Editors' Note: In reference to "Practice guideline summary: Use of fMRI in the presurgical evaluation of patients with epilepsy," Dr. Papanicolaou et al. discuss whether functional MRI (fMRI) evaluation for language dominance in epilepsy surgery can be considered reliable given the high rate of false-positives inherent in fMRI data processing. In support, guideline editors Gloss et al. cite the high concordance between fMRI and amobarbital testing and explain how the method of analysis used in hemispheric language assessment has been shown to be less prone to statistical error. Drs. Zack and Kobau bring up several questions in regards to "Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies," including the exclusion of at least 2 relevant references and the suitability of the statistical methodology chosen. Authors Jette et al. further explain their statistical approach but agree that one reference was omitted. A correction appears on page 642.

—Megan Alcauskas, MD, and Robert C. Griggs, MD

**LETTER RE: PRACTICE GUIDELINE SUMMARY:
USE OF FMRI IN THE PRESURGICAL
EVALUATION OF PATIENTS WITH EPILEPSY:
REPORT OF THE GUIDELINE DEVELOPMENT,
DISSEMINATION, AND IMPLEMENTATION
SUBCOMMITTEE OF THE AMERICAN ACADEMY
OF NEUROLOGY**

Andrew C. Papanicolaou, James W. Wheless, Abbas Babajani-Feremi, Shalani Narayana, Roozbeh Rezaie, Asim Choudhri, Frederick Boop, Memphis, TN: The American Academy of Neurology (AAN) endorsement for the use of fMRI evaluation of hemispheric dominance for language in epilepsy surgery candidates¹ appears as an odd and disconcerting sequel to the article by Eckland et al.,² which reported that the clustering approach in functional MRI (fMRI) data processing may be responsible for an excessively high rate of false-positive findings. The latter report implied that up to 70% of the significant fMRI effects reported in approximately 40,000 peer-reviewed publications could represent no brain physiology facts, but type I statistical errors to the degree that they employed clustering of activated voxels.² Consequently, it is fitting to suggest users of these popular fMRI software packages (SPM, FSL, AFNI)

reconsider conclusions based on differences in activation levels of voxel clusters between task conditions. This raises the question of whether those who use the clustering procedure for the purpose of assessing hemisphere dominance for language should be alarmed for having made incorrect assessments in the past and refrain from using them for the same purpose in the future. Our answer is no, since language laterality judgments are typically made on the basis of laterality indices (i.e., the relative degree of activation defined as the ratio of left- and right-hemisphere activated voxels that are equally likely or unlikely to be activated). However, depending on how users of these automated software packages derive estimates of localization of the language network hubs (a practice not endorsed by the AAN),¹ they may need to exercise more caution now that the shortcomings of these data reduction and analysis procedures were directly demonstrated and made widely known.

1. Szaflarski JP, Gloss D, Binder JR, et al. Practice guideline summary: use of fMRI in the presurgical evaluation of patients with epilepsy: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2017;88:395–402.
2. Eklund A, Nichols TE, Knutsson H. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. *Proc Natl Acad Sci USA* 2016;113:7900–7905.

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**AUTHOR RESPONSE: PRACTICE GUIDELINE
SUMMARY: USE OF FMRI IN THE PRESURGICAL
EVALUATION OF PATIENTS WITH EPILEPSY:
REPORT OF THE GUIDELINE DEVELOPMENT,
DISSEMINATION, AND IMPLEMENTATION
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David Gloss, Charleston, WV; Jerzy P. Szaflarski, Birmingham, AL; Scott K. Holland, Cincinnati, OH; Jeffrey R. Binder, Milwaukee, WI; William H. Theodore, Bethesda, MD: We thank Papanicolaou et al. for the comment on our article,¹ and agree that important issues were raised regarding thresholding methods in functional MRI (fMRI).² However, the original estimate of the number of studies potentially affected was substantially lowered.^{3,4} Imprecision is part of every diagnostic test; its presence in thresholded fMRI activation maps is unlikely to lead to spurious

lateralized correlations between cognitive tasks and blood oxygenation level–dependent signal, or to agreement between fMRI and other investigations. As Papanicolaou et al. note, laterality measures are likely robust to the occurrence of false-positive clusters, since they are derived from side-to-side ratios.

The statistical analysis techniques used to examine group data differ fundamentally from single-subject clinical fMRI methods. In the 10 Class I or II articles that compared fMRI to amobarbital testing, there was high concordance.¹ If the very high rate of false positivity originally claimed by Eklund et al.² were typical in clinically used fMRI, there is little chance that the 87% concordance between fMRI and amobarbital testing in temporal lobe epilepsy would be seen. The correlations observed occurred regardless of software or algorithm used; the studies reviewed affirm the efficacy of fMRI methods when thoughtfully performed. None of the conclusions concerned the use of fMRI for localizing language network hubs. For these reasons, none of the conclusions or recommendations needs to be altered.

We agree that careful understanding of software performance and its limitations is important in understanding how a test is used. As stated in our article, “Presurgical fMRI may be used instead of the IAP for language lateralization in patients with epilepsy who are undergoing evaluation for brain surgery (Level C). However, when fMRI is used for this purpose, task design, data analysis methods, and epilepsy type (temporal vs extratemporal, lesional vs nonlesional) need to be considered.”⁴

1. Szaflarski JP, Gloss D, Binder JR, et al. Practice guideline summary: use of fMRI in the presurgical evaluation of patients with epilepsy: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2017;88:395–402.
2. Eklund A, Nichols TE, Knutsson H. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. *Proc Natl Acad Sci USA* 2016;113:7900–7905.
3. Correction for Eklund et al. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. *Proc Natl Acad Sci USA* 2016;113:E4929.
4. Mumford J, Pernet C, Yeo T, et al. Keep calm and scan on. In: Organization for Human Brain Mapping [online]. Available at: ohbmbrianmappingblog.com/blog/keep-calm-and-scan-on. Accessed March 11, 2017.

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LETTER RE: PREVALENCE AND INCIDENCE OF EPILEPSY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF INTERNATIONAL STUDIES

Matthew Zack, Rosemarie Kobau, Atlanta, Georgia: Noting variability around epilepsy burden estimates, Fiest et al.¹ aimed to provide “a comprehensive synthesis of the prevalence and incidence of epilepsy from

published international studies.”¹ This article, which may be widely cited, is problematic.

The authors omitted at least 2 references that meet the study’s search criteria (appendix e-1)¹ but not its exclusionary criteria (figure 1).^{1–3} The authors noted the possibility of missing other studies (i.e., from Australia), but did not adequately account for this discrepancy relative to efforts around conducting a comprehensive synthesis.

Despite some acknowledgement of the heterogeneity of the estimates of active period prevalence (figure 2) and incidence (figure 3, A and B), based on *P* statistics close to 100% and statistically significant *Q* statistics, the authors still reported pooled estimates.¹ These latter estimates misrepresent the extreme heterogeneity evident in the figures. At minimum, the authors should more clearly indicate and discuss the unreliability of these pooled estimates to alert readers about the possible misuse. Readers might consider citing the range of all or country-specific estimates when referencing study outcomes.

Further, the authors miscited reference 167 (appendix e-3) used in figure 2,^{1,4} which should instead be referenced as the Centers for Disease Control and Prevention.⁵

1. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. *Neurology* 2017;88:296–303.
2. Centers for Disease Control and Prevention (CDC). Epilepsy in adults and access to care: United States, 2010. *MMWR Morb Mortal Wkly Rep* 2012;61:909–913.
3. Holden EW, Thanh Nguyen H, Grossman E, et al. Estimating prevalence, incidence, and disease-related mortality for patients with epilepsy in managed care organizations. *Epilepsia* 2005;46:311–319.
4. Centers for Disease Control and Prevention (CDC). Detection of notifiable diseases through surveillance for imported plague: New York, September–October 1994. *MMWR Morb Mortal Wkly Rep* 1994;43:805–807.
5. Centers for Disease Control and Prevention. Current trends prevalence of self-reported epilepsy: United States, 1986–1990. *MMWR Morb Mortal Wkly Rep* 1994;43:810–811, 817–818.

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AUTHOR RESPONSE: PREVALENCE AND INCIDENCE OF EPILEPSY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF INTERNATIONAL STUDIES

Nathalie Jette, Kirsten M. Fiest, Khara M. Sauro, Samuel Wiebe, Scott B. Patten, Calgary, Canada: We thank Zack and Kobau for their interest in our article.¹ We agree there is marked heterogeneity among studies and acknowledged this throughout the article. We attempted to mitigate heterogeneity by using a random effects model and reported medians with 25th and 75th percentiles alongside pooled

estimates to provide readers with a more complete picture of data distribution and heterogeneity. In the article, we also identified geographic outliers.¹ Despite marked heterogeneity, pooled estimates and medians were similar. Together, they provide a valid overview of this literature and were accompanied in the article by appropriately cautionary statements about their interpretation.¹ Further, we attempted formal analyses of sources of heterogeneity, which proved difficult and did not yield definitive conclusions, and provided these results in supplementary e-tables.¹

Zack and Kobau also indicate that 2 studies were missed from our review. One study was excluded because it was not population-based according to our definition (not representative of general population [i.e., patients from a managed care organization]).² The other study was indeed missed at the abstract review stage (though captured by our search)³; we thank Zack and Kobau for pointing

out this omission. Including this study³ yielded estimates that were nearly identical, thus the conclusions remain unchanged. Missing studies that meet eligibility criteria is always a possibility despite rigorous adherence to guidelines for systematic review, as highlighted in our discussion. For this reason, updating systematic reviews periodically is recommended.

1. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. *Neurology* 2017;88:296–303.
2. Holden EW, Thanh Nguyen H, Grossman E, et al. Estimating prevalence, incidence, and disease-related mortality for patients with epilepsy in managed care organizations. *Epilepsia* 2005;46:311–319.
3. Centers for Disease Control and Prevention (CDC). Epilepsy in adults and access to care: United States, 2010. *MMWR Morb Mortal Wkly Rep* 2012;61:909–913.

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CORRECTIONS

Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies

In the article “Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies” by K.M. Fiest et al.,¹ there are missing and incorrectly cited references in appendix e-3, table e-1, and table e-3. Please find the corrected supplementary materials with the article at Neurology.org. The authors regret these errors and omissions.

REFERENCE

1. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. *Neurology* 2017;88:296–303.

Optimal management of patients with asymptomatic carotid stenosis

In the editorial “Optimal management of patients with asymptomatic carotid stenosis” by R.M. Starke,¹ there is an error in the first sentence of the last paragraph, which should have read “Studies on CEA have shown the superiority, time and time again, to carotid stenting for the primary outcome of decreasing the future risk of stroke.” The publisher regrets the error.

REFERENCE

1. Starke RM. Optimal management of patients with asymptomatic carotid stenosis. *Neurology* 2017;88:1988–1989.

Author disclosures are available upon request (journal@neurology.org).

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Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies

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