

Editors' Note: In WriteClick this week, authors Hannawi and Stevens respond to questions and comments about their article, "Resting brain activity in disorders of consciousness: A systematic review and meta-analysis." Drs. Shen et al. report that they were unable to reproduce the authors' analysis using the provided settings. Drs. Garbarino and Sannita inquire whether viewing disorders of consciousness as a continuum may help explain heterogeneity in clinical measures. Author Schoenen outlines additional statistical analyses performed on the data presented in "Migraine prevention with a supraorbital transcutaneous stimulator: A randomized controlled trial." An update related to this letter was published in the December 1, 2015, print issue.

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

RESTING BRAIN ACTIVITY IN DISORDERS OF CONSCIOUSNESS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Dongchao Shen, Linyi; Zhaobo Shen, Liying Cui, Beijing, China:

I read the article by Hannawi et al.¹ on resting brain activity in disorders of consciousness. Activation likelihood estimate (ALE) meta-analysis allows the investigation of shared brain activation across individual experiments by quantitatively identifying brain locations consistently associated with different tasks or at resting state.² When the datasets are too small for the analysis, it might not find significant convergence. The developers of GingerALE have warned that this may be the case for datasets smaller than 15 experiments.³ The authors' ALE meta-analysis consisted of 3–16 experiments. Therefore, I conducted some parts of the analysis—vegetative state (VS) vs healthy control (HC), minimally conscious state vs HC, patients with disorders of consciousness (DOC) related to anoxia vs HC, and areas that correlated with Coma Recovery Scale–Revised score—according to the references and by the settings that the authors provided. I found no clusters. Furthermore, in the analysis of patients with DOC related to anoxia vs HC, no useful coordinate was provided in 1 of the 5 references that the authors included with the ALE meta-analysis.⁴ I wonder if the authors erred, used another model, or used

alternate GingerALE settings. It would be best if the authors could provide the text files for each contrast that was imported into GingerALE, so the differences can be found.

Sergio Garbarino, Walter G. Sannita, Genoa, Italy:

Neural activity is reduced in DOC across a number of brain structures that are thought to contribute to sustaining consciousness and are interfered with in these conditions. The reduction is reportedly more pronounced in VS compared with minimally conscious state (MCS) and even more in coma compared to VS and MCS.^{1,5} This observation is supported by electrophysiologic findings,⁶ suggesting a possible pathophysiologic continuum from coma to recovered consciousness, of which coma and evolution into the arousal/awareness dissociation characterizing VS and MCS would be only transitional phases. The functional core impairment was shared by all DOC conditions in the meta-analyses by Hannawi et al.¹ and Lutkenhoff et al.,⁵ but more complex patterns were common, including associations of clinical measures characterizing VS and MCS with tissue atrophy in subcortical structures.^{1,5} Heterogeneities in etiology or in the extension and severity of brain damage (possibly crucial in this regard) would result in preserved neural structures and residual resources⁷ and could question the boundaries between the conventional DOC conditions. Fluctuations in brain functional state are known to reflect the variations of neuronal/non-neuronal biological parameters in response to the functional or homeostatic requirements.⁸ The correlation between clinical responsiveness suggesting residual consciousness and the sympathetic/parasympathetic balance indicates how these end effects may be relevant and deserving of systematic investigation in DOC.⁸

Author Response: Yousef Hannawi, Columbus, OH; Robert D. Stevens, Baltimore: We thank Shen et al. and Garbarino and Sannita for the comments on our article.¹

To answer the concerns raised by Shen et al., "too few experiments" is a generic GingerALE software message that appears when contrast analysis is performed using less than 15 studies; this approach is based on using within-group results.³ However, as

detailed in our Methods and recommended by the software developers when within-group effects are rarely reported, we tested consistency of between-group differences across studies.^{1,3} This approach was employed successfully before and may yield findings with a minimum of 2 inputs, with increased generalizability of the results as the number of studies increases.^{3,9}

We also found no significant difference when we performed contrast analysis of MCS vs VS.² Unlike those of Shen et al., our datasets included additional data that were obtained by contacting the corresponding authors.¹ Our findings are consistent with the published literature, including the systematic review.¹ We can only conclude that Dr. Shen has erred in reproducing our analysis or did not follow the same methods.

Finally, the coordinates were correctly selected for the anoxia vs HC analysis, yet there was an error in citation. The correct reference is Norton et al.,¹⁰ not Ovadia-Caro et al.⁴ Nevertheless, our results and conclusions remain the same.

We agree with Drs. Garbarino and Sannita that heterogeneities in etiology, severity, or distribution of injury are a major constraint in any neuroimaging study of patients with DOC. To minimize these effects on our meta-analysis, we performed separate subgroup analyses of patients with VS, MCS, and according to the underlying etiology of DOC (if enough studies existed).¹

We also agree that fluctuations in resting brain activity may affect DOC classification at the individual level, which may change group level inferences.¹¹ Thus, we investigated consistency of group level differences across studies on a large scale. Included studies used clear definitions of DOC as much as possible. Our results matched the majority of the studies that were included in our extensive systematic review.¹ Overall, however, the impact of these factors on the interpretation of functional activation time courses in patients with DOC is not well-understood and needs to be explored further. A comprehensive and painstaking analysis would be warranted to elucidate how low-frequency resting-state fluctuations in patients with DOC might be modulated by a range of neuronal and non-neuronal variables, including the sympathetic/parasympathetic balance.¹²

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MIGRAINE PREVENTION WITH A SUPRAORBITAL TRANSCUTANEOUS STIMULATOR: A RANDOMIZED CONTROLLED TRIAL

Jean E. Schoenen, Liege, Belgium: Additional statistical analyses were performed on the outcome measures presented by Schoenen et al.¹ to account for covariates. A rank analysis of covariance was performed, using the nonparametric Spearman rank correlation coefficient.² The results showed that age and disease duration do not influence study outcomes. However, the number of migraine days during the 1-month baseline period had an influence on the decrease in migraine days during the 3rd month of treatment. In the original publication, the difference between verum and sham groups in the reduction of migraine days (respectively –29.7% and –4.9%) just missed the significance threshold ($p = 0.054$).¹ However, when baseline migraine days are considered as a covariate, this difference becomes significant ($p = 0.044$).

This new analysis indicates that the beneficial effect of Cefaly for migraine prevention might be greater in patients with more frequent migraines, which is of interest for clinical practice.

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