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# An ICA Investigation into the Effect of Physiological Noise Correction on Dynamic Functional Network Connectivity and Meta-state Metrics

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***Abstract*— Physiological fluctuations such as cardiac pulsations (heart rate) and respiratory rhythm (breathing) have been studied in the resting state functional magnetic resonance imaging (rs-fMRI) studies as the potential sources of confounds in functional connectivity. Independent component analysis (ICA) provides a data driven approach to investigate functional connectivity at the network level. However, the effect of physiological noise correction on the dynamic of ICA-derived networks has not yet been studied. The goal of this study was to investigate the effect of retrospective correction of cardiorespiratory artifacts on the time-varying aspects of functional network connectivity. Blood oxygenation-level dependent (BOLD) rs-fMRI data were collected from healthy subjects using a 3.0T MRI scanner. Whole-brain dynamic functional network connectivity (dFNC) was computed using sliding time window correlation, and k-means clustering of windowed correlation matrices. Results showed significant effects of physiological denoising on dFNC between several network pairs in particular the subcortical, and cognitive/attention networks (false discovery rate [FDR]-corrected $p < 0.01$). Meta-state dynamics further revealed significant changes in the number of unique windows for each subject, number of times each subject changes from one meta-state to other, and sum of L1 distances between successive meta-states. In conclusion, removal of artifacts is important for achieving reliable fMRI results, however a more cautious approach should be adapted in regressing such "noise" in ICA functional connectivity approach. More experiments are needed to investigate impact of denoising on dFNC especially across different datasets.**

## I. INTRODUCTION

Brain functional connectivity, a technique that infers the connectivity among spatially remote brain regions by measuring the correlation (or other statistical dependency) has been gaining increasing popularity [1]. Recently, there is growing interest in studying functional connectivity among brain networks. Blind source separation techniques such as spatial independent component analysis (ICA), can decompose imaging data such as blood oxygen level-dependent functional magnetic resonance imaging (BOLD fMRI) signals, into a set of spatially segregated but temporally coherent brain networks [2]. Functional network connectivity (FNC) [3] measures the statistical correlations among these brain networks, which are often referred to as intrinsic connectivity networks (ICNs). Dynamic FNC (dFNC) [4] is a more recent extension of the FNC method, which takes into account the FNC changes over time as recent studies have demonstrated that resting state brain functional connectivity is particularly dynamic [4].

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One of the challenges in conventional functional connectivity methods especially in resting state fMRI (rs-fMRI) studies is that the BOLD signal measurements can be confounded by several cardiorespiratory processes such as cardiac pulsations, fluctuations in heart rate, and respiration volume [5]. One widely used approach to eliminate physiological noise is the retrospective image space correction of physiological noise (RETROICOR) [6], which uses a low-order Fourier transform to eliminate the components that correspond to the respiration, cardiac pulsation and their related harmonics. It has been shown that ICA decompositions are also capable of separating out different sources of artifact including physiological noise. Given that physiological denoising is becoming more and more common in preprocessing rs-fMRI data, it is important to examine how RETROICOR can impact fMRI data analysis that are conducted with ICA for the purpose other than artifact removal. Previously, we showed that ICN temporal properties such as BOLD power spectra and static FNC may suffer from physiological corrections by RETROICOR [7]. In this study we aim to examine the effect of physiological denoising on dFNC in a sample of healthy subjects. To this aim, brain activity, heartbeat, and respiration are measured during resting-state scan. We use group ICA [2] to decompose resting-state data into ICNs and estimate the time-varying functional connectivity by computing sliding time-window correlation, and k-means clustering of windowed correlation matrices [4]. Finally, we measure the temporal dynamic in both raw and denoised data using the meta-state approach recently introduced by Miller et al. [8].

## II. MATERIALS AND METHODS

### A. Sample and Data Acquisition

BOLD rs-fMRI data were collected from 22 right-handed healthy subjects (10 males, 12 females, mean age 37.73 $\pm$ 11.32 years). Written informed consent was obtained from all subjects in accordance with a protocol approved by the university IRB. Scans were acquired on a 3T GE Discovery scanner with 8-channel head coil (TR/TE = 2000/30 ms, field-of-view (FOV) = 22 cm$\times$22 cm, acquisition matrix = 64$\times$64, flip angle = 76$^o$, slice thickness = 4 mm, gap = 1 mm, 31 slices, sequential ascending acquisition). Subjects' heart beats were recorded using a pulse-oximeter placed on the left index finger. Respiration was measured with a MR-compatible plethysmograph. During the resting state scan, subjects were asked to relax with their eyes closed and refrain from sleeping or thinking of anything in particular.

### B. Data Preprocessing

Following the scan, two copies of the images were created. One copy was corrected for physiological noise prior to preprocessing using the RETROICOR algorithm [6] (denoised data), while the other copy was not (raw data). Both copies were preprocessed using SPM12 (Wellcome Department of Cognitive Neurology, UK). Images were motion and slice-time corrected, spatially normalized to MNI space, smoothed with 8 mm FWHM Gaussian kernel and intensity normalization was applied [1].

### C. Group ICA and post-processing

Data were decomposed into ICNs using Group ICA of fMRI Toolbox (GIFTv3.0c; University of New Mexico, USA). For better functional parcellation, a relatively high model order ICA (number of IC = 75) was used [1]. In the subject-specific data reduction step, 100 principal components (PCs) were retained using a standard economy-size decomposition. Group data reduction step retained 75 PCs using the expectation-maximization algorithm. The Infomax ICA algorithm was repeated 20 times in ICASSO software to estimate the reliability of the decomposition. Subject-specific spatial maps and corresponding time courses were estimated using the GICA3 back-reconstruction method. Time courses were post-processed by detrending and despiking using AFNI 3dDespike, then filtering between [0.01 and 0.15] Hz with a 5th order Butterworth filter.

### D. dFNC Estimation and Meta-states

dFNC was computed using the sliding window approach. Each rs-fMRI scan contained 360 volumes per subject resulting in time courses of 720 s (TR = 2 s) each. Tapered windows were created by convolving a rectangle (length = 22 TRs) with a Gaussian of $\sigma$ = 3 TRs. Using an L1 regularization, a window step size of 30 s (15 volumes) was implemented [4]. The dFNC windows resulting from the above process were then clustered using a k-means algorithm with a random initialization of the centroid positions and cosine distance was used to cluster the data into meta-states. The number of k-means clusters was estimated using gap statistic, and information criteria. To speed up the process, estimate clusters step was done only on subject exemplars. All 22 subjects were used in this step. dFNC properties, i.e., reoccurrence fraction, dwell time in each state, and total transition number between states, were calculate for each subject and for both raw and denoised data. The paired *t*-test was used to detect differences in dFNC properties between the raw and denoised data at the false discovery rate [FDR]-corrected threshold of 0.01. Furthermore, the meta-state dynamics method [8] was performed by reducing the number of windowed FNC correlations to a few (i.e., 8) components/clusters using k-means. The number of changes of meta-states, number of distinct meta-states, span of meta-states, i.e., maximum L1 distance between states for each subject and total distance, i.e., sum of L1 distances between successive meta-states for each subject were calculated for the raw vs. denoised data.

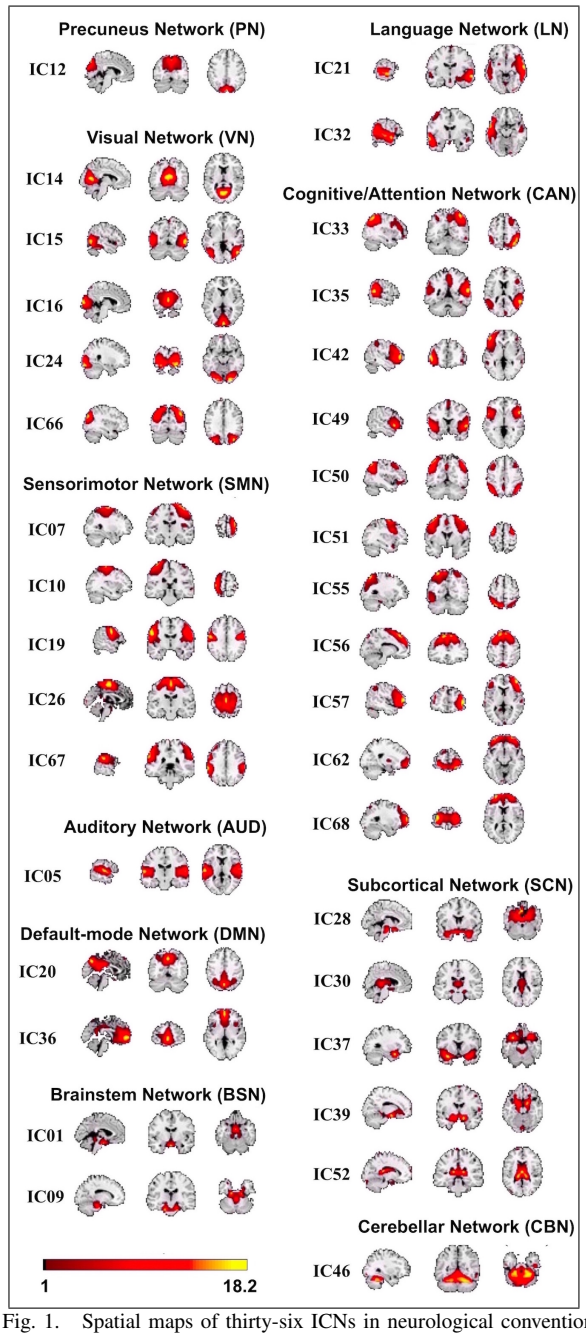


Fig. 1. Spatial maps of thirty-six ICNs in neurological convention

## III. RESULTS

Of 75 components, 36 were identified as ICNs (Fig. 1) using the procedures described in our earlier work [7], [9]. They are grouped by their anatomical and functional properties, which include the following: precuneus (PN), visual (VN), sensorimotor (SMN), auditory (AUD), default-mode (DMN), language (LN), cognitive/attention (CAN), sub-cortical (SCN), and cerebellar (CBN) networks. The observed ICNs are similar to those found in previous studies with high model order ICA [1]. Time-courses of these 36 ICNs were used to compute dFNC matrices. Optical number of dFNC clusters was estimated to be 10 using the Gap, the Bayesian information criterion (BIC), and Akaïke information criterion (AIC) (Fig. 2).

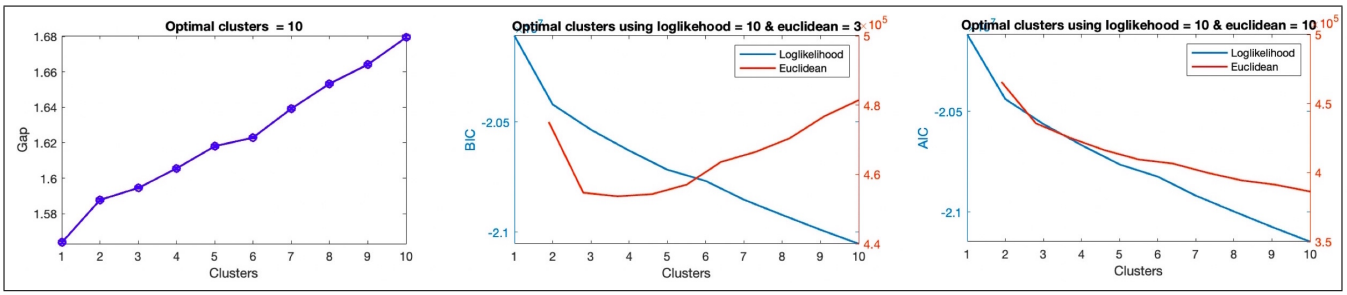


Fig. 2. dFNC Cluster estimation using Gap, Bayesian information criterion (BIC), and Akaïke information criterion (AIC)

The dynamic states obtained from k-means clustering of all datasets, averaged across all 10 cross-validation folds, number of cluster occurrences for states 1 – 10 using 100 bootstrap iterations, frequency of each cluster, mean dwell time in windows and mean of state transition matrix across subjects are showed in Fig. 3. Different state vectors were observed for raw (Fig. 4A) and denoised (Fig. 4B) data in some subjects. Cluster mean correlations and cluster paired *t*-test results of raw vs. denoised at FDR-corrected *p*-value of 0.01 is shown in Fig. 5. Differences in mean dwell time in windows vs. cluster states are shown in Fig. 6. Number of subjects with finite correlations (n) is also shown. Results of meta-state analysis using k-means are listed in Table 1.

TABLE 1

META STATE: PAIRED T-TEST BETWEEN RAW AND DENOISED

| | T-value | P-value | Mean of Raw | Mean of Denoised |
|---|---|---|---|---|
| Number of States | -2.7216 | **0.0128*** | 45.7273 | 52.9545 |
| Change Between States | -3.7336 | **0.0012*** | 58.7727 | 67.5000 |
| State Span | -1.2169 | 0.2371 | 12.7273 | 13.6364 |
| Total distance | -4.4985 | **0.0002*** | 66.0000 | 78.1364 |

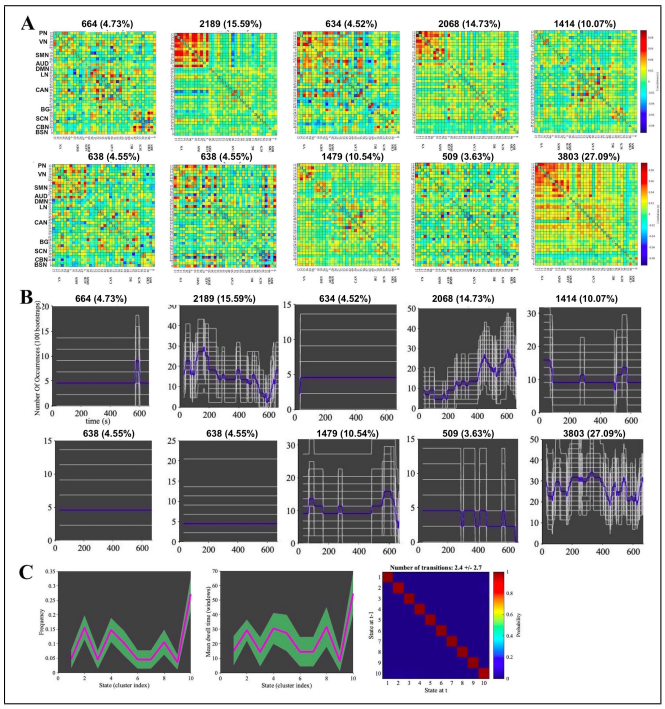


Fig. 3. **A** The dynamic states obtained from k-means clustering **B** Number of cluster occurrences using 100 bootstrap iterations **C** Plots showing (from left to right) frequency of each cluster, mean dwell time in windows, mean of state transition matrix across subjects.

## IV. CONCLUSION

Results revealed that denoising induces significant changes in time-varying whole-brain network connectivity patterns. Changes were observed in dFNC across a wide range of ICNs including the default-mode, subcortical, and a variety of cognitive/attention networks when raw data were compared with the denoised data. Additional analyses on inspecting meta-states showed a significant difference in (i) the number of changes of meta-states, i.e., how often does a subject switch between distinct meta-states, (ii) the number of distinct meta-states, i.e., how many unique distance vectors are present in an individual and (iii) the total distance travelled through the meta-state space between raw and denoised data. Removal of artifacts are important for achieving reliable fMRI results, however a more cautious approach should be adapted in regressing such "noise" in ICA functional connectivity approaches especially if there is any overlap between two sources in the filtering and ICA domain. More research is still needed on effect of denoising.

## REFERENCES


[1] E. A. Allen, E. B. Erhardt, Damaraju, *et al.*, "A baseline for the multivariate comparison of resting-state networks," *Frontiers in systems neuroscience*, vol. 5, 2011.

[2] V. Calhoun, T. Adali, G. Pearlson, and J. Pekar, "A method for making group inferences from functional mri data using independent component analysis," *Human brain mapping*, vol. 14, no. 3, pp. 140–151, 2001.

[3] M. J. Jafri, G. D. Pearlson, M. Stevens, and V. D. Calhoun, "A method for functional network connectivity among spatially independent resting-state components in schizophrenia," *Neuroimage*, vol. 39, no. 4, pp. 1666–1681, 2008.

[4] E. A. Allen, E. Damaraju, S. M. Plis, E. B. Erhardt, T. Eichele, and V. D. Calhoun, "Tracking whole-brain connectivity dynamics in the resting state," *Cerebral cortex*, vol. 24, no. 3, pp. 663–676, 2014.

[5] R. M. Birn, J. B. Diamond, M. A. Smith, and P. A. Bandettini, "Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fmri," *Neuroimage*, vol. 31, no. 4, pp. 1536–1548, 2006.

[6] G. H. Glover, T.-Q. Li, and D. Ress, "Image-based method for retrospective correction of physiological motion effects in fmri: Retroicor," *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, vol. 44, no. 1, pp. 162–167, 2000.

[7] B. Jarrahi and S. Mackey, "Measuring the influence of physiological noise corrections on ica derived intrinsic connectivity brain networks in rest and task fmri," in *2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. IEEE, 2018, pp. 1046–1049.

[8] R. L. Miller, M. Yaesoubi, J. A. Turner, D. Mathalon, A. Preda, G. Pearlson, T. Adali, and V. D. Calhoun, "Higher dimensional meta-state analysis reveals reduced resting fmri connectivity dynamism in schizophrenia patients," *PloS one*, vol. 11, no. 3, p. e0149849, 2016.

[9] B. Jarrahi and D. Mantini, "The nature of the task influences intrinsic connectivity networks: An exploratory fmri study in healthy subjects," in *2019 9th International IEEE/EMBS Conference on Neural Engineering (NER)*. IEEE, 2019, pp. 489–493.

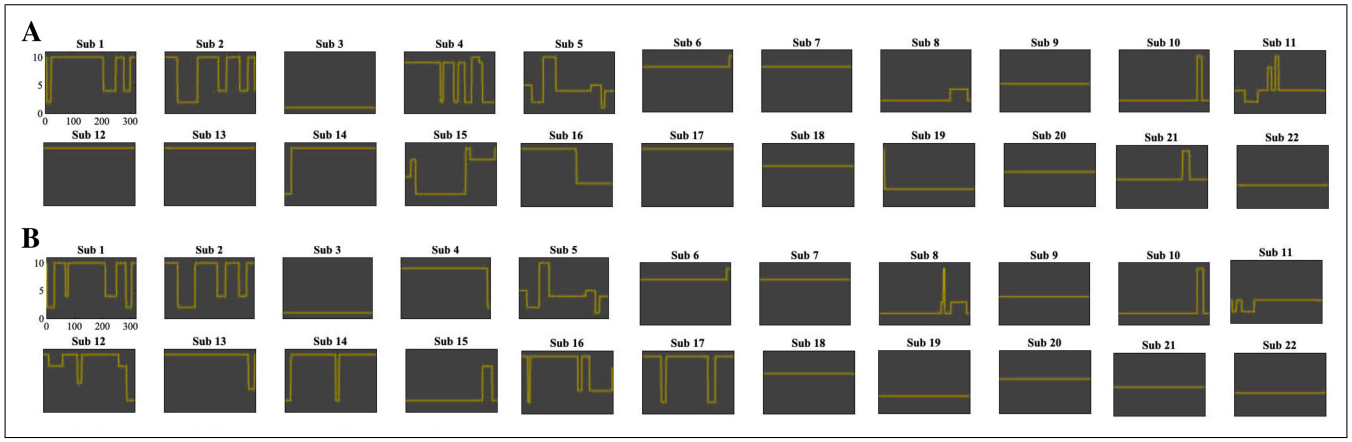


Fig. 4. State vectors for **A** raw data **B** denoised data

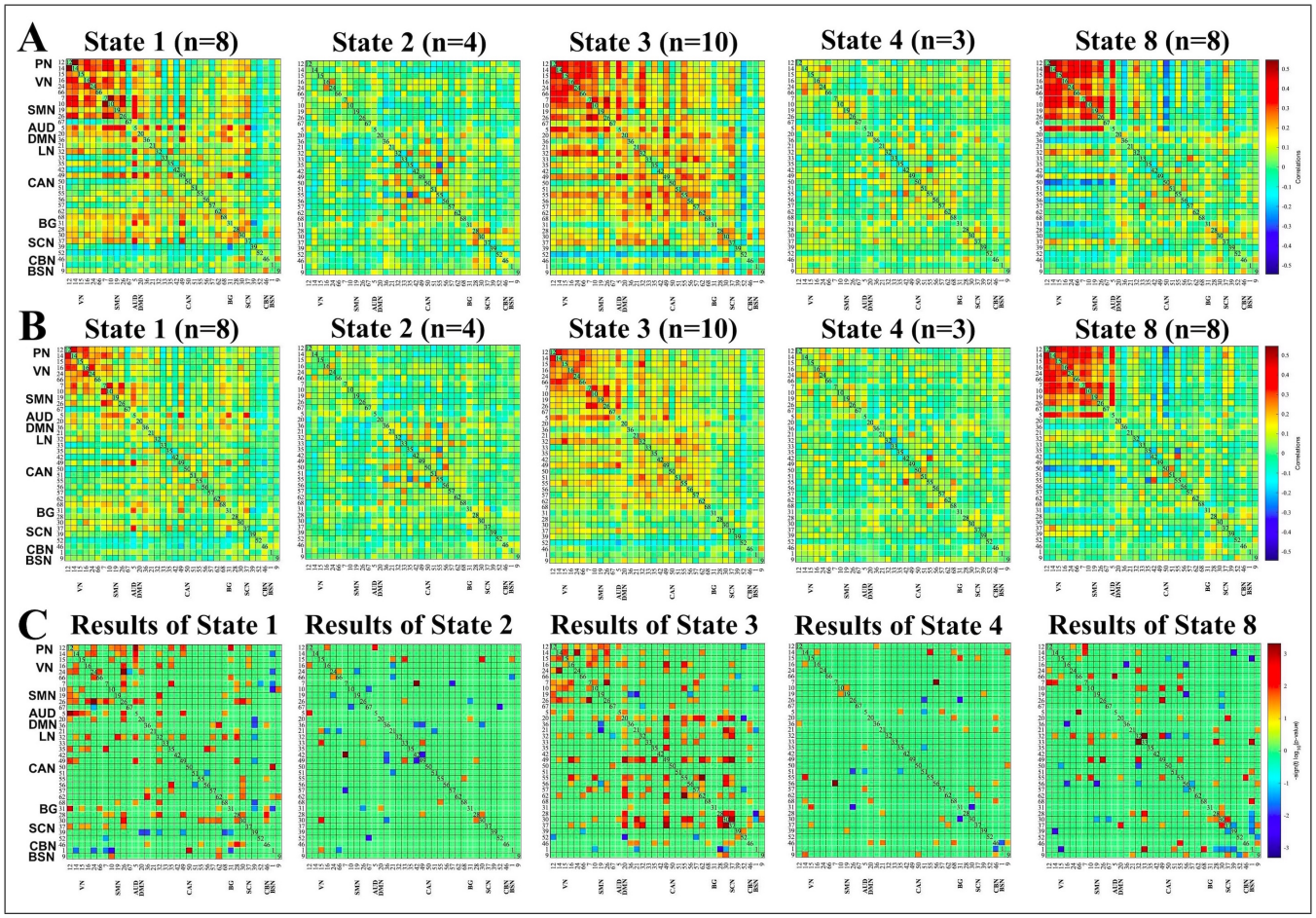


Fig. 5. **A** Cluster mean correlations of raw data, **B** Cluster mean correlations of denoised data, **C** Cluster paired *t*-test results of raw – denoised data. (FDR-corrected $p < 0.01$). n = Number of subjects with finite correlations.

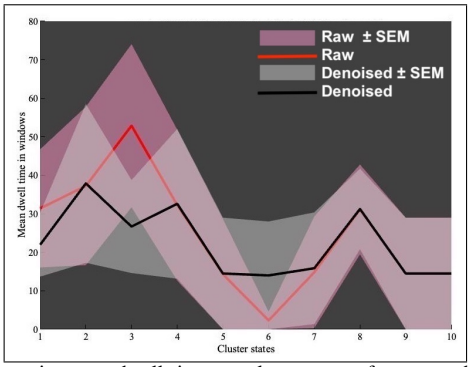


Fig. 6. Differences in mean dwell time vs. cluster states for raw and denoised datasets