interest the article by Thomson et al.<sup>1</sup> that describes the use of the model of post-kainic acid (kainate [KA]) spontaneous recurrent seizures (SRS) in screening for antiseizure medication (ASM) effects. We believe that the use of this model adds to the previously used methods to screen for ASM effects. We have used this model previously and are writing this letter to suggest how our prior research could help improve the usefulness of this model further.<sup>2-4</sup>

We have shown, in a series of articles, that therapy of post-KA SRS in prepubescent rats resulted in the following.<sup>2-4</sup> (1) Phenobarbital, valproate, and gabapentin showed antiseizure effects when given after KA, from prepubescence into adulthood. This is similar to what Thomson et al. found in adult rats with respect to phenobarbital and gabapentin but differs with respect to valproate. In their study, valproate was not found to be effective. The difference could be related to any one or combination of the factors that differed between our study and that of Thomson et al. These include differences in the dosing of KA, differences in the dosing of valproate, and the different developmental stages studied. (2) We also found that testing the above rats after tapering each of the three medications showed that both gabapentin and valproate demonstrated strong evidence of behavioral and histological neuroprotective effects, whereas phenobarbital-treated rats showed greater disturbances in memory, learning, and activity level, even more than control animals that received KA and no treatment for SRS.

Taken together, the observations of our group and of Thomson et al. show that the post-KA SRS model can be used not only for screening for ASM effects in the adult but also in the developing brain. It can also be used to study or screen for potential neuroprotective or neurotoxic effects, particularly in the developing brain. All of this also highlights the importance of always taking into consideration different age groups and dosing regimens, and of avoiding generalizations based on a single age group or single dosing regimen.

## KEYWORDS

antiepileptogenic, antiseizure, developing brain, kainic acid, neuroprotection

## CONFLICT OF INTEREST

Neither of the authors has any conflict of interest to disclose.

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**LETTER****Response: Usefulness of the post-kainate spontaneous recurrent seizure model for screening for antiseizure and for neuroprotective effects**

To the Editors,

We are grateful for the opportunity to respond to the kind letter written by Drs. Mikati and Holmes regarding our recently published manuscript by Thomson et al, 2020.<sup>1</sup> Their letter expertly highlights some very important considerations regarding the interpretation of rodent data across the age span, across laboratories, and across dosing paradigms. Although we did not evaluate either neuropathology or behavioral outcomes other than seizures, their earlier work elegantly demonstrates that those types of studies can illuminate the potential risks that subchronic dosing of antiseizure drugs have in the developing brain.<sup>2-4</sup> Furthermore, the differences obtained between laboratories with valproate inspire future research in disease progression as well as adult vs juvenile epilepsy. Finally, we enthusiastically agree with Drs. Mikati and Holmes that the post-kainic acid spontaneously seizing rat is a very useful and robust model for screening novel antiseizure drugs across the lifespan.

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**KEYWORDS**

brain, kainic acid, pharmacology, spontaneous seizures, temporal lobe epilepsy

**CONFLICT OF INTEREST**

Neither one of the authors has any conflicts of interest. 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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**ANNOUNCEMENT****Epilepsia – May 2021 – Announcements****ILAE CONGRESSES****10–13 June 2021****13th Asian and Oceanian Epilepsy Congress (AOEC)**

Virtual Congress

<https://www.epilepsycongress.org/aoec/>**28 August–1 September 2021****34th International Epilepsy Congress**

Virtual Congress

<https://www.epilepsycongress.org/iec/>**9–12 September 2021****11th Summer School for Neuropathology and Epilepsy Surgery (INES 2020)**

University Hospital, Erlangen, Germany

<https://www.ilae.org/congresses/11th-international-summer-school-for-neuropathology-and-epilepsy-surgery-ines-2021>**9–13 July 2022****14th European Congress on Epileptology (ECE)**

Geneva Switzerland

<http://www.epilepsycongress.org/ece/>**ILAE WEBINARS****ILAE-EMR Webinars in French and English**

Monthly webinars covering various subjects of epilepsy, ranging from basic to advanced, from neonatal epilepsy to issues in the elderly, chosen according to the needs of and suggestions from members of chapters in the Eastern Mediterranean region. See all future and past webinars – <https://www.ilae.org/regions-and-countries/regions/ilae-eastern-mediterranean/events>

**YES Webinars**

The ILAE-Young Epilepsy Section Epilepsy Webinars provide educational content and hot topics in epilepsy care and research, presented by international experts. Join the live broadcast or browse the database of previous talks.

<https://www.ilae.org/about-ilae/topical-commissions/yes/young-epilepsy-section-yes>

**ILAE-Europe Webinars**

Key experts cover some of the most relevant topics in clinical practice based on the ILAE Curriculum. The level will indicate the level of competence of each individual presentation.

An interactive platform combined with live moderation will allow active participation and give you the opportunity to get an answer to your questions directly from the experts! See all future and past webinars - <https://www.ilae.org/regions-and-countries/regions/ilae-eastern-mediterranean/events>

**OTHER CONGRESSES****13–16 May 2021****International Training Course on Neuroimaging of Epilepsy**

McConnell Brain Imaging Centre, Montreal, Canada

<https://www.mcgill.ca/neuro/events/international-training-course-neuroimaging-epilepsy>**20–22 May 2021****13th International Epilepsy Colloquium**

Digital event

<http://www.epilepsy-colloquium2021.com/>**17–20 June 2021****10th Migrating Course on Epilepsy**

Lviv, Ukraine

<http://ulae.org.ua/index.php/en/congresses/future-events>**19 August 2021****Annual meeting-Basler Epilepsietag und Jahrestagung Schweizerische Epilepsie-Liga 2021.**

Basel, Switzerland

<https://www.epi.ch/veranstaltung/basler-epilepsietag-und-jahrestagung/>

**13–15 September 2021**

**Annual Meeting on Imaging in Epilepsy, Epilepsy Surgery, Epilepsy Research and Cognitive Neurosciences (AMIE 2021)**

Bochum, Germany

<https://www.ilae.org/congresses/annual-meeting-on-imaging-in-epilepsy-epilepsy-surgery-epilepsy-research-and-cognitive-neurosciences-amie-2021>

**15–17 September 2021**

**Summer School on Imaging in Epilepsy, Epilepsy Surgery, Epilepsy Research, and Cognitive Neurosciences (SuSIE 2021)**

Bochum, Germany

<https://www.ilae.org/congresses/summer-school-on-imaging-in-epilepsy-epilepsy-surgery-epilepsy-research-and-cognitive-neurosciences-susie-2021>

**23–24 September 2021**

**ILAE British Branch Virtual Annual Scientific Conference**

<https://www.ilaebritishconference.org.uk/>

**27 September–1 October 2021**

**11th EPODES - Epilepsy Surgery – Basic**

Brno, Czech Republic

<http://www.ta-service.cz/epodes2021>

**10–15 October 2021**

**9th Eilat International Educational Course: Pharmacological Treatment of Epilepsy**

Jerusalem, Israel

<https://www.eilatedu2021.com/>

**28–29 October 2021**

**13th World Stroke Congress**

Virtual Congress

<https://worldstrokecongress.org/>

**28–30 October 2021**

**3rd International Congress on Mobile Devices and Seizure Detection in Epilepsy**

Copenhagen, Denmark

<https://na.eventscloud.com/mch2021>

**29–30 October 2020**

**7th UAE Epilepsy Congress**

Dubai, UAE

<http://congress2020.elae.ae/>

**2022**

**8–10 April 2022**

**1er Curso Latinoamericano Teórico práctico de Electroencefalografía Clínica**

Santiago, Chile

[https://www.clinicaepilepsia.cl/curso\\_electroencefalografia\\_clinica](https://www.clinicaepilepsia.cl/curso_electroencefalografia_clinica)

**28 April–2 May 2022**

**EPNS: 14th European Paediatric Neurology Society Congress: Precision in Child Neurology**

Glasgow, UK

‘hybrid’ event combining both a physical meeting in Glasgow with virtual attendance also possible

<https://epns-congress.com/>

**27–28 May 2022**

**Neurophysiology, neuropsychology, and epilepsy in 2022: Hills we have climbed and hills ahead**

Honoring Professor Jean Gotman and Marilyn Jones-Gotman Montreal Neurological Institute-Hospital, Montrealin Canada

<https://www.ilae.org/congresses/neurophysiology-neuropsychology-and-epilepsy-in-2022-hills-we-have-climbed-and-hills-ahead>

**16–23 July 2022**

**5th Dianalund Summer School on EEG and Epilepsy**

Dianalund, Denmark

<https://www.ilae.org/congresses/5th-dianalund-summer-school-on-eeg-and-epilepsy>

**18–29 July 2022**

**2022 Advanced San Servolo Epilepsy Course Bridging Basic with Clinical Epileptology - 7: Accelerating Translation in Epilepsy Research**

San Servolo (Venice), Italy

<https://www.ilae.org/congresses/2022-advanced-san-servolo-epilepsy-course>

**2023**

**20–24 June 2023**

**15th European Paediatric Neurology Society Congress (EPNS) From genome and connectome to cure**

Prague, Czech Republic

<https://www.epns.info/epns-congress-2023/>