Review of: "Measuring brain beats: cardiac-aligned fast fMRI signals"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

The authors have submitted a manuscript for publication entitled: "Measuring brain beats: cardiac-aligned fast fMRI signals". In this manuscript, the authors used off-line retrocardiac gating applied to fMRI BOLD acquisitions to study signal fluctuations during the cardiac cycle in a limited number of subjects. The manuscript demonstrates a significant effort of very hard work and I read the article with most sincere interest. The authors used insightful statistical techniques to draw out their conclusions.

However, my enthusiasm is limited in reading this article. If the paper were rewritten to focus on the technical impact of cardiac pulsations with elimination of the broad physiological discussions, which are often confusing and disjoint, the article would deserve publication.

The results were obtained from two different paradigms of fMRI: five subjects with resting state protocols and five subjects recruited for fast simultaneous multislice (SMS) analysis. This split in data populations is concerning as there was no means of external testing justifying this split into very low cohort size. The authors try to justify these low numbers in the discussion, but cohorts of 10 or more would be much more believable than cohorts of five prospective studies and the afterthought addition of applying a non-randomized cohort of resting state MRI subjects.

Another concern is voxel size, which the authors state as 4 mm isotropic voxels. The gray matter varies from 1-4.5 mm in thickness and the surface is curved and convoluted. Thus, the voxel size does not allow for any true measurements of the "cortex" in isolation from the extensive arterial network within the cortex or the pial vascular networks on the brain surface. Additionally, perforating arteries and veins are widespread and encircled by VR spaces and perivascular spaces that penetrate with all vessels, such that CSF pulsations, arterial pulsations and venous pulsations cannot be separated, especially by 4 mm voxels. Instead, I suspect the author's results simply show the volume averaging of these sources of pulsation. The authors touch on this in the discussion, but they must be up front about it and state that they are merely trying to establish the artifactual changes in fMRI signal that are created by cardiac pulsations, rather than make meaningless discussions about blood flow and CSF movements at the cellular level. The author's also need to clarify that when the speak of CSF-related signal, they are only referring to gross cisternal and ventricular signal, not pervasicular CSF movement, which they cannot resolve.

The imaging sequence used was an EPI (presumed spin echo), which has known distortion concerns that are not easily

unraveled in this study and are known to suffer from pulsation artifacts. Are the authors trying to quantify these artifacts? These artifacts show up in ASL perfusion. GE, the manufacturer of the magnet used in this current research, has put great effort into controlling this artifact on the ASL sequence. I am not sure that it has been eliminated in BOLD imaging for the SMS technique but is dealt with using extensive random sampling in typical BOLD acquisitions. Cardiac gating negates the random sampling over the cardiac cycle, thus “undoes” the sampling required to negate volume averaging effects. Are the authors implying a different means of correcting for this artifact? Just what is their aim?

BOLD imaging is usually targeted at measuring venous blood oxygenation in an attempt to extract information about local oxygen usage. While theoretically the authors have concluded cardiac gating will measure the temporal variation of spin-coherence, the factors are confounded, which they explain somewhat in their discussion, but their goals need to be better defined in their introduction and setting up the hypothesis they are trying to test. Are they suggestion temporal changes in oxygen supply vs. demand? AS they discuss after the fact, vascular compliance interferes with the tissue demand signal in this manner: the veins collapse, VR spaces collapse and the arteries expand at systole (opposite in diastole) creating an unsolvable volume averaging problem at the voxel level that convolutes the signal change from tissue demand with increased arterial volume, decreased venous volume and decreased water volume.

The author’s own data in Figure 3 empresses what is already known. It shows the same pattern of signal as CT perfusion, MRI perfusion and ASL perfusion (by some manufactures), when proper corrections are not applied. The author’s regions of interpretable signal in Figures 2, 3 and 4 are regions that are uniformly high flow perfusion regions. Even ignoring that they are fraught with volume averaging concerns, it would be no surprise that vascular and perivascular pulsations are greatest as overall arterial flow is also greatest with significant pulsations widely documented by transcranial ultrasound. Thus, the author’s data tell us nothing new. Furthermore, the author’s data tell us nothing about true tissue level oxygen level changes, nor does it tell us anything about CSF production. In fact, CSF production, which implies greater pulsatility, has been shown to be greatest in the very areas of no discernible pulsation using the author’s technique. This is well known to any imager who performs cisternography and has been reviewed in multiple publications. The authors should familiarize themselves with the review of Brinker et al on CSF movements.

Pulse gating: Why the authors chose to pulse gate rather than cardiac gate is obtuse. The consequences of pulse gating in CSF flow measurements have been quantitated by Bert et al but those results are untested in the methods used by the current authors, who themselves site the differences in pulse delay between the brain and the arm. Why add an unknown delay artifact into the reference pulse? ECG-gating would have made interpretation of the results clearly more meaningful.

Figure 7 is confusing. The authors should include a graph of the maxima and minima relative to the PPG signal so the reader does not have to laboriously cross reference. The authors need to quit using the term “opposite” without a figure shown opposite to what. This is just not good writing. The authors should include a comparison against many well-documented phase contrast flow measurements to confirm the validity of their technique.

The introduction does not flow well or set up the hypothesis to be tested by the authors. It weakly reviews other flow imaging techniques and this could be left out entirely. Instead, the introduction needs to better set up the author's hypothesis to be tested and how they test it. The first paragraph of the methods need to be moved to the introduction and rewritten.

Discussion: Page 17, paragraph beginning with "Rajna et al….." The statement "…cardia pulse has opposite effects on blood and CSF (Wagshul et al, 2006)… needs considerable clarification. What are the "opposite effects"? This broad claim contradicts the results of multiple CSF flow studies showing a very high correlation of CSF pulsations with ICA and VA pulsations, albeit in opposite directions, the net effect is increased flow out of the foramen magnum coinciding with arterial inflow into the brain. If this is the author's understanding, they should state so more clearly, rather than using ambiguous terms such as "opposite". Their use of this word is misguided in a number of paragraphs and should be replaced with more exact explanations. Clarity would be further improved in their discussions of "in and out" between blood and CSF. Are they referencing a voxel? Whole brain volume? The authors are often unclear whether they are discussing the divergence of a voxel, the curl of a volume, or movements in adjacent spaces.