REPLY TO SPRENG ET AL.:

Multiecho fMRI denoising does not remove global motion-associated respiratory signals

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In 2 human functional magnetic resonance imaging (fMRI) datasets (89 "ME" subjects; 12 "NA" subjects), we used signal decay properties to separate 2 kinds of signals: S0 artifacts, which were spatially specific, and T2* modulations, which occurred over the whole brain (1). We established that whole-brain (global) fMRI signals were nearly unchanged before and after removal of S0 signals. Hence, most global signals are T2* signals, compatible with neural activity or with respiratory-related pCO_2 changes. In a dataset with paired respiratory records (NA data), we illustrated that changes in respiratory traces were temporally accompanied by prominent global signal modulations, an association visible in "gray plots" of single scans (2). Across scans, variance in global signals correlated with variance in respiratory measures.

Spreng et al. (3) critique our paper, stating that "there is no definitive evidence . . . that respiration effects . . . even substantively contribute . . . to residual global signal [following removal of S0 artifacts]." This is a strange assertion. Deep breaths and changes in breathing rate and depth plainly occur in the NA respiratory records. Changes in ventilation alter arterial pCO_2, which governs cerebral blood flow and thus whole-brain T2* signals; removal of S0 signals should have no influence on these respiratory signals (4). To illustrate the matter, Fig. 1*A* shows global signals surrounding isolated spontaneous deep breaths in 4 NA subjects before and after multiecho denoising. We also present instructed breaths before and after multiecho denoising. The waveform persists in either scenario, as expected, since it is a T2* signal. Furthermore, the waveform is similar in both scenarios, and "arousal," the putative "neural" accompaniment of spontaneous respiratory signals implied by our critics (5), should play little role in externally instructed deep breath signals.

Across subjects, global signal variance scales with variance in respiratory traces, and with head motion. We obtain these effects separately in both runs of our NA subjects after multiecho denoising, shown in Fig. 1*B*. We understand skepticism about effects in few subjects, but similar relationships had already been reported in larger datasets, such as the single-echo NIH dataset of ref. 6. We also see the effects in a newly acquired 56-subject "AG" dataset after multiecho independent components analysis (ICA) denoising (data partially reported in ref. 7).

In short, the assertion that respiratory variance is removed by multiecho denoising is both conceptually nonsensical and empirically unfounded. We reiterate our stance that it is important to either remove or control for respiratory confounds in data. Our critics are surely aware of our thorough consideration of this issue (8, 9). We did not selectively advocate the use of global signal regression, but rather considered a variety of univariate and multivariate approaches to removing motion-associated global signal modulations. Those of us with long-standing opposition to global signal regression remain of that opinion, based on both our prior work (cited by our critics) and our ongoing work delineating the basis of global fMRI signals. Those of us who endorse global signal regression continue to find it among the most effective techniques for removing respiratory and other unwanted signals from fMRI scans (10, 11).

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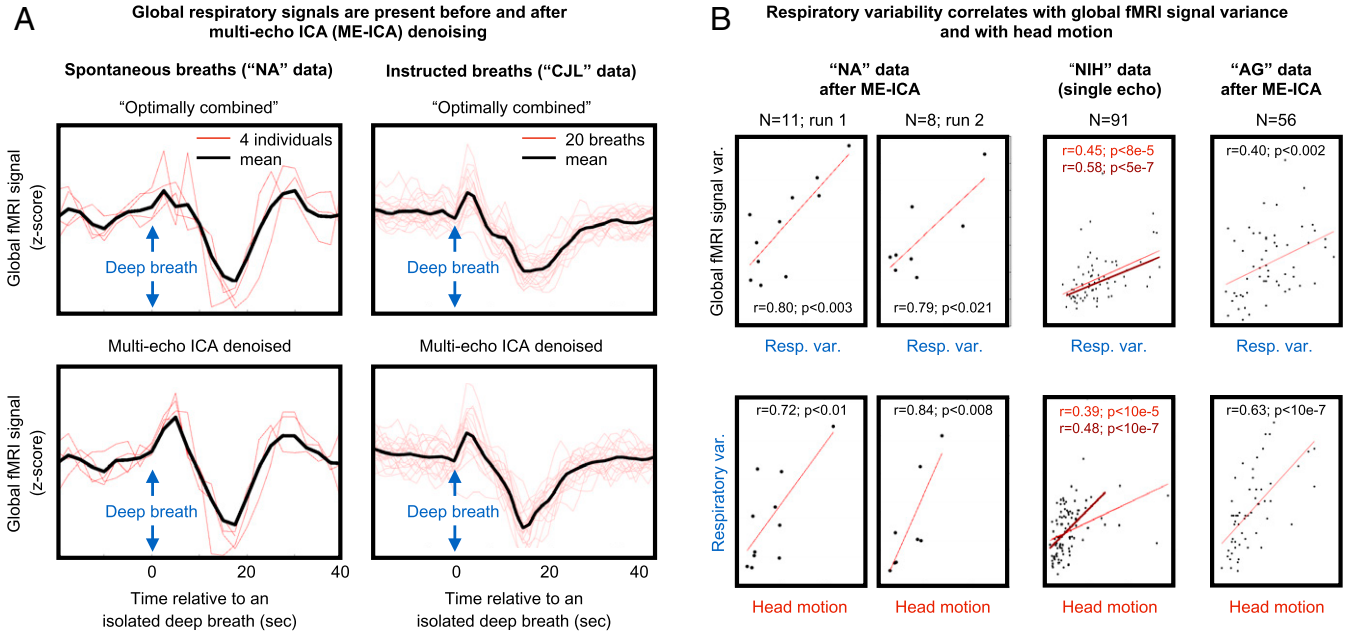

Fig. 1. Deep breath global signals, and relationships of global signal variance to respiratory variance and head motion in 3 datasets. (*A*) In the first column, for 4 well-isolated, spontaneous deep breaths in the NA dataset, global fMRI signals before and after multiecho ICA are shown, illustrating that the global signal is largely unchanged and therefore that the time-locked signals are largely T2* signals. In the second column, global fMRI signals of 20 widely spaced instructed deep breaths in a single subject are shown before and after multiecho ICA denoising, again showing little alteration by multiecho ICA denoising. Comparison of the spontaneous and instructed breath waveforms yields evident similarities. Both conditions include comparable respiratory phenomena, but endogenous "neural" signals that might prompt deep breaths ought to be minimized when an instructed paradigm is used. Data from ref. 1. (*B*) Cross-subject correlations between global signal variance and respiratory variability, and between respiratory variability and mean head motion, are shown separately for both runs of the multiecho ICA denoised NA data, for a separate single-echo dataset previously published [Modified from ref. 6. Copyright (2017), with permission from Elsevier. Data from ref. 1.], and for 56 AG subjects scanned with multiecho sequences [data partially published in Gilmore et al. (7)].

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