Title: Temporal ICA has not properly separated global fMRI signals: a comment on Glasser et al., 2018

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Body:

Recent work has shown that whole-brain (global) respiratory signals are prevalent in functional magnetic resonance imaging (fMRI) scans, that these signals scale with head motion, and that numerous denoising strategies do not remove these signals (Power, 2017; Power et al., 2018; Power et al., 2017b). These findings have been established in several datasets, including the Human Connectome Project (HCP), in which global respiratory signals persist through spatial independent component analysis (ICA) denoising routines (Burgess et al., 2016; Power, 2017; Power et al., 2017b). These respiratory signals have special importance in resting state analyses, which assay signal covariance and thus are highly susceptible to being influenced by unremoved artifacts in timeseries.

Motivated by such findings, in "Using temporal ICA to selectively remove global noise while preserving global signal in functional MRI data", Glasser and colleagues used temporal ICA to further denoise HCP scans after spatial ICA (Glasser et al., 2018). They report that "much… global noise is likely due to… changes in respiratory rate and depth…" and that their approach "can selectively segregate and remove global structured noise while retaining global neural signal", thus providing an "urgently needed but previously lacking" means of removing unwanted global signals.

In the article, the signals are hand-classified as "neural signal" or "noise". Because there are no neural records to anchor these decisions, it is imperative to properly identify artifactual components, especially respiratory signals. One might therefore expect close attention to respiratory measures in the data. However, respiratory measures were not examined. The methods state that "[the authors were] unable to manually review and quality assure…" the respiratory data. Oddly, the very next sentence states "we rely on prior work in a smaller study that did manual quality control", referring to (Power et al., 2017b), a paper that stressed the importance of visually inspecting physiology records, which are often corrupted.

Out of curiosity, after reading the target article, I obtained the "900 subject" release of the HCP data, visually inspected each physiological record, and obtained the following statistics: 831 subjects had 4 runs of fMRI data, 760 of these had 4 runs of physiological data, and 446 of these had data in which I believed I could identify peaks in cardiac and respiratory traces in all runs. Peak-finding is the basis of measures such as the "RVT" respiratory measure used in the target article to identify physiological noise. Thus, about half of the subjects have fully usable physiology data (though more would be partially usable). These statistics underscore the importance of personally assessing physiologic data[1]. Parenthetically, these proportions are broadly comparable to those of multiple other datasets I have examined.

[1] A movie of all traces and a spreadsheet with my impression of trace usability is posted online at www.jonathanpower.net/2018-glasser-comment.html, as are software tools to help visualize and correct physiology measures, should readers wish to form their own impressions. Examining the ~3600 runs for trace suitability took about half a day, and correcting peaks on cardiac and respiratory traces in the 446 suitable subjects would likely take 1-2 work weeks.

These issues aside, the important question is whether temporal ICA (tICA) isolated global respiratory signals from other global signals, and, relatedly, whether the human decisions that categorized tICA components as “neural signals” or “noise” were correct. There is reason to think the separation is flawed. In the first place, it is evident that global signals are simultaneously being assigned to both noise and signal components. Four instances of single-subject data are presented in the paper, three of which are reformatted in Figure 1 (with gray plots moved next to each other to facilitate comparison). In each subject there are multiple instances of global signals that are partially assigned to “noise” components (and are thus removed by tICA, see pink boxes) and partially assigned to “signal” components (and are thus retained after tICA, see green boxes). The simplest explanation for classifying global signals with shared temporal features as noise in one part of the brain and signal in another part of the brain is that noise was incompletely removed and/or improperly identified as “neural signal”. Second, and likely relatedly, the authors identify as “neural signal” several tICA components in a “sensorimotor” distribution whose amplitudes are related to subject motion (“DVARS dips” in the paper) or to sleep (which displays altered respiration). As mentioned above, respiratory signals scale with head motion (Power et al., 2018; Power et al., 2017b), and recent work shows that large motions in HCP data are statistically accompanied by respiratory-like signal modulations spanning dozens of seconds (Byrge and Kennedy, 2018). What is not mentioned in the target article is that in studies of instructed or spontaneous breathing, where pCO_2 is measured or where abdominal belts are used to estimate respiration, regressors accounting for respiratory signals load positively across all gray matter, but most strongly in a “sensorimotor” distribution with prominence in peri-Rolandic, occipital, and superior temporal locations (Birn et al., 2006; Birn et al., 2008; Wise et al., 2004). Similarly, it is not mentioned that these respiratory patterns have been explicitly linked to the “sensorimotor” patterning of the global fMRI signal (Power et al., 2017a; Power et al., 2018; Power et al., 2017b). In sum, global signals are being identified as both “neural signal” and “noise” simultaneously, and this phenomenon may be related to the decision to identify as “neural signal” a set of sensorimotor components that display properties of respiratory signals.

If in future work an investigator wished to demonstrate that respiratory signals are isolated by tICA from “neural” signals, she could model in an event-related manner the period following isolated deep breaths, since single breaths are common and have well-characterized fMRI signal modulations spanning ~30-40 seconds (Birn et al., 2008; Chang and Glover, 2009; Power et al., 2018; Power et al., 2017b). Those modulations ought to be placed in the “discarded” components and not the “neural” components, and it would strain credulity for modulations with the same characteristics to be placed in both categories. To justify such simultaneous categorization, one would have to posit the existence of a “neural” signal, associated with respiration, with a hemodynamic response function several times slower than the standard evoked response function familiar from decades of task fMRI, with dynamics that happen to coincidentally match the timing of pCO_2-related blood flow changes.

There is one other aspect of the study that deserves comment. The target article reports that the (discarded) physiological global signal is spatially homogeneous, and states that this distribution is what practitioners of global signal regression “aspire” to remove. I am unaware of such aspirations, and the spatial inhomogeneity of the global fMRI signal has been discussed at length previously (Power et al., 2017a; Power et al., 2018; Power et al., 2017b). The point of performing global signal regression during denoising is to remove whole-brain artifacts from fMRI data, though, separately, investigators may also wish to remove whole-brain neural signals (see discussion in (Power et al., 2017a)). Respiratory signals occur everywhere in the brain but are especially prominent in a sensorimotor distribution, which is one reason that the global signal also follows a sensorimotor distribution (Power et al., 2017b). Temporal ICA may have a useful role to play in denoising fMRI data, but the current implementation falls short of convincingly separating respiratory effects from whatever other effects may be present in global fMRI signals.

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