

## Estimating brain network activity through back-projection of ICA components to GLM maps



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### HIGHLIGHTS

- ICA traditionally back-projects component betas to fMRI data then estimates GLM.
- We instead back-projected ICA components to the GLMs, with identical results.
- Neuroimaging publications typically report component *t*-scores but not betas.
- We obtained different results when back-projecting component *t*-scores vs. betas.
- Replication of ICA components should use betas rather than *t*-scores.

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### ABSTRACT

Independent component analysis (ICA) is a data-driven approach frequently used in neuroimaging to model functional brain networks. Despite ICA's increasing popularity, methods for replicating published ICA components across independent datasets have been underemphasized. Traditionally, the task-dependent activation of a component is evaluated by first back-projecting the component to a functional MRI (fMRI) dataset, then performing general linear modeling (GLM) on the resulting time-course. We propose the alternative approach of back-projecting the component directly to univariate GLM results. Using a sample of 37 participants performing the Multi-Source Interference Task, we demonstrate these two approaches to yield identical results. Furthermore, while replicating an ICA component requires back-projection of component beta-values ( $\beta$ s), components are typically depicted only by *t*-scores. We show that while back-projection of component  $\beta$ s and *t*-scores yielded highly correlated results ( $\rho = 0.95$ ), group-level statistics differed between the two methods. We conclude by stressing the importance of reporting ICA component  $\beta$ s, rather than component *t*-scores, so that functional networks may be independently replicated across datasets.

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### Introduction

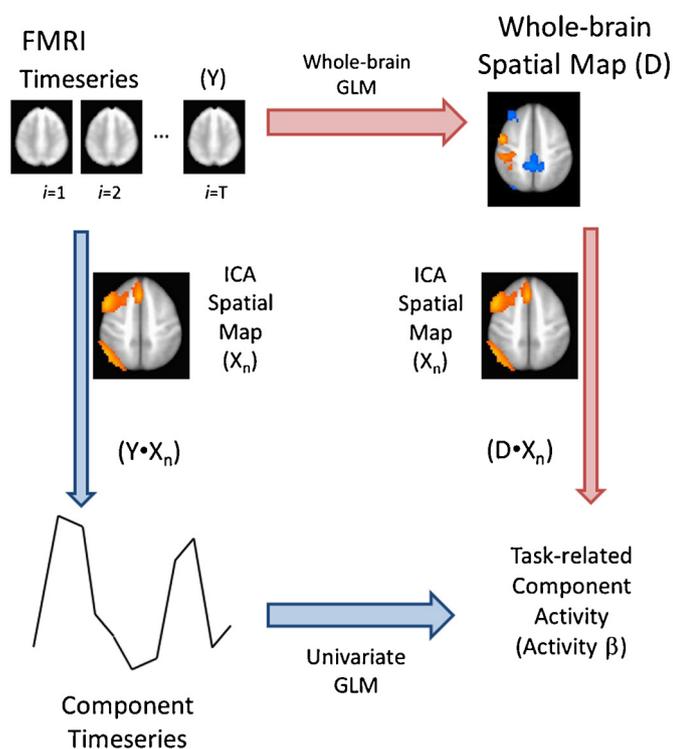
Independent component analysis (ICA) is a statistical approach for blind separation of a composite multivariate signal into its constituent source signals. ICA has been broadly used in functional magnetic resonance imaging (fMRI) to identify task-activated brain networks [1–4]. ICA is frequently followed with general linear modeling (GLM) to assess how these ICA-identified networks are recruited by fMRI tasks [5,6]. As a data-driven approach, ICA does not require *a priori* information about the source signals to identify them; it has thus been used to identify brain networks in the absence of task (i.e. during wakeful rest) in independent

samples [7–9]. Disruptions of these “resting-state networks” have been attributed to numerous disorders including schizophrenia, Alzheimer's disease, and epilepsy [10–12].

The growth of data-sharing initiatives such as the 1000 Functional Connectomes Project and International Neuroimaging Data-sharing Initiative has allowed replication of ICA-derived networks in independent datasets. For example, one may hypothesize that an anterior cingulate network identified from the Stroop task [13] is also recruited by the Flanker task [14]. To test this hypothesis, the cingulate network's task-related activity could be assessed by back-projecting the component beta-values (component  $\beta$ s) to a participant fMRI dataset, effectively weighting each timepoint by the component. GLM of this weighted dataset would then provide an activity beta-value (activity  $\beta$ s) describing that component's task-related activation.

However, two barriers impede the replication of ICA-derived networks. First, this approach requires participants' fMRI datasets. These datasets may not be accessible due to confidentiality issues,

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**Fig. 1.** Overview of methodological approach. (Blue arrows, proceeding counter-clockwise from top left) Task-based recruitment of an ICA component is traditionally assessed by first back-projecting the ICA spatial map (via multiplication with the  $n$ th ICA component's spatial map) to each timepoint in the fMRI timeseries, thus generating a 1D timeseries weighted by the component. Univariate GLM then determines an activity beta-value (activity  $\beta$ s) and  $t$ -score describing that component's recruitment by one or more task contrasts. (Red arrows, proceeding clockwise from top left) We propose an alternative approach whereby the fMRI timeseries undergoes whole-brain GLM to generate a spatial map for each GLM contrast. The ICA component is then back-projected (again via multiplication) to produce activity  $\beta$ s for that component. Abbreviations: ICA, independent component analysis; fMRI, functional MRI; 1D, one-dimensional; GLM, general linear modeling. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

and back-projection of ICA components to these datasets can be computationally intensive (particularly for sample sizes  $>100$ ). Second, back-projection should be conducted using component  $\beta$ s, but the neuroimaging field traditionally depicts components by  $t$ -scores (describing the significance of  $\beta$ s) and rarely reports the  $\beta$ s themselves. While component beta-values and  $t$ -scores are generally positively correlated, a voxel could have a small yet highly significant contribution to the component—or conversely, a large yet non-significant contribution.

To address the first issue, we propose an alternative approach of directly back-projecting components to univariate (voxelwise) GLM maps, as depicted in Fig. 1. Traditionally, the relationship between component and task is determined by (1) back-projecting the component to participant fMRI data to generate a weighted timecourse for that component and (2) using GLM to determine if component activity significantly relates to task [5]. We propose (1) first assessing task-related activity of participant's fMRI data with GLM, then (2) back-projecting the ICA component to the resulting GLM map to assess task-related component activity. We assessed the feasibility of our approach by comparing group-level results obtained by each method. To address the second issue, we contrasted results obtained through traditional back-projection of components using (1) voxel beta values or (2) voxel  $t$ -statistics.

## Methods

### Participants

Thirty-seven participants (mean  $\pm$  sd age =  $31 \pm 9.9$  years; 15 male, 22 female; 21 self-reported as Caucasian, 14 African-American, 1 Hispanic, and 1 as bi-racial; 35 right-handed and 2 left-handed) were selected from participants recruited for a parent study, the Cognitive Connectome Project. Participants were recruited via community advertisements in accordance with University of Arkansas for Medical Sciences Institutional Review Board approval and oversight. Inclusion criteria for the study were healthy men and women, ages 18–50 years, without histories of psychiatric or neurologic illness and who were native English speakers with at least an 8th grade reading and writing proficiency. Exclusion criteria included the presence of psychiatric disorders (with the exception of nicotine dependence) as determined by structured clinical interview (SCID-NP), and contraindications to the high-field MRI environment, such as ferromagnetic implants (determined through a medical history) and pregnancy (determined through a urinalysis).

### Procedures

All procedures were conducted in the Brain Imaging Research Center at the Psychiatric Research Institute of the University of Arkansas for Medical Sciences. The Cognitive Connectome Project consists of two MRI sessions (1 h each), a battery of computerized assessments (1 h) and a comprehensive neuropsychological assessment (3–4 h). For this work, we analyze data acquired from the Multi-Source Interference Task (MSIT) [15]. Of the 48 participants recruited for the Cognitive connectome project, 37 were included in these analyses; 11 participants were excluded for not completing the MSIT scan ( $n=1$ ), not reporting handedness ( $n=2$ ), having poor spatial coverage of the brain ( $n=4$ ), or having excessive head motion ( $n=4$ ).

### Image acquisition

Participants were scanned using a Philips 3T Achieva X-series MRI scanner (Philips Healthcare, USA). Anatomic images were acquired with a magnetization prepared gradient echo (MPRAGE) sequence (matrix =  $256 \times 256$ , 160 sagittal slices, repetition time (TR) = 2600 ms, echo time (TE) = 3.05 ms, flip angle (FA) =  $8^\circ$ , final resolution =  $1 \times 1 \times 1$  mm $^3$ ). Functional images were acquired for the first 22 participants using an 8-channel head coil with an echo planar imaging sequence [TR/TE/FA = 2000 ms/30 ms/ $90^\circ$ , field of view =  $240 \times 240$  mm, matrix =  $80 \times 80$ , 37 oblique slices (parallel to orbitofrontal cortex to reduce sinus artifact), slice thickness = 4 mm, interleaved slice acquisition, final resolution  $3 \times 3 \times 4$  mm $^3$ ]. Functional data were acquired on remaining 14 participants after an equipment upgrade to a 32-channel head coil using the same parameters, except thinner slices (slice thickness = 2.5 mm with 0.5 mm gap) and sequential ascending slice acquisition to reduce orbitofrontal signal loss due to sinus cavity artifact.

### MSIT

The MSIT was administered as previously described by [15]. For each trial, participants viewed a row of three numbers, two of which were identical. Participants indicated which number differed from the other two by pressing a button corresponding to the number's location (right index, middle, or ring fingers for "1", "2", or "3", respectively). For Congruent trials, the target number's identity matched its location, and all distracter (non-target) numbers were zeros (i.e. "100", "020" or "003"). For Incongruent trials, the target

number's identity (1, 2, or 3) did not correspond to its position, and the distracter numbers were also 1s, 2s, or 3s (e.g. "211", "232", "331", etc.). Participants practiced the task to proficiency outside of the MRI scanner prior to performing it inside the scanner.

Stimuli were presented as a block design using Presentation 14.4 (Neurobehavioral Systems Inc.). Each trial lasted approximately 2000 ms and began with a stimulus presentation, lasting for 1750 ms or until participants responded, followed by a fixation cross shown for the remainder of trial. Congruent (Con) and Incongruent (Incon) trials were presented in 4 blocks of 24 trials (48 s) each, along with three 30 s Rest blocks. During Rest blocks, participants were instructed to fixate their gaze upon a centrally presented fixation cross and wait for the next trial. The experimental block order was Rest-Con-Incon-Con-Incon-Rest-Con-Incon-Con-Incon-Rest, for a total duration of 480 s (8 min).

### fMRI data preprocessing

Unless otherwise noted, all MRI data preprocessing was performed as previously described [6] using AFNI version 2011.12.21.1014 [16]. Anatomic data underwent skull stripping, spatial normalization to the icbm452 brain atlas, and segmentation into white matter, gray matter, and cerebrospinal fluid with FSL [17]. Functional data underwent despiking, slice timing correction, deobliquing (to  $3 \times 3 \times 3$  mm<sup>3</sup> voxels), motion correction, transformation to the spatially normalized anatomic image, regression of motion parameters, mean timecourse of white matter voxels, and mean timecourse of cerebrospinal fluid voxels, spatial smoothing with a 6 mm full-width-half-maximum Gaussian kernel, scaling to percent signal change, and identification and removal of motion-related noise components with Group ICA of fMRI Toolbox (GIFT v1.3) [5] for Matlab.

### General linear modeling (GLM)

GLM was conducted using AFNI's 3dDeconvolve program (code available upon request). The GLM modeled Congruent and Incongruent MSIT conditions as 48 s blocks convolved with AFNI's default hemodynamical response function, including participant's head motion parameters (roll, pitch, yaw, and displacement in x, y, and z) as predictors of no interest in the baseline model. A general linear test contrasted Incongruent and Congruent conditions. GLMs were conducted upon fMRI timeseries and upon ICA component timeseries (see below) as depicted in Fig. 1.

### ICA

ICA components were identified from the preprocessed MSIT data using Matlab and the GIFT v1.3 toolbox. ICA was run using Infomax algorithm and solved for 30 components. The following options were used: back-reconstruction using GICA3, subject-specific principal component analysis using expectation maximization and stacked datasets, full storage of covariance matrix to double precision, usage of selective eigenvariate solvers, two-step data reduction with 50 principal components in the first step, and scaling to z-scores. ICA was repeated 20 times using the ICASSO algorithm to identify the most reliable and stable components across all iterations. The ICASSO stability indices (all  $i_Q > 0.95$ ) indicated a reliable solution using 30 components.

### Comparing ICA and GLM order effects

Order effects of ICA and GLM were compared as depicted in Fig. 1. The traditional approach (shown via blue arrows) calculated the voxelwise product of the  $n$ th ICA component ( $X_n$ ) with each image of an fMRI dataset ( $Y$ ) to generate an activity timeseries

for each component; these components then underwent univariate GLM to identify task-based component activity (activity  $\beta$ s). An alternate approach (red arrows) conducted task-based GLMs for each fMRI dataset ( $Y$ ), and then calculated the product of the whole-brain spatial map to each ICA component ( $X_n$ ). Correlational analyses compared similarity of activity  $\beta$ s derived from these two methods.

### Comparing component $\beta$ s and $t$ -scores

The ICA back-projections depicted in Fig. 1 were performed using components' voxelwise  $\beta$ -values as well as components' voxelwise  $t$ -scores. Group-level  $t$ -tests calculated task-related change in activity for each component and contrast (congruent vs. rest, incongruent vs. rest, congruent vs. incongruent), with Bonferroni correction for 90 comparisons (30 components  $\times$  3 contrasts). Group results were compared between back-projections of component  $\beta$ s and  $t$ -scores. Variables such as age, gender, handedness, and acquisition parameters were not modeled as covariates of no interest, since we are comparing results obtained via different methods, and these variables would systemically influence all methods equally.

### Univariate GLM

Subjects' univariate GLM results were analyzed with mixed-effects meta-analysis to generate a univariate group map of MSIT-related brain activity. MSIT-related brain activations have been well-documented elsewhere and are beyond the scope of this study [15]. However, these univariate maps may be valuable for interpreting differences between the proposed methods.

## Results

Table 1 describes the ICA components generated from the MSIT fMRI task. Twenty-one components resemble neuroanatomical networks previously identified with ICA [18]. The remaining networks represented noise from head motion or pulsation artifact of cerebrospinal fluid in ventricles and subarachnoid space.

Activity  $\beta$ s were identical whether obtained (a) via back-projection of ICA components to subject fMRI data then GLM or (b) via whole-brain GLM of subject fMRI data then back-projection of ICA components. These activity  $\beta$ s were perfectly correlated ( $r = 1.00$ ) and differed only by rounding error.

Activity  $\beta$ s were highly correlated whether obtained via back-projection of (a) ICA component  $\beta$ s or (b) ICA component  $t$ -scores. The mean  $\pm$  sd correlation was  $0.95 \pm 0.08$  across all 30 components and 3 contrasts, with a correlation range of 0.68–0.99. Correlations were higher for the 21 non-noise components: mean  $\pm$  sd =  $0.98 \pm 0.04$ , range 0.79–0.99. Although highly correlated, two-sample Kolmogorov–Smirnov goodness-of-fit tests showed component  $\beta$ s and  $t$ -scores to arise from significantly different distributions (minimum Kolmogorov–Smirnov statistic = 0.341 for component 22, all component  $p < 0.001$ ). GLT results were largely consistent for activity  $\beta$ s obtained via back-projection of (a) component  $\beta$ s or (b) component  $t$ -scores. Both methods found the anterior cingulate component (no. 28) as significantly more active during incongruent vs. congruent contrast, as previously reported [15]. The univariate GLM showed MSIT-related cingulate activation to be more superior than typically reported, encompassing pre-SMA and peri-cingulate rather than anterior cingulate proper (Fig. 2). By comparison, the anterior cingulate component (no. 28) includes pre-SMA and peri-cingulate as well as dorsal anterior cingulate. This component also captures some left dorsolateral prefrontal cortex, which is also present in the univariate contrast.

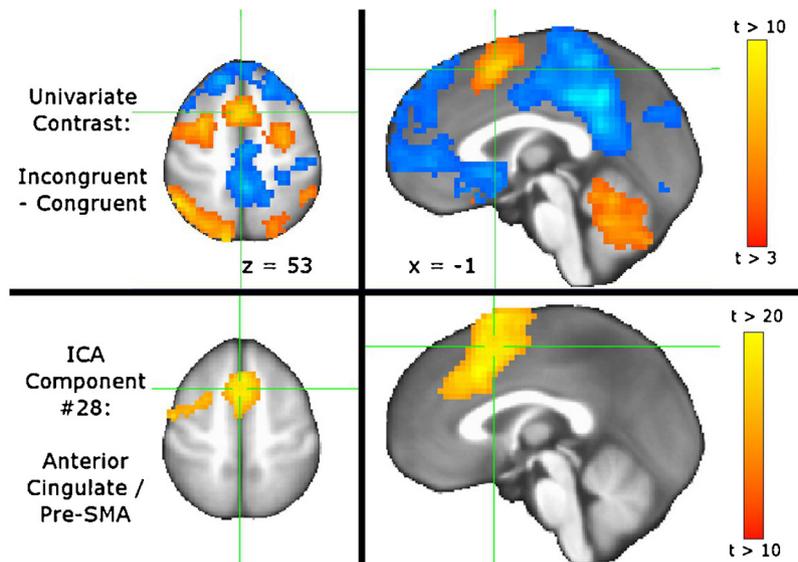
**Table 1**  
Description of ICA components.

Comp.	Label	Cluster size (mm <sup>3</sup> ) <sup>‡</sup>	Peak voxel location			Contrast results using ICA <i>b</i> -values <sup>†</sup>			Contrast results using ICA <i>t</i> -scores <sup>†</sup>		
			x	y	z	Congruent vs. rest	Incongruent vs. rest	Incongruent vs. congruent	Congruent vs. rest	Incongruent vs. rest	Incongruent vs. congruent
1	Noise (cerebral aqueduct)	241	-1	-40	-34	0	0	0	0	0	0
2	Insulae (bilateral, ventral)	1645	-40	11	-10	-1	-1	0	-1	-1	0
3	Noise (4th ventricle)	267	-1	-37	-25	1	1	0	1	1	0
4	Noise (Lateral ventricles)	1290	-4	5	14	0	0	0	0	0	0
5	Dorsal visual stream	3268	-1	-82	8	-1	-1	-1	-1	-1	-1
6	Noise (3rd ventricle)	1537	1	-22	14	0	0	1	0	0	1
7	Cerebellum	3037	23	-53	-19	1	1	0	1	1	0
8	Ventromedial prefrontal cortex	2808	-1	53	8	-1	-1	-1*	-1	-1	0*
9	Posterior cingulate cortex	2258	5	-49	5	-1	-1	-1*	-1	-1	0*
10	Noise (3rd ventricle)	1558	-1	-22	-1	0	0	1	0	0	1
11	Basal ganglia	2714	-25	8	5	0	0	0	0	0	0
12	Noise (cerebellar CSF)	834	-13	-28	-19	0	0	0	0	0	0
13	Corpus Callosum	1317	-4	2	23	0	0	0	0	0	0
14	Dorsomedial prefrontal cortex	2237	-1	56	29	0	-1	-1	0	-1	-1
15	Amygdala and hippocampus (bilateral)	1898	-10	-4	-13	0	-1	-1	0	-1	-1
16	Noise (superior sagittal sinus)	2431	-1	-40	-71	-1	-1	0	-1	-1	0
17	Superior temporal sulci (bilateral)	3524	-58	-19	14	-1	-1	-1	-1	-1	-1
18	Ventral visual stream	3015	26	-76	-19	1	1	1	1	1	1
19	Left primary motor and right cerebellum	2877	-34	-16	68	1	1	1	1	1	1
20	Default mode network	2476	-1	-43	23	-1	-1	-1	-1	-1	-1
21	Noise (cerebellar CSF)	1072	3	-38	1	0	0	0	0	0	0
22	Left frontoparietal	3711	-43	44	8	0	0	0	0	0	0
23	Right frontoparietal	3519	47	14	47	0	0	0	0	0	0
24	Noise (cerebellar CSF)	1164	-4	-37	-7	0	0	0	0	0	0
25	Brain stem	530	-1	-10	-16	0	0	0	0	0	0
26	Inferior frontal and middle temporal (bilateral)	3363	56	-52	17	-1	-1	-1	-1	-1	-1
27	Lateral premotor (bilateral)	1211	53	-10	32	0	0	0	0	0	0
28	Anterior cingulate and pre-SMA	2790	-1	20	41	0	0	1	0	0	1
29	SMA	2263	-1	-19	50	-1	-1	-1	-1	-1	-1
30	Noise (ventricles)	2449	-1	17	11	0	0	0	0	0	0

<sup>‡</sup> Volume of largest cluster in component; for bilateral components, represents the sum of left and right clusters (ex: left and right insulae for component 2).

<sup>†</sup> +1 indicates more activity for contrast, -1 indicates less activity for contrast, 0 indicates no significant difference.

\* Contrast differs when using ICA *b*-values or ICA *t*-scores.

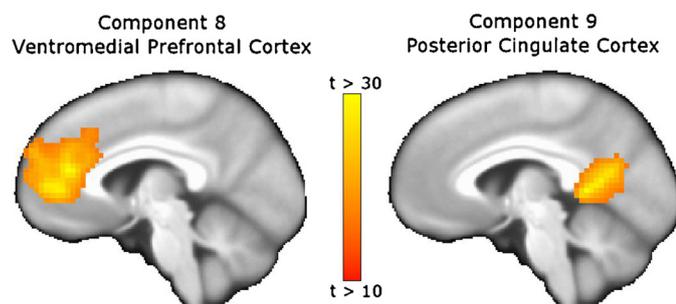


**Fig. 2.** Contrasting overlap of cingulate ICA component with univariate GLM map. (Top) Mixed effects meta-analysis of individual subjects' univariate GLM generated a group map of brain regions with differing activity between incongruent and congruent MSIT conditions. Results are thresholded at uncorrected  $p < 0.005$ , minimum cluster size = 39 contiguous voxels for FDR corrected  $\alpha = 0.05$ . Crosshairs depict the most significant voxel in the peri-cingulate/pre-SMA cluster. (Bottom) Of the 30 ICA components, no. 28 has best spatial coverage of anterior cingulate. This component includes peri-cingulate, pre-SMA, dorsal anterior cingulate, and left dorsolateral prefrontal. Images are presented in neurological convention.

However, activity  $\beta$ s differed between methods for two components: the ventromedial prefrontal cortex (no. 8) and posterior cingulate (no. 9). Both were significantly less active during incongruent vs. congruent contrast when back-projecting component  $\beta$ s but not significantly different when back-projecting  $t$ -scores. Fig. 3 depicts sagittal views of these components. Fig. 2 shows the regions encompassed by these components to be task deactivated for the univariate contrast; the component  $\beta$  method (but not the component  $t$ -score method) also found these components to be task deactivated. We attribute these differing results to the aforementioned differences in component  $\beta$ s and  $t$ -score distributions, which are depicted for Component 8 in Fig. 4. The component  $\beta$  distribution shows higher kurtosis and lower variance than the  $t$ -score distribution, which accounts for differences in GLM findings.

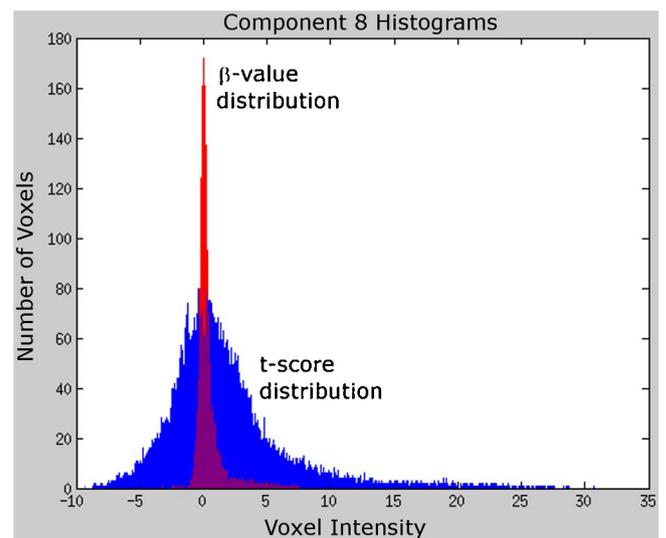
## Discussion

We have demonstrated that our novel approach of back-projecting ICA components to GLM maps yields identical results as



**Fig. 3.** Components with differing GLM contrast results when back-projecting ICA component  $\beta$ s vs. component  $t$ -scores. Components 8 (ventromedial prefrontal cortex and rostral cingulate, left) and 9 (posterior cingulate cortex, right) showed task-related deactivation for the incongruent vs. congruent contrast when back-projecting component  $\beta$ s, but no difference in activation when back-projecting component  $t$ -scores. As shown in Fig. 2, these regions were deactivated for the univariate incongruent vs. congruent contrast, supporting the back-projection of component  $\beta$ s as more reliable than back-projection of component  $t$ -scores.

the traditional approach. Our approach was developed as a means for replicating ICA components in the parent Cognitive Connectome Project without requiring back-projection of each component to each timepoint of each fMRI dataset, which is the most computationally intensive aspect of the traditional approach. For the MSIT fMRI task with 240 timepoints and 3 GLM contrasts, our ICA approach is approximately 80-times faster than the traditional approach. Using a 1 GHz processor, back-projecting 30 components to one MSIT fMRI dataset took 40s with the traditional approach and <1 s with the novel approach. While these savings are small,



**Fig. 4.** Histograms of ICA component  $\beta$ -values and  $t$ -scores. Histograms depict the frequency of voxel intensities for ICA component 8  $\beta$ -values (red) and  $t$ -scores (blue). The distribution of  $\beta$ -values has less variance and greater kurtosis than the distribution of  $t$ -scores. These differences in distributions account for the differing results obtained when back-projecting component  $\beta$ -values compared to back-projecting component  $t$ -scores. Two-sample Kolmogorov–Smirnov goodness-of-fit tests showed the distributions of  $\beta$ s and  $t$ -scores to significantly differ for all components ( $p < 0.001$ ). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

they add up with large sample sizes and multiple fMRI tasks, as is the trend in Big Data initiatives.

These calculations assume that univariate GLM maps already exist. We estimate a single subject's univariate GLM to take approximately 20 s, halving the estimated efficiency of the novel approach for situations where GLM maps do not already exist. Furthermore, computer processing speed, number of timepoints, and number of GLM contrasts can influence computation time. But given that the typical fMRI dataset has an order of magnitude more timepoints than contrasts (i.e. 100–300 timepoints and 1–10 contrasts), we still contend this approach to be more efficient than the traditional approach.

A caveat of this approach is that it only provides activity  $\beta$ s for each participant, whereas the traditional approach provides activity  $\beta$ s and  $t$ -statistics. Subject-level statistics may be valuable for descriptive purposes, such as determining what percentage of the sample had a significantly active component. But for group-level statistics, such as determining if component activity significantly differs from zero, these methods produce identical results. The same holds for individual differences research, such as asking if component activity scales with a demographic variable such as age or education.

We also demonstrate that, while back-projecting ICA components'  $\beta$ s and  $t$ -scores yield highly correlated activity  $\beta$ s (particularly for non-noise components), these approaches lead to differing GLM results. We attribute these findings to differences in the distributions of component  $\beta$ s and  $t$ -scores. For each component, the distribution of  $\beta$ s had less variance and greater kurtosis than  $t$ -scores, as is depicted in Fig. 4 for component 8. These distribution differences could easily result in false positives and false negatives, reinforcing the need to use component  $\beta$ s over  $t$ -scores. Furthermore, back-projection of component  $\beta$ s for components 8 and 9 showed task-related deactivation of these components, which is consistent with the univariate GLM results depicted in Fig. 2—providing additional evidence for back-projecting component  $\beta$ s rather than component  $t$ -scores.

A limitation to our second finding is that GLM and ICA  $\beta$ s are rarely reported. We acknowledge that the neuroimaging audience has more experience interpreting  $t$ -statistics, and thus these may be better suited for publication than  $\beta$ s. Nonetheless, we encourage authors to make GLM and ICA  $\beta$ s publicly available, whether as Supplementary Materials, through data-sharing initiatives, or by request.

## Conclusions

We conclude by stressing the need to replicate neuroimaging findings across independent samples. Historically, the expense and inaccessibility of MRI scanners has caused functional neuroimaging to garner the reputation as generating “more heat than light”. The recent growth of data sharing initiatives provides an opportunity to refute this reputation. Toward this aim, our research highlights advantages and pitfalls to replicating ICA findings across samples.

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