and not related to this specific topic. We do not consider this relevant to the report. The authors declare no other conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Niklas Larsson, M.D., Malin L. Nording, Ph.D., Jonas Tydén, M.D., Ph.D., Joakim Johansson, M.D., Ph.D., Richard Lindberg, Ph.D., Michael Haney, M.D., Ph.D., M.Sc.
Umeå University, Umeå, Sweden (N.L.).
niklas.larsson@regionvasterbotten.se

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Supplemental Digital Content

Supplemental Digital Content, https://links.lww.com/ALN/D48

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Sign-reversed *versus* Orthodox Granger Causality Analysis of the Electroencephalogram in General Anesthesia: Research Letter

To the Editor:

We wish to report on a serendipitous technical observation regarding the calculation of the Granger causality between electroencephalogram (EEG) channels in subjects given propofol, as reported by Pullon *et al.*[1] From subsequent application of this analysis to a separate patient dataset in 2022, it became apparent that there is no accepted convention for the sign of the autoregressive coefficients returned by the "armorf.m" MATLAB function; this means that the transfer function we used in the original analysis had been derived from sign-reversed coefficients. This letter compares the results from the originally published sign-reversed Granger analysis with the "corrected" orthodox Granger analysis methods for the Pullon dataset. The first stage of the Granger algorithm derives the auto- and cross-regression coefficients; thus, the sign reversal alters the subsequent transformation to the frequency domain, effectively acting like a complicated filter. Further mathematical investigations into this are underway, but, empirically, the sign-reversal filter produces very low amplitude auto- and cross-spectra in which narrowband oscillations are not represented and power is shifted to high frequencies. This is evident in figure 1, which shows the frequency spectrum

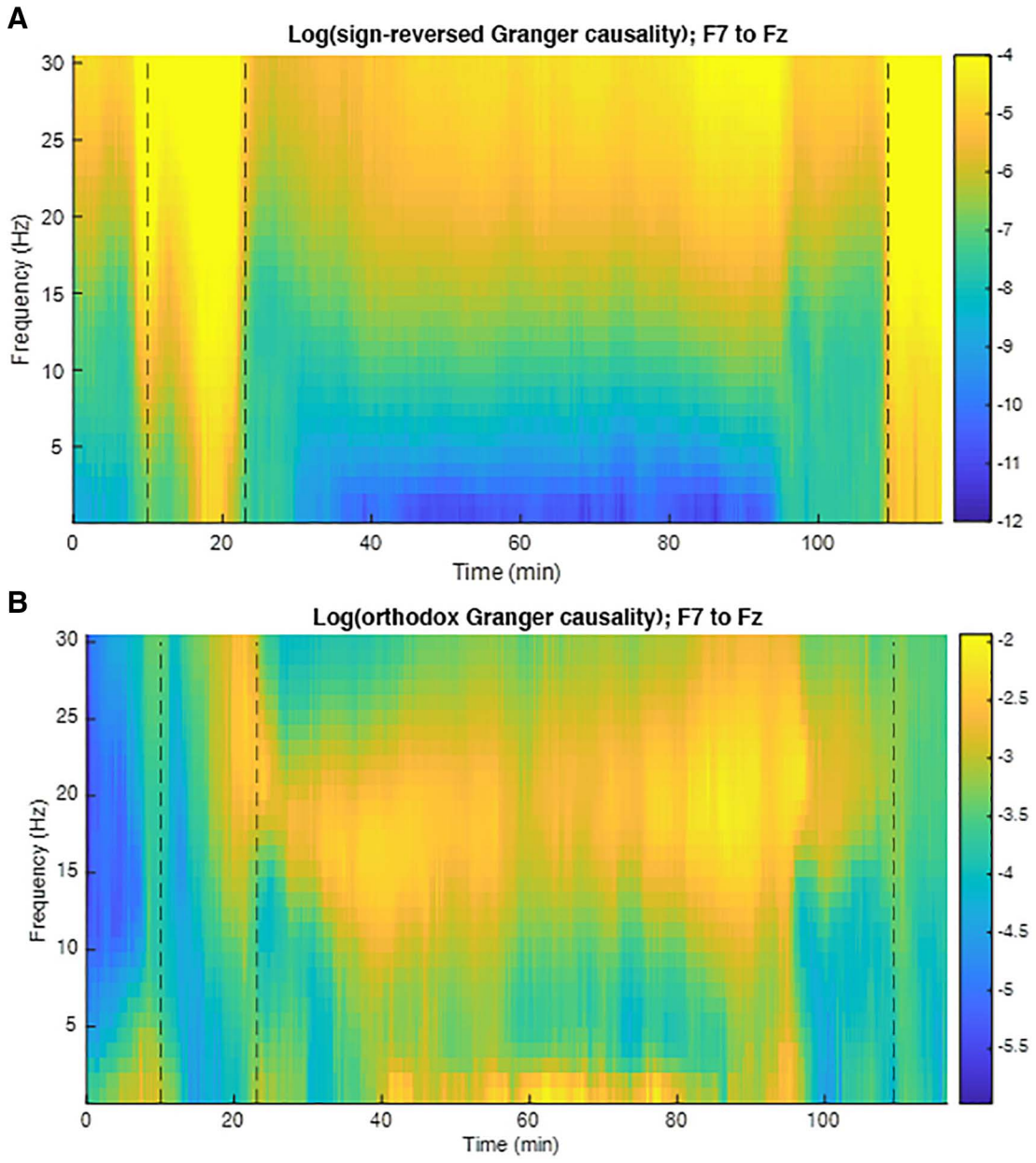

Fig. 1. Comparison of Granger spectra. (*A*) Time-frequency spectrum for sign-reversed Granger causality on a log scale. This is from participant 1, bivariate electrode pair F7 to Fz (*i.e.*, front left to front central). (*B*) A time-frequency spectrum for orthodox Granger causality on a log scale for the same participant and bivariate electrode pair. Note the smaller color scale than in *A*. *Vertical dashed lines* are, sequentially, the points of: eyes closed, loss of behavioral response, regain of behavioral response.

for electrode pair F7 to Fz for participant 1 for both the sign-reversed and orthodox Granger analyses.

Principal component analysis identified the electrode pairs with the largest and smallest change over loss and regain of responsiveness per frequency band, summarized in figure 2. Other graphical comparisons of the two methods are shown in the Supplemental Digital Content (figs. S1, S2, and S3, https://links.lww.com/ALN/D35). Subjects in the wakeful state showed a much more consistently elevated sign-reversed Granger causality than when using the orthodox Granger method (fig. 2 middle column, and fig. S1, https://links.lww.com/ALN/D35). When *sign-reversed* Granger analyses were used, the propofol-induced state of unresponsiveness was marked by a profound decrease in information flow over most of the brain (figs. S1, S2, and S3, https://links.lww.com/ALN/D35)—most marked in

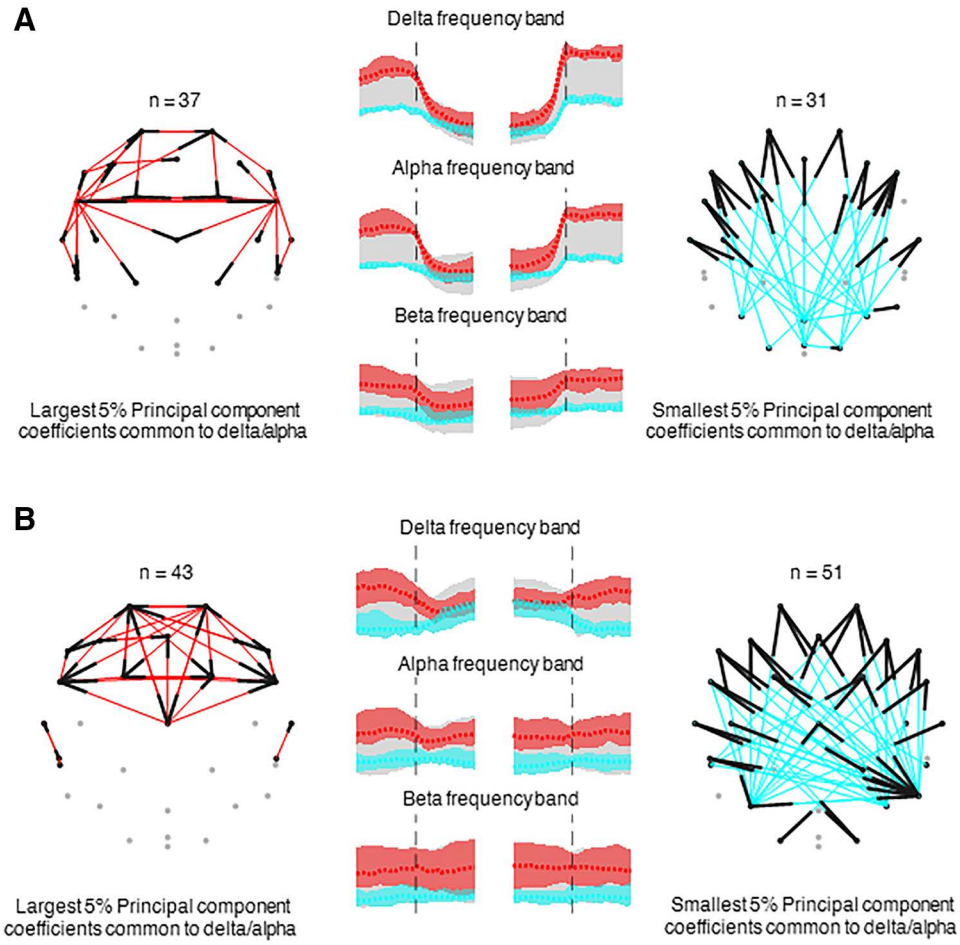

Fig. 2. Regional differences. Largest and smallest 5% principal components of low-frequency Granger causality identified from the sign-reversed (*A*) and orthodox (*B*) methods.

the delta waveband and in a posteromedial direction (fig. 2, median [25th, 75th] decrease from 0.82 [0.35, 2.02] at 2 min before loss of responsiveness to 0.17 [0.07, 0.44] at 2 min after loss of responsiveness, repeated-measures ANOVA $P < 0.001$). This agrees with other related measures of directed connectivity such as symbolic transfer entropy. In comparison, the propofol-induced changes in global information flow seen when using the *orthodox* Granger analysis were much more heterogeneous and subtle; and most marked around the transition point of loss of responsiveness (fig. 1; fig. 2, middle column; and fig. S3, https://links.lww.com/ALN/D35). Consistent decreases were confined to only a few brain regions, such as posteromedial flow from frontal regions in the delta band, similar to that seen in the sign-reversed results (fig. 2, median [25th, 75th] decrease from 0.58 [0.35, 1.08] 2 min before loss of responsiveness to 0.30 [0.19, 0.52] 2 min after loss of responsiveness, $P < 0.001$). Counterintuitively, with the orthodox method, propofol unresponsiveness appeared to be associated with no change, or even some slightly *increased* information flow in higher frequencies. This apparent lack of effect, or increased information flow under anesthesia with orthodox Granger analyses was also reported by Barrett *et al.*[2] It is hard to explain, but it is very reminiscent of the changes with anesthesia seen when using undirected connectivity measures, such as coherence (see fig. 2 in Pullon *et al.*[3] obtained from the same subject group).

We suggest two possible explanations for our original, sign-reversed results. The first concerns the issues of linearity and stationarity in the EEG signal. It could be argued that the prime characteristic of the wakeful state is the existence of active metastability—where the directed connectivity or information flow between different brain regions shows abrupt fluctuations during time intervals of seconds to minutes, as the cortex switches between functional states,[4] and that this metastability is reduced with the induction of propofol anesthesia.[2] By definition, the existence of metastability precludes stationarity. In EEG analyses, it can be difficult to satisfy the stationarity and

linearity requirements for Granger causality. For example, we found that 96% of EEG windows in the unmodified Granger analysis would have been excluded by the Durbin-Watson test for autocorrelation, but only 3.4% of EEG windows were excluded by the Durbin-Watson test if using the sign-reversed Granger method.

Another plausible explanation is that the sign-reversed Granger filtering of the narrowband oscillatory peaks in the spectra might, in some way, allow propofol-induced changes in underlying nonoscillatory broadband brain co-ordination to become more apparent. And that it is these processes that are mechanistically more important than the much more obvious oscillatory components in the altered information flow underlying loss of responsiveness. It is noteworthy that the process noise components of the Granger causality show the most dramatic decreases with unresponsiveness. Although a full theoretical understanding has not yet been developed, we suggest that researchers consider using sign reversal when applying Granger causality analysis to neurobiologic signals.

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Competing Interests

The authors declare no competing interests.

Jamie W. Sleigh, M.D., Rebecca M. Pullon, Ph.D.
University of Auckland, Auckland, New Zealand (J.S.).
Jamie.sleigh@waikatodhb.health.nz

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Flow Effects of High-flow Nasal Oxygenation: Comment

To the Editor:

While the ability of high-flow nasal cannula to achieve apneic oxygenation is well established, the ability to remove carbon dioxide is less clear. The recent investigation by Riva and colleagues on the issue, in which various flow rates were examined during apneic periods, interested us.[1] The study could not identify a meaningful ventilatory contribution attributable to high-flow nasal cannula. While we applaud the authors' methodology, we feel that the working methodology of high-flow nasal cannula needs to be considered in context with the conclusion and interpretation.

Variations in lung mechanics need to be considered when the interplay of high-flow nasal cannula oxygenation and carbon dioxide exchange are examined. Respiratory mechanics during high-flow nasal cannula oxygenation is likely to differ substantially between the paralyzed and unparalyzed states as in spontaneous and assisted or controlled breathing. The high-flow nasal cannula is believed to generate a level of pharyngeal pressure.[2] Thus, the air being expired from the lung will be opposed by the fresh gas flow from the high-flow nasal cannula, which will produce a positive end-expiratory pressure–like effect, changing the lung volume and influencing ventilation.[2,3] With paralysis, the resistance against the expiratory flow will be lost.

Furthermore, the continuous positive airway pressure–like effect of the high-flow nasal cannula with the patient's mouth open due to jaw thrust maneuvers, laryngoscopy, or the presence of an oropharyngeal airway in the paralyzed patient is difficult to envisage and probably negligible.[4] Nevertheless, these factors are likely to alter oropharyngeal gas washout, the mechanism whereby a high-flow nasal