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Epilepsia®

LETTER

Bridging the gap between analytical methods and their clinical interpretation

Our team took great interest in the recent paper entitled, "Temporal epilepsy in children: A connectomic analysis in magnetoencephalography" by Martire et al.[1] In this study, the authors analyzed the data of 121 children with temporal (TL) or temporal plus epilepsy (TL+) using resting-state connectomes derived from their magnetoencephalograms. Using this connectivity profile, they found that patients with TL+ epilepsy could be distinguished from those with TL epilepsy alone. This is a relevant finding because it can be difficult to distinguish TL+ epilepsy in clinical practice and the presence of epileptogenic networks extending beyond the temporal lobe can be a cause of surgical failure in patients who undergo temporal resection.[2]

The study was backed by extensive analysis using the partial least squares method (PLS). Although the methodology used for PLS was fairly well explained, the practical interpretation of the same was difficult to fathom for clinicians who are typically not trained in methods of advanced multivariate analysis. Therefore, this posed a challenge to the comprehension as well as critical analysis of the methodology used in this study. As an example, the authors found that a single latent variable explained 66% of the variance in the data and identified significant contributions from the extent of epilepsy (TL vs TL+). However, we found it difficult to gauge the clinical interpretation of this variable and its relevance with respect to the results.

On a similar note, we greatly looked forward to findings and discussion related to how extratemporal connectivity differed between TL and TL+ epilepsy. Such investigations can help us understand how resting-state networks differ fundamentally between TL and TL+ epilepsy and explore the relation of these differences with clinical outcomes. Although the authors did present the mean brain connectivity (limited to only the top 1% of the connections) in TL and TL+ epilepsy associated with the latent variable mentioned above (Figure 4), the interpretation of these patterns was not clearly discernible to the reader, and it was not covered comprehensively in the discussion section.

Another relevant observation was the absence of measures of diagnostic performance such as sensitivity, specificity, predictive values, and so on. Even though the study concluded that resting-state connectomic analysis can distinguish between TL and TL+ epilepsy, the reader was left wondering about the margin of error and the accuracy of this method.

Finally, with the advent of this century, studies featuring "big data," whole brain connectivity and multivariate analysis have become common in all branches of neurology including epilepsy,[3–8] and their applications are only expected to increase in near future. The purpose of this letter therefore is not only to critique this exemplary work undertaken by Martire et al, but also to generate a discussion regarding the up and coming use of advanced methods of analysis such as PLS, connectomics, and so on, and the best way to equip the clinicians with these new tools.

To conclude, bridging the gap between the clinician and the analyst is going to be a relevant challenge for modern neurology and the study in question beautifully brings this to notice.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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 these guidelines.

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Epilepsia®

LETTER

Multidimensional analytical methods and their clinical interpretation

To the Editors:

We appreciate timely comment of Kaur and colleagues on our work[1] and are encouraged that they see a bright future for such approaches in clinical research. We present a method that reveals hidden (latent) variables missed through conventional approaches. Such advanced tools can facilitate greater understanding of neural networks in epilepsy and other disorders.

Fundamentally, partial least squares (PLS) is a multivariate tool that has several advantages in finding meaning in imaging data. Foremost, this method addresses multicollinearity in data.[2] In epilepsy, multiple covariates are often collinear, including duration of epilepsy, severity of illness, and extent of disease. Through mathematical rotations of the data, PLS allows hidden associations to be identified between combinations of neuroimaging biomarkers and sets of clinical findings.

Although the emerging PLS method may be more foreign to the clinician than traditional generalized linear models (GLMs), it does offer major advantages, namely, it models associations both within and between clinical and neuroimaging measurements simultaneously. The GLM can be applied to neuroimaging measurements to show independent associations of a voxel or connection with clinical variables or vice versa. PLS, specifically behavioral PLS, discovers neuroimaging and clinical variables that covary together both within and between modality—the latent (hidden) variable.[3]

As such, it is not surprising that a single latent variable explained much of the variance in the data. Multiple patient covariates contribute to this latent variable. To the clinician, this offers a pragmatic and real-world understanding of the relation of neural networks to patient phenotypes. This latent variable shows a set of characteristics that tend to appear together and were related to the consistent cluster of neuroimaging findings.[3] We found that temporal-plus epilepsy (TL+) in children was more likely to result from developmental causes and was associated with a longer duration of epilepsy. This patient phenotype is associated with more widespread neurophysiological connectivity in the magnetoencephalographic resting state.

PLS, therefore, models patient phenotypes in a multivariate and data-driven manner. This allows our analysis to move beyond one-dimensional views of patient populations (ie, clinical group vs control group) and presents a detailed real-world view of the data albeit at the cost of increased complexity. In our report, we show that the latent variable we discovered with PLS differs between TL+ and TL- groups. Although the diagnostic yield (ie, margin of error) is represented by the brain scores (presented in Figure 3 of Martire et al[1]), we agree that had we sought to build a classifier or diagnostic test based on data modeling, a full evaluation of model sensitivity and specificity on a withheld validation dataset would be useful.

We thank our colleagues for their excellent comments and wholeheartedly agree that future research should aim to close the gap between analytical methods and their clinical interpretation. Greater emphasis on complex analytics in the neurology literature, increasing collaborations between scientists and clinicians, and cross-training of clinician-scientists will certainly contribute to this goal.

CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

Both authors have been substantially involved in the study and preparation of the manuscript. No undisclosed group or persons have had a primary role in the study or manuscript preparation. Both coauthors have seen and approved the final version of the paper and accept responsibility for its content.

ETHICAL PUBLICATION STATEMENT

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Epilepsia®

LETTER

The challenges of continued antiseizure medicine trials

To the Editors:

We read with interest the letter from Blond et al in a recent issue of *Epilepsia* discussing seizure freedom with antiseizure medications (ASMs).[1] The authors sought to clarify misperceptions of a 2018 article by Chen et al.[2] Blond et al accurately state that a third ASM trial resulted in seizure freedom for 23.6% and that even a sixth ASM trial led to seizure freedom in 14% instead of the inaccurate assertion that individuals have only a 5% chance of seizure freedom after a second ASM.[2] However, as Blond et al note in their own letter, seizure *freedom* is not entirely accurate, as the 2018 study definition indicated seizure *control* after lack of seizures for the previous 12 months or longer. The authors conclude that continued ASM trials remain of value, particularly for less-than-ideal surgical candidates.[1]

Additional context helps define the challenges in suggesting additional ASM trials to drug-resistant epilepsy (DRE) patients as a meaningful path to long-term seizure freedom. When examining perhaps a natural course of DRE, Brodie et al found 16% have a "relapsing/remitting" course, a course accurately not viewed as seizure freedom.[3] Callaghan et al demonstrated that remissions of at least 1 year occur in 5% of DRE patients annually, although the majority relapse.[4] Furthermore, Wang et al in 2013 found that DRE patients without ASM change had a 1.66 times *higher* likelihood of entering remission compared to DRE patients with ASM change after covariate adjustment.[5] In short, these three studies independently suggest that remissions in DRE patients occur regardless of ASM changes. In contrast, long-term epilepsy surgery outcomes prove far more robust, with 10-year seizure-free rates ranging between 33% and 47%[6,7] in addition to a sharp decline in mortality risk following successful epilepsy surgery.[8]

When examining ASMs themselves, the Chen 2018 paper found no difference in seizure-free rates during three different time periods of the 30-year follow-up (and thus of various ASM availability), suggesting that increased ASM availability unfortunately has not resulted in greater seizure-free rates.[2] Further analysis of that data found the risk of intolerable adverse events (AEs) from ASM increased with each subsequent ASM trial, particularly if an ASM had been previously changed due to an AE.[9]

In sum, the accurate clarification that 5% of people as a whole become seizure-free after a failed second ASM is certainly important. The misperception that an individual has a <5% seizure-free chance after that second ASM should not be perpetuated. However, using that clarification as a robust rationale for continued ASM trials is challenging when acknowledging the relapsing/remitting nature of DRE, an unchanged seizure-free rate despite increased ASM development, and the risk of new potential AEs with further ASM trials. Further ASM trials in DRE patients, although well intentioned, can likely only lead to surgical delay.[10]

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.

CONFLICT OF INTEREST

P.X.L. has received consultation fees from Monteris Medical. C.M.U. has no conflict of interest to disclose.

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Epilepsia – November 2020 – Announcements

ILAE CONGRESSES

11th EPODES - Epilepsy Surgery – Basic

25–29 January 2021
Brno, Czech Republic
http://www.ta-service.cz/epodes2021

XI Congreso Latinamericano de Epilepsia

27 February–1 March 20201
Modalidad Presencial a Distancia | Virtual congress
https://www.epilepsycongress.org/lace/

International Training Course on Neuroimaging of Epilepsy

13–16 May 2021
McConnell Brain Imaging Centre, Montreal, Canada
https://www.mcgill.ca/neuro/events/international-training-course-neuroimaging-epilepsy

13th Asian and Oceanian Epilepsy Congress (AOEC)

10–13 June 2021
Fukuoka, Japan
https://www.epilepsycongress.org/aoec/

34th International Epilepsy Congress

28 August–1 September 2021
Paris, France
https://www.epilepsycongress.org/iec/

11th Summer School for Neuropathology and Epilepsy Surgery (INES 2020)

9–12 September 2021
Erlangen, Germany
https://www.ilae.org/congresses/11th-international-summer-school-for-neuropathology-and-epilepsy-surgery-ines-2021

14th European Congress on Epileptology (ECE)

9–13 July 2022
Geneva Switzerland
http://www.epilepsycongress.org/ece/

OTHER CONGRESSES

http://cony.comtecmed.com/

Epilepsy Society of Australia, 34th Annual Scientific Meeting

4–6 November 2020
Hobart, Australia
https://www.ivvy.com.au/event/ESA20/

Irish Epilepsy League Annual Meeting

6 November 2020
Dublin, Ireland
https://www.ilae.org/congresses/irish-epilepsy-league-annual-meeting

Update on Febrile Seizures (short course) Autoformación virtuales al incio y finalizar el curso

9–15 November 2020
Convocatoria and other information: https://www.ilae.org/congresses/update-on-febrile-seizures-short-course-capsule

64th Annual meeting of DGKN 64. Jahrestagung der Deutschen Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung

10–14 November 2020
7th International Conference on Non-invasive Brain Stimulation 4th European Conference of Brain Stimulation in Psychiatry
Virtual Congress: DGKN and NIBS 2020 go digital in November!
https://www.ilae.org/congresses/64th-annual-meeting-of-dgkn

4th Dianalund International Conference on Epilepsy:

12–13 November 2020
Virtual Congress https://www.ilae.org/congresses/4th-dianalund-international-conference-on-epilepsy

First Seizure: diagnosis and management (Short Course) Cápsula virtual sobre Manejo de Primera Crisis para América Latina 2020

16–22 November 2020
Autoformación virtuales al incio y finalizar el curso
https://www.ilae.org/congresses/first-seizure-diagnosis-and-management-short-course

AES 2020: A new virtual event from the American Epilepsy Society

4–8 December 2020
Virtual congress
https://www.ilae.org/congresses/aes-2020-annual-meeting

2021

Fetal and Neonatal Neurology Congress

3–5 March 2021
Paris, France
https://www.mcascientificevents.eu/brain/

65th Annual meeting: DGKN 2021. German Society for Clinical Neurophysiology and Functional Imaging

10–12 March 2021
Frankfurt, Germany
https://www.dgkn-kongress.de/index.php?id=618

1er Curso Latinoamericano Teórico práctico de Electrocencefalografía Clínica

8–10 April 2021
Santiago, Chile
https://www.ilae.org/congresses/1er-curso-latinoamericano-te-rico-pr-ctico-de-electrocencefalograf-a-cl-nica

Treatment Strategies in Pediatric Epilepsies 2nd cycle, 1st EPIPED course

21–24 April 2021
Girona, Spain
https://www.epiped-course.com/

Epilepsy 2020: A vision of the future in epilepsy research

7–8 May 2021
Montreal Neurological Institute-Hospital (The Neuro) in Canada
https://www.ilae.org/congresses/epilepsy-2020-a-vision-of-the-future-in-epilepsy-research

International Training Course on Neuroimaging of Epilepsy

13–15 May 2021
Montreal Neurological Institute-Hospital (The Neuro) in Canada

https://www.ilae.org/congresses/international-training-course-on-neuroimaging-of-epilepsy

5th Dianalund Summer School on EEG & Epilepsy

18–24 July 2021
Dianalund, Denmark
https://www.ilae.org/congresses/5th-dianalund-summer-school-on-eeg-and-epilepsy

2021 Advanced San Servolo Epilepsy Course Bridging Basic with Clinical Epileptology - 7: Accelerating Translation in Epilepsy Research

20–31 July 2021
San Servolo (Venice), Italy
https://www.ilae.org/congresses/2020-advanced-san-servolo-epilepsy-course

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

13–15 September 2021
Bochum, Germany
https://www.ilae.org/congresses/annual-meeting-on-imaging-in-epilepsy-epilepsy-surgery-epilepsy-research-and-cognitive-neurosciences-amie-2021

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

15–17 September 2021
Bochum, Germany
https://www.ilae.org/congresses/summer-school-on-imaging-in-epilepsy-epilepsy-surgery-epilepsy-research-and-cognitive-neurosciences-susie-2021

2020 ILAE British Branch Annual Scientific Meeting

28–30 September 2021
Cardiff, UK
https://www.ilaebritishconference.org.uk/

9th Eilat International Educational Course: Pharmacological Treatment of Epilepsy

10–15 October 2021
Jerusalem, Israel
https://www.eilatedu2021.com/

7th UAE Epilepsy Congress

22–23 October 2021
Dubai, UAE
http://congress2020.elae.ae/

2022

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

28 Apr–2 May 2022
Glasgow, UK
https://epns-congress.com/

2023

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

20–24 June 2023
Prague Conference Centre, Prague, Czech Republic
https://www.epns.info/epns-congress-2023/