DETECTION OF CONSISTENT COGNITIVE PROCESSING AT THE SINGLE SUBJECT LEVEL USING WHOLE-BRAIN FMRI CONNECTIVITY

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INTRODUCTION

Recent studies have demonstrated that resting state fMRI (rs-fMRI) connectivity patterns are dynamic in nature; and that significant changes in the strength and distribution of connections occur as scanning progresses [1,2,3]. Consequently, connectivity patterns obtained using one portion of a scan (e.g., first 2 mins) may differ greatly from patterns observed using the rest of the data or when the whole scan is used at once. In particular, there are three main observations reported with respect to rs-fMRI connectivity dynamics so far: (1) rs-fMRI connectivity changes substantially in the scale of seconds to minutes [1]; (2) changes occur both during awake and anesthetized conditions [3]; and (3) a certain level of recurrent structure can be found, with a limited set of connectivity configurations (functional connectivity states; FC states) being stable for short durations, and recurring in time and across subjects [4]. These observations pose important questions regarding the biological significance and interpretation of rs-fMRI dynamics at these shorter time scales.

Of particular interest is the potential relationship between FC states and cognition. It has been previously shown that a classifier could differentiate between four different cognitive states on the basis of whole-brain connectivity [5]. Accuracies as high as 80% were reported for time windows as short at 60 s. Nonetheless, the methods described in that work are not suitable for evaluating the relationship between FC and cognitive state in rs-fMRI due to the need for: (1) a training dataset, (2) a-priori information about informative connections, and a (3) well-defined/limited search domain of cognitive states. Here we describe and evaluate an alternative data driven approach based on K-means clustering that does not have any of the restrictions enumerated above.

In order to further elucidate the strength of the relationship between FC states and cognitive states, and also to evaluate the validity of our method, 18 participants were scanned continuously while engaging in and transitioning between a limited set of tasks (rest, math, memory recollection and visual attention). This setup constrains the cognitive states of participants so that FC states can be compared with the "ground truth" established by the experimental paradigm. Our results show that connectivity patterns contain sufficient information to correctly classify time-periods according to ongoing mental processes for windows as short as 30 s. Moreover, for 15s windows, decreases in accuracy correlate with lack of consistency in response time across task blocks. Our results also show that methodology may substantially affect results, and we provide some guidelines on how to best process the data.

METHODS (Data Acquisition)

Imaging was performed on a Siemens 7T MRI scanner equipped with a 32-element receive coil (Nova Medical, Wilmington, MA). Functional runs were obtained using a gradient-recalled, single-shot, echo planar imaging (EPI) sequence (TR = 1.5 s, TE = 25 ms, FA = 50°, 40 oblique slices, slice thickness = 2 mm, spacing = 0.2 - 0.3 mm, in-plane resolution = 2 × 2 mm, field-of-view (FOV) = 192 mm, acceleration factor (GRAPPA) = 2). T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) data were also acquired for presentation and alignment purposes (axial prescription, number of slices per slab = 192, slice thickness = 1 mm, square FOV = 256 mm, image matrix = 256 × 256).

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METHODS (Experimental Paradigm & Data Analysis)

FIGURE 1 **EXPERIMENTAL PARADIGM.** Subjects were scanned for approximately 25 minutes as they performed and transitioned between four distinct mental tasks: undirected rest (REST), 2-back memory task (2BACK), simple mathematical computations (MATH), and a spatial visual attention task (VIDEO). Each task was performed for 3 mins on two different occasions within the 25 mins of scanning.

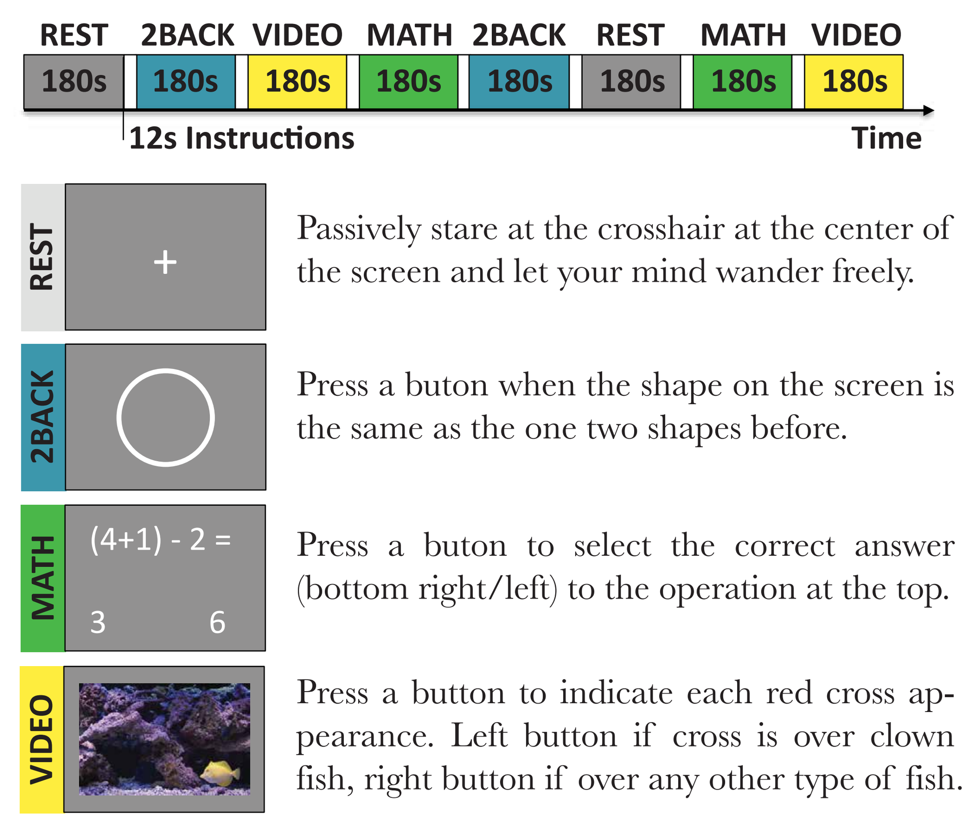
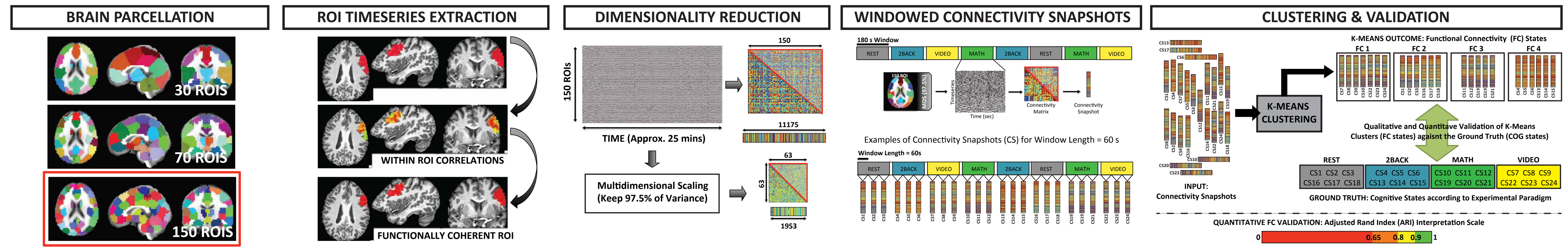


FIGURE 2 **ANALYSIS PIPELINE.** Data pre-processing was conducted with AFNI. Pre-processing steps included: (i) despike, (ii) physiological noise correction (except in two subjects); (iii) slice-time correction, (iv) head motion correction, (iv) removal of local white matter signal, CSF signal, motion and first derivative of motion, (v) intensity normalization; (vi) bandpass filtering ([0.001 - 0.2] Hz), (vi) spatial smoothing (FWHM = 4mm). For each subject, transformation matrices to go between MNI, anatomical and EPI space were computed in order to bring functional parcellations from the Craddock atlas [6] into each subject EPI space. The analysis pipeline used to evaluate the relationship bewteen FC and COG states is depicted below.



The Craddock atlas [6] was used to obtain sets of functionally defined ROIs at different spatial scales. ROIs at different scales (30, 70, and 150) were brought into alignment with each subject's functional data. Main analysis was conducted with the 150 ROI atlas. Other atlases were used to evaluate the effect of spatial specifcity on the classification.

Each ROI was first brought into each subject space. Timeseries for each ROI were then extracted using only the voxels that were most highly correlated to each other within the ROI. In this way, we compute timeseries using only most functionaly coherent voxels and reduce potential confounds associated with using non-invididualized atlases.

A 150 ROI atlas produces 11175 connections or feautures defining the connectivity of the brain at any given moment. This highly dimensional space is difficult to classify. Multidimensional scaling (MDS) was used to reduce the dimensionality of this space while keeping most of the variance (97.5%). After applying MDS, only 63 timeseries and 1953 connections remain on average.

We computed connectivity snapshots (CS) using Pearson's correlation. These CS include information about how the brain is interconnected at a given moment in time using different window lengths (180s, 90s, 60s, 45s, 30s, 15s). The windows were aligned with the experimental paradigm, so that for each window we know the subject was engaged in a given cognitive state. The snapshots contain the connectivity between the timeseries resulting from the MDS step.

The CS for the different windows were input to a K-means algorithm that grouped them into four functional connectivity states (FC states). No information about paradigm timing enters the algorithm. To evaluate the relationship between FC and cognitive states, we compared the K-means output to how CS should be grouped based on the timing of the experiment (ground truth). We used the adjusted rand index (ARI) to quantify this similarity [7]. This metric is commonly used in the clustering literature, and has a clear interpretation ([0-0.65]: Poor recovery of real groups; [0.66 - 0.8]: moderate recovery; [0.81 - 0.9]: good recovery; [0.91 - 1]: excellent recovery).

RESULTS

BEHAVIORAL RESULTS. Tables show average response time (RT) and response accuracy (RA) for all subjects in each task block. The row labeled Δ shows the difference in absolute value across blocks for each metric and task. Averages across all subjects are also shown. Faster and more accurate responses occurred for the 2BACK task. Slower response times happened for the MATH task, while the task with the lowest accuracy was the VIDEO task. All subjects were compliant with the tasks, however variability in RT and RA across subject exists. We use this variability to further test the relationship between FC and cognitive states. (Fig. 3.B)

RESPONSE TIME (RT) [secs]

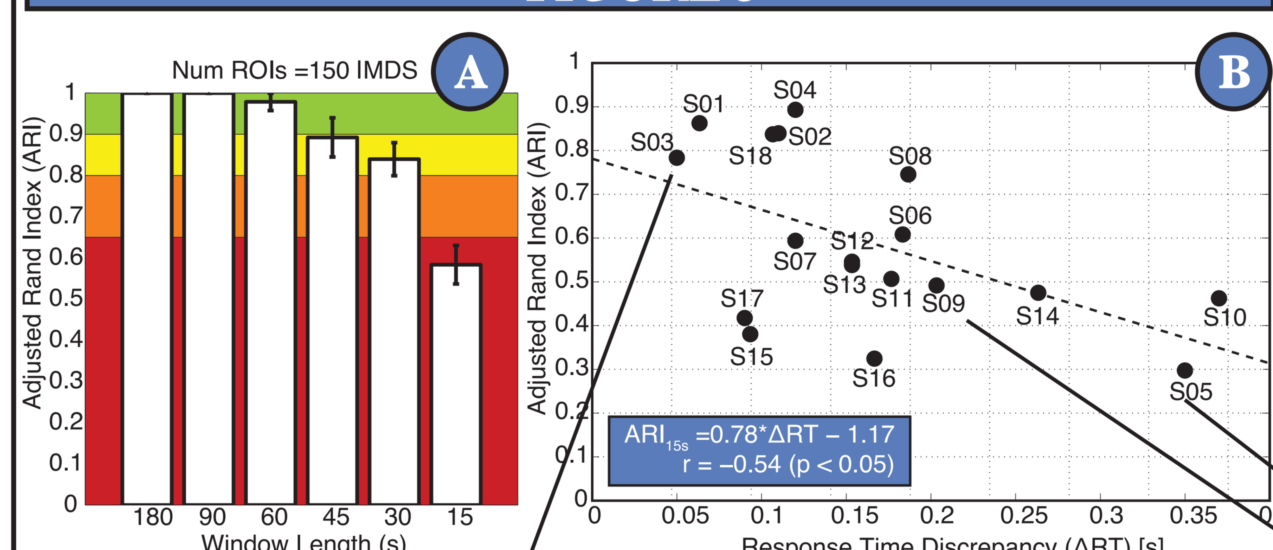
SUBJECT		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	AVERAGE
2BACK	BLOCK A	0.51	0.82	0.57	0.52	0.87	0.52	0.46	0.43	0.61	0.72	0.56	0.68	0.89	0.69	1.18	0.77	0.52	1.01	**0.68**
	BLOCK B	0.43	0.90	0.56	0.65	1.26	0.48	0.44	0.42	0.43	0.80	0.78	0.77	0.81	0.86	1.16	1.00	0.47	1.13	**0.74**
	Δ	0.08	0.08	0.01	0.13	0.39	0.04	0.02	0.01	0.18	0.08	0.22	0.09	0.08	0.17	0.02	0.23	0.05	0.12	**0.11**
MATH	BLOCK A	2.73	1.90	1.89	2.49	3.40	2.00	2.50	2.21	1.96	2.11	2.75	2.40	1.59	2.30	2.49	2.75	1.78	2.08	**2.30**
	BLOCK B	2.73	1.99	1.99	2.62	3.81	2.38	2.81	2.63	2.30	2.38	2.94	2.72	1.91	2.71	2.68	2.59	1.99	2.24	**2.52**
	Δ	0.00	0.09	0.10	0.13	0.41	0.38	0.31	0.42	0.34	0.27	0.19	0.32	0.32	0.41	0.19	0.16	0.21	0.16	**0.25**
VIDEO	BLOCK A	1.00	1.33	1.30	1.17	1.18	1.19	1.17	1.14	1.10	1.10	1.01	1.17	0.98	1.08	1.25	1.33	1.07	1.30	**1.16**
	BLOCK B	0.89	1.49	1.34	1.07	1.43	1.06	1.14	1.01	1.01	0.34	1.13	1.12	1.04	0.88	1.32	1.44	1.06	1.26	**1.11**
	Δ	0.11	0.16	0.04	0.10	0.25	0.13	0.03	0.13	0.09	0.76	0.12	0.05	0.06	0.20	0.07	0.11	0.01	0.04	**0.14**

RESPONSE ACURACY [% Correct]

SUBJECT		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	AVERAGE
2BACK	BLOCK A	93.33	96.67	96.67	83.33	81.67	96.67	100.00	96.67	95.00	98.33	91.67	90.00	86.67	96.67	73.33	86.67	100.00	95.00	**92.13**
	BLOCK B	96.67	100.00	98.33	96.66	81.67	98.33	100.00	95.00	100.00	98.33	81.67	91.67	85.00	90.00	81.67	85.00	98.33	93.33	**92.87**
	Δ	3.34	3.33	1.66	13.33	0.00	1.66	0.00	1.67	5.00	0.00	10.00	1.67	1.67	6.67	8.34	1.67	1.67	1.67	**3.52**
MATH	BLOCK A	88.89	100.00	94.44	88.89	91.67	97.22	100.00	91.67	100.00	100.00	91.67	100.00	100.00	100.00	94.44	88.89	100.00	100.00	**95.99**
	BLOCK B	86.11	97.22	100.00	80.56	66.67	97.22	97.22	86.11	100.00	97.22	75.00	91.67	100.00	80.56	91.67	80.56	97.22	100.00	**90.28**
	Δ	2.78	2.78	5.56	8.33	25.00	0.00	2.78	5.56	0.00	2.78	16.67	8.33	0.00	19.44	2.77	8.33	2.78	0.00	**6.33**
VIDEO	BLOCK A	62.50	75.00	62.50	68.75	18.75	81.25	87.50	62.50	87.50	87.50	75.00	81.25	81.25	68.75	81.25	50.00	75.00	56.25	**70.14**
	BLOCK B	100.00	50.00	75.00	75.00	31.25	68.75	81.25	87.50	87.50	81.30	87.50	68.80	81.25	18.75	62.50	25.00	87.50	81.25	**69.45**
	Δ	37.50	25.00	12.50	6.25	12.50	12.50	6.25	25.00	0.00	6.20	12.50	12.45	0.00	50.00	18.75	25.00	12.50	25.00	**16.66**

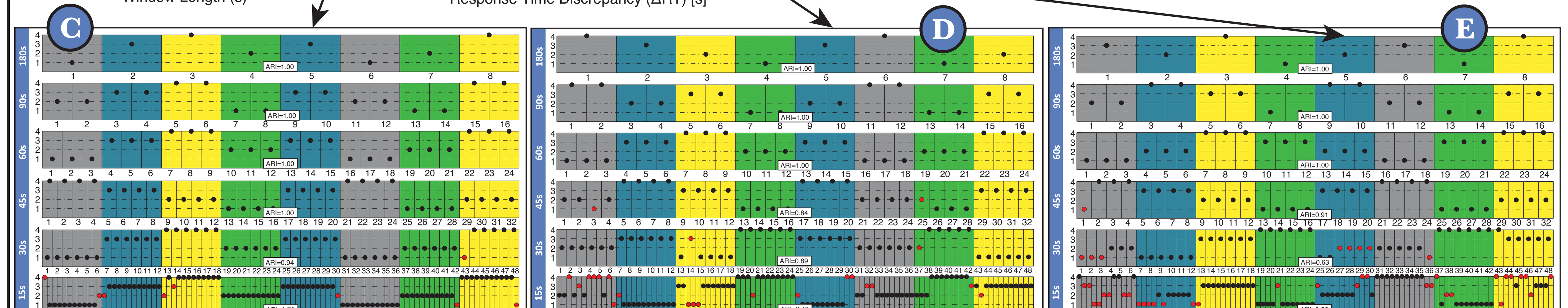
RELATIONSHIP BETWEEN FC AND COGNITIVE STATES. Figure 3.A shows average ARI across all subjects for different window durations. Background colors represent the criteria for interpretation of the ARI metric (green = excellent recovery; yellow = good recovery; orange = moderate recovery; red = poor recovery). Recovery of cognitive states was excellent for window durations longer than 45s. Recovery decreases monotonically with window duration, and goes into poor recovery for 15 s windows only. Figure 3.B shows there is a relatonship between ARI for 15s windows and average discrepancy in RT across task blocks (see formula below). In particular, the greater the difference in RT across blocks (which can be considered a proxy for consistency on how subjects performed the task), the lower the ARI (effectiveness in properly recovering cognitive states).

FIGURE 3



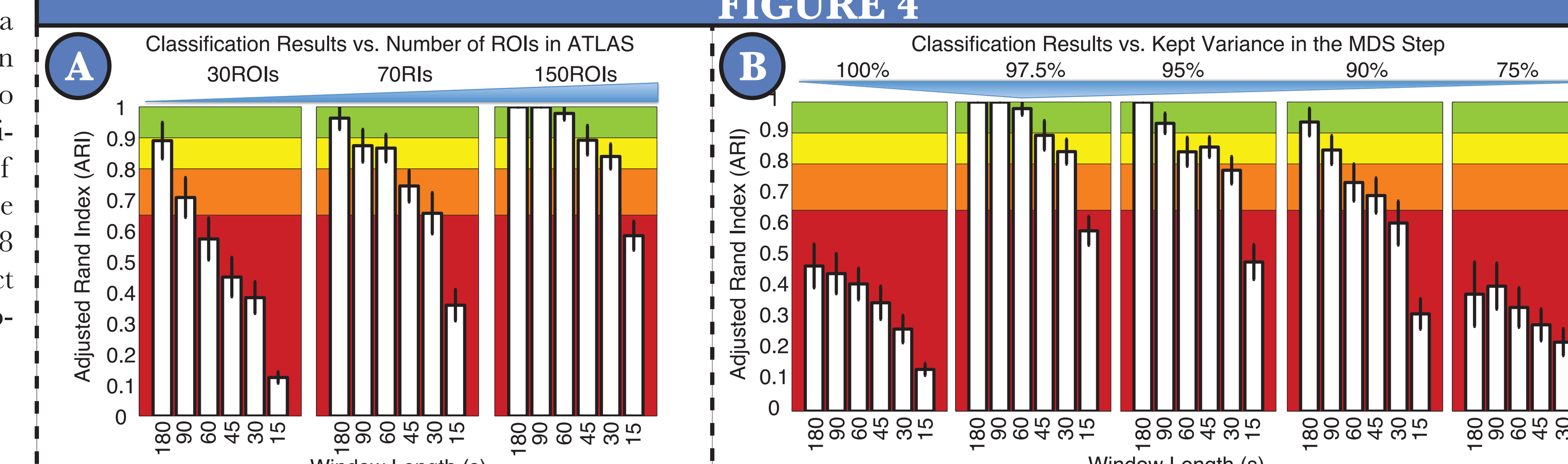
Figures 3.C-E show cognitive states detection results for three representative subjects. For each subject we show results for all window durations. Each window is represented as a vertical brick whose color represents the cognitive state it belongs to (gray = REST, green = MATH, etc.). Each window has a dot (black = correct, red = incorrect) that signifies to which FC state (1, 2, 3 or 4) the window was assigned by the K-means algorithm. In addition, the ARI for each condition is reported in a white box. Fig 3.C shows result for one of the best subjects. For windows longer than 30s, FC and cognitve states show a one-to-one relationship which translated into an ARI =1. For the 96 available 15 s windows, only 8 were misclassified (red dots), bringing the ARI down to 0.78. Figure 3.D shows a subject for whom the classification worked moderately well at 15 s, and Figure 3.E shows the subject with the worse results at this window duration.

$$\Delta RT = (|RT_{math,1} - RT_{math,2}| + |RT_{2back,1} - RT_{2back,2}| + |RT_{video,1} - RT_{video,2}|)/3$$



HOW METHODS AFFECT RESULTS. Figures 4.A-B show how the goodness of empirical relationships between FC and cognitive states depends substantially on analysis methods. In particular, Figure 4.A shows how the ARI changes as a function of the number of ROIs in the atlas. Data suggest an atlas with a greater number of smaller ROIs performs better than an altas with a small number of large ROIs. In Figure 4.B, we show how the ARI changes as a function of the amount of vairance kept at the dimensionality reduction step. Not perfoming this step (100% variance kept) heavily degreades classification. Excessive dimensionality reduction also affects negatively the classification; most likely due to discaring of too much valuable information.

FIGURE 4



CONCLUSIONS

DIRECT RELATIONSHIPS BETWEEN FC STATES AND COGNITIVE STATES WERE DISCOVERED AT THE SINGLE SUBJECT LEVEL WITHOUT THE NEED TO TRAIN A CLASSIFIER:

* Cognitive states were recovered robustly for windows as short as 30s.
* Worse recovery of cognitive states for 15 s windows can be partially explained by behavioral covariates.
* Limitation: the number of cognitive states needs to be set by the experimenter. Future work: extract these from the data.

METHODOLOGICAL DECISIONS AFFECT THE STRENGTH OF THE RELATIONSHIPS FOUND BETWEEN FC AND CONGNITIVE STATES:

* Atlas Selection affects. Better to use more and smaller ROIs
* Moderate Dimensionality Reduction improved results considerably. Excessive dimensionality reduction worsened results.