Interparticipant Correlations: A Model Free FMRI Analysis Technique

Martin P. Hejnar,¹ Kent A. Kiehl,^{1,2} and Vince D. Calhoun^{1,2*}

¹*Olin Neuropsychiatry Research Center, Institute of Living, Hartford, Connecticut*

²*Department of Psychiatry, Yale University, New Haven, Connecticut*

Abstract: FMRI analysis techniques can be broadly divided into model based and data driven techniques. The most widely used approach assumes an explicit temporal hemodynamic model based upon the experimental paradigm. Such an approach has proven very useful and powerful even though it is limited by the accuracy of the prespecified model. An alternative approach is to use data driven techniques like independent component analysis or fuzzy cluster analysis. These approaches have proven useful for exploratory analysis in a multivariate sense; however, they can present additional difficulties in the interpretation of the results. An alternative to these approaches is to take advantage of similarities in the patterns of the hemodynamics between participants [i.e., interparticipant correlation (IPC)]. This FMRI analysis technique enjoys the parsimony of the general linear model (GLM) but does not assume a specific FMRI time course. The technique consists of calculating voxel-wise correlations between participants resulting in IPC maps, which indicate the activated regions the participants have in common. We applied the IPC approach to data collected from healthy controls in an auditory odd-ball task. As expected, high inter-participant correlations were detected in auditory cortical regions in the temporal lobes where highest correlations were evident. In addition, areas that appear to be involved in the task were detected using IPC's but not the GLM regression. This technique, designed to have increased sensitivity to inter-subject correlations that are not necessarily task-related, may potentially be useful as a compliment to model-based approaches. *Hum Brain Mapp* 28:860–867, 2007. © 2006 Wiley-Liss, Inc.

Key words: FMRI; functional; brain; correlation; model; hemodynamic; GLM

INTRODUCTION

The most widely used FMRI analysis technique is based on the General Linear Model (GLM) (Friston et al.,

1995a,d) and involves fitting the acquired FMRI data to a canonical hemodynamic response function (Friston et al., 1995c; Rajapakse et al., 1998). Consequently, an explicit assumption is made about the form of the temporal evolution of FMRI data when the canonical hemodynamic response function is used (Friston et al., 1995b). However, it is known that the hemodynamic response can vary from one brain region to another, as well as from one participant to another (Aguirre et al., 1998; Handwerker et al., 2004). Thus, there is a need for more flexible analysis approaches. An alternative is to use data driven techniques like independent component analysis (ICA) and fuzzy cluster analysis (Dimitriadou et al., 2004; Windischberger et al., 2003). These approaches have proven useful for exploratory analysis in the multivariate sense. ICA is a multi-

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*Correspondence to: Vince Calhoun, Olin Neuropsychiatry Research Center, Institute of Living, 200 Retreat Ave, Hartford, CT 06106. E-mail: vince.calhoun@yale.edu

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variate data driven technique which does not assume a specific hemodynamic response (Calhoun et al., 2003a; McKeown et al., 2003). This is a powerful approach, which can reveal task-related or transiently task-related regions, but does not constrain the revealed regions to be synchronized between subjects (Calhoun et al., 2004; Chen and Yao, 2004). We propose an alternative and complementary approach that incorporates the simplicity of the GLM with the flexibility of data driven techniques like ICA. The main goals were to create a technique that (1) had the parsimony of the GLM and (2) minimized the assumptions of a hemodynamic model. To meet these goals, interparticipant voxel-wise correlations were utilized to construct interparticipant correlation maps (IPC) of hemodynamic activity. Each participant's hemodynamic time course was correlated with every other participant's hemodynamic time courses voxel by voxel. This procedure thus does not use any model of the hemodynamic response function typically used in FMRI studies. Additionally, a visualization method is introduced using the IPC matrix that allows for the measurement of the consistency of hemodynamics for a specific task in any voxel for every participant. Finally, detected voxels are classified by temporal similarity using a clustering algorithm.

METHODS

Auditory Oddball Task

The protocol was approved by the Hartford Hospital Institutional Review Board. All participants provided written informed consent. The protocol was adapted from the one used in (Kiehl and Liddle, 2003). The participants consisted of 20 healthy controls (12 males, 8 females, mean age 41). Two runs of auditory stimuli were presented to each participant by a computer stimuli presentation system (VAPP: <http://nilab.psychiatry.ubc.ca/vapp/>) via insert earphones embedded within 30 dB sound attenuating MR compatible headphones. The standard stimulus was a 500 Hz tone, the target stimulus was a 1,000 Hz tone, and the novel stimuli consisted of non-repeating random digital noises (e.g., tone sweeps, whistles). The target and novel stimuli each occurred with a probability of 0.10; the non-target stimuli occurred with a probability of 0.80. The stimulus duration was 200 min with a random 1,000, 1,500, or 2,000 min inter-stimulus interval. All stimuli were presented at ~80 dB. All participants reported that they could hear the stimuli and discriminate them from the background scanner noise. The headphones were designed to work together with the head restraint system in order to minimize head movement. As a result, there was less than 2 mm translation or 2° of rotation for any participant.

An MRI compatible fiber-optic response device (Light-wave Medical, Vancouver, B.C.) was used to acquire behavioral responses. Prior to entry into the scanning room, each participant performed a practice block of 10 trials to ensure understanding of the instructions. The participants

were instructed to respond as quickly and accurately as possible with their right index finger every time they heard the target stimulus and not to respond to the non-target stimuli or the novel stimuli.

Imaging was implemented on a 3T Siemens Allegra MR system. Conventional spin-echo T_1 weighted sagittal localizers were acquired to view the positioning of the participant's head in the scanner and to graphically prescribe the functional image volumes. Functional image volumes were collected with a gradient-echo sequence ($TR = 1,500$ min, $TE = 27$ min, $FA = 60^\circ$, $FOV = 22 \times 22$ cm², 64×64 matrix, 4 kHz bandwidth, 3.44 by 3.44 mm in plane resolution, 4 mm slice thickness, 1 mm gap, 29 slices acquired axially) effectively covering the entire brain (145 mm). There were two runs of 255 time points each, prefaced by a 9-s rest session allowing T_1 effects to stabilize. INRIA-align, a motion correction algorithm unbiased by local signal changes, was used to estimate movement (Freire and Mangin, 2001; Freire et al., 2002). Mean functional images were spatially normalized to the MNI space using SPM2 (Friston et al., 1995a). The normalized data was smoothed with a 12 mm Gaussian kernel.

Event-related responses to the novel and target stimuli were modeled using a synthetic hemodynamic response function composed of two gamma functions [see (Josephs et al., 1997) for a mathematical model, and (Friston et al., 1998) for an illustration]. The second gamma function was used to model the small "overshoot" of the hemodynamic response on recovery. Variations in peak latency of the hemodynamic response were adjusted using the respective temporal derivatives of the two gamma functions. A high pass filter was incorporated into the model to remove noise associated with low frequency confounds (e.g., respiratory artifact). All images were normalized to a mean of 100 (arbitrary units) for each run to compensate for any intensity variations across runs. A low pass filter (cutoff 0.25 Hz) was employed to remove any high frequency noise in the time series.

Statistical Analysis

An interparticipant Pearson correlation was computed for each voxel between all pair-wise combinations of participants over their respective time courses. Thus participant n_1 and participant n_2 correlation computed between each of their voxels over their entire respective time course data sets according to the following rules:

1. If $n_1 = n_2$ where n_1 and n_2 are participants, then no correlation was performed.
2. If n_1 was not correlated with n_2 , then n_2 was not correlated with n_1 .

After applying these rules, an example of the resulting Pearson correlation matrix for a single voxel is shown in Figure 1. Following the creation of the correlation matrix, an average correlation value was computed for each voxel as a measure of the group wise correlation.

		n_2							
		1	2	3	4	5	6	7	8
n_1	8								
	7								ρ
	6							ρ	ρ
	5						ρ	ρ	ρ
	4					ρ	ρ	ρ	ρ
	3				ρ	ρ	ρ	ρ	ρ
	2			ρ	ρ	ρ	ρ	ρ	ρ
	1		ρ	ρ	ρ	ρ	ρ	ρ	ρ

Figure 1.

Example correlation matrix: Illustration of voxel-wise correlations obtained for all pair wise combinations of subjects n_1 and n_2 .

In addition to the correlations, a standard regression analysis (i.e., GLM) was calculated for each of the participants. For the auditory oddball task the regressors were standard, target, and novel stimuli. The auditory oddball regression and correlation images were imported, contiguity filtered (where only a minimum of 10 spatially neighboring “activated” voxels are displayed), thresholded and overlaid on an anatomic brain template. After estimating the targets, novel and standard activation maps for each participant, and a second level ANOVA was performed using all three contrast in order to have a reasonable com-

parison for the IPC maps. The IPC maps apply across all trial types for the auditory oddball task (novels, standards, and targets) together.

Finally, voxels with high correlations may have very different time courses from one another (since the only requirement for a high correlation value is that the time courses are similar for all participants). In order to examine these time courses, a k-means clustering algorithm was used on the auditory oddball task correlation data (Duda et al., 2001). The results were then overlaid on an anatomic brain template with each cluster’s respective time course.

RESULTS

For comparison purposes, an empirical thresholding approach was used for all analyses. Maps were converted to standardized z-scores and thresholded at a z-level of 1.96. This allowed for a qualitative comparison of the “most active” voxels across analysis methods. Figure 2 contains the SPM ANOVA analysis from the auditory oddball task and Table I shows the corresponding Talairach brain regions.

Figure 3 contains a correlation matrix of the mean of the 10 most highly correlated voxels in the auditory oddball task. This figure provides a measure of the consistency of activation across participants. From this figure, we can see, for example, that participant 2 had the least similarity to the group, represented as a consistently low correlation value.

Figure 4 contains slices 5, 9, 16, and 29 for a select group of the participants in the auditory oddball task thresholded at a z-level of 1.96.

TABLE I. Auditory oddball SPM ANOVA “effects of interest”

Area	Brodmann	L/R volume (cc)	L/R max T (x, y, z)
Superior temporal gyrus	13, 21, 22, 29, 38, 39, 41, 42	5.4/4.3	9.4 (−65, −26, 4)/7.1(59, −26, 7)
Middle temporal gyrus	20, 21, 22, 37, 38	3.5/1.0	8.4 (−56, −38, 5)/5.2 (56, −9, −5)
Middle frontal gyrus	6, 8, 9, 10, 46	2.7/0.4	4.4 (−39, 47, 14)/2.5 (33, −6, 53)
Inferior frontal gyrus	9, 10, 13, 44, 45, 46, 47	2.2/0.2	4.0 (−50, 17, −6)/2.6 (39, 20, −4)
Inferior parietal lobule	40	1.6/1.8	4.7 (−62, −34, 21)/3.9 (50, −27, 46)
Lentiform nucleus		1.1/0.2	4.1 (−12, 0, 6)/2.3 (18, −5, 11)
Superior frontal gyrus	6, 8, 10	1.1/0.2	3.8 (−39, 53, 14)/3.2 (3, 5, 49)
Thalamus		1.0/1.8	3.9 (−9, −2, 8)/4.4 (18, −17, 12)
Cingulate gyrus	23, 24, 32	1.0/0.6	3.9 (−6, 20, 40)/3.3 (3, 14, 38)
Insula	13, 22, 40, 45, 47	0.9/1.5	5.2 (−56, −37, 16)/3.9 (56, −34, 18)
Fusiform gyrus	18, 19, 20, 37	0.6/0.4	3.4 (−21, −56, −15)/3.4 (18, −74, −19)
Medial frontal gyrus	6, 8, 32	0.6/0.3	3.7 (−3, 14, 44)/3.1 (3, 5, 44)
Clastrum		0.5/0.5	3.6 (−30, 17, −1)/2.7 (36, −12, −9)
Caudate		0.5/0.3	3.7 (−9, 3, 3)/2.5 (9, −2, 14)
Postcentral gyrus	1, 2, 3, 5, 40, 43	0.3/2.9	4.0 (−62, −25, 18)/4.8 (53, −24, 48)
Precentral gyrus	4, 6, 43, 44	0.3/1.5	2.8 (−59, 9, 5)/3.5 (33, −21, 51)
Lingual gyrus	18, 19	0.3/0.2	3.0 (−15, −68, −14)/2.9 (18, −80, −19)
Transverse temporal gyrus	41, 42	0.2/0.6	3.2 (−62, −17, 12)/4.7 (62, −17, 9)
Supramarginal gyrus	40	0.1/0.2	2.4 (−53, −42, 35)/2.6 (62, −45, 24)

Voxels above the threshold were converted from MNI to Talairach coordinates and entered into a database to provide anatomic and functional labels for the left (L) and right (R) hemispheres. The volume of activated voxels in each area is provided in cubic centimeters (cc). Within each area, the maximum T value and its coordinate are provided.

Figure 2.

Auditory oddball SPM contiguity filtered ANOVA "Effects of Interest": Regressors corresponding to the target, novel, and standard stimuli were entered into a second level ANOVA using the SPM2 software.

Figure 3.

Auditory oddball correlation matrix: The correlation matrix was computed for the mean of the 10 most highly correlated voxels in the auditory oddball task. One participant (participant 2) is showing consistently lower similarity than the others are.

Figure 4.

Auditory oddball individual correlation analysis: Individual average correlation maps for each participant.

Figure 5.

Auditory oddball group correlation results: Group aggregate results for IPC method applied to auditory oddball task data.

TABLE II. Auditory oddball correlation group Talairach table

Area	Brodmann	L/R volume (cc)	L/R max T (x, y, z)
Superior temporal gyrus	13, 21, 22, 29, 38, 41, 42	4.9/4.3	9.7 (-65, -20, 1)/9.3 (53, -20, 1)
Middle temporal gyrus	19, 20, 21, 22, 39	3.8/1.4	9.0 (-65, -26, 1)/6.3 (53, -21, -4)
Lingual gyrus	17, 18	0.5/0.5	6.4 (-27, -96, -3)/7.9 (27, -96, -3)
Inferior occipital gyrus	17, 18, 19	0.9/0.7	5.7 (-30, -94, -5)/7.1 (33, -93, -3)
Transverse temporal gyrus	41, 42	0.4/0.5	4.3 (-62, -17, 9)/5.9 (56, -17, 9)
Cuneus	7, 17, 18, 19, 23, 30	0.6/0.5	5.0 (-24, -96, 2)/5.7 (21, -93, 0)
Middle occipital gyrus	18, 19	0.7/0.6	4.7 (-27, -93, 5)/4.9 (30, -90, -1)
Insula	13, 22, 40, 47	0.7/1.4	3.8 (-56, -34, 16)/4.6 (56, -34, 16)
Postcentral gyrus	1, 2, 3, 5, 7, 40, 43	1.3/4.2	3.1 (-9, -52, 72)/4.6 (62, -23, 15)
Precentral gyrus	4, 6, 44	0.2/2.3	2.5 (-53, -3, 50)/4.4 (42, -12, 59)
Fusiform gyrus	18, 19, 20, 36, 37	0.6/1.1	4.2 (-24, -94, -10)/3.3 (30, -45, -20)
Superior frontal gyrus	6, 8, 9, 10, 11	0.8/1.2	3.9 (-27, 61, -11)/4.0 (3, 5, 49)
Thalamus		0.4/0.5	3.1 (-12, -14, 6)/3.7 (12, -17, 4)
Medial frontal gyrus	6, 8, 9, 10, 11, 25, 32	0.9/0.7	3.5 (0, 3, 52)/3.7 (6, 8, 47)
Middle frontal gyrus	6, 9, 10, 11, 46	0.6/0.4	2.9 (-42, 16, 21)/3.7 (36, -6, 61)
Cingulate gyrus	24, 31, 32	1.1/0.8	3.5 (-9, 20, 40)/3.6 (6, 2, 47)
Precuneus	7, 19, 31, 39	3.2/2.2	3.5 (0, -58, 64)/3.6 (3, -55, 61)
Clausttrum		0.4/0.2	3.5 (-30, 20, -1)/3.3 (27, 18, 5)
Inferior temporal gyrus	19, 20, 37	0.2/0.1	3.3 (-50, -27, -19)/2.4 (50, -70, -2)
Inferior parietal lobule	40	1.4/1.4	3.3 (-62, -34, 21)/3.1 (48, -32, 57)
Inferior frontal gyrus	6, 9, 44, 45, 47	1.2/0.1	3.2 (-30, 20, -6)/2.7 (30, 20, -4)
Superior occipital gyrus	19, 39	0.1/0.1	2.2 (-33, -71, 28)/3.0 (30, -80, 26)
Superior parietal lobule	7	0.9/0.8	3.0 (-6, -64, 58)/2.9 (3, -70, 59)
Supramarginal gyrus	40	0.1/0.1	2.0 (-56, -39, 32)/3.0 (56, -46, 22)
Paracentral lobule	5	0.2/0.1	2.7 (0, -46, 63)/2.5 (3, -44, 60)
Lentiform nucleus	Putamen, lateral globus Pallidus, medial globus Pallidus	0.2/0.2	2.4 (-21, 3, 3)/2.6 (21, 0, -5)
Anterior cingulate	24, 25, 32	0.1/0.1	2.5 (-3, 29, -6)/2.6 (3, 26, -6)
Caudate	Caudate body, caudate tail	0.2/0.0	2.5 (-30, -37, 10)/2.0 (9, -2, 22)
Angular gyrus	39	0.1/0.0	2.2 (-39, -74, 31)/2.1 (42, -74, 31)

Voxels above the threshold were converted from MNI to Talairach coordinates and entered into a database to provide anatomic and functional labels for the left (L) and right (R) hemispheres. The volume of activated voxels in each area is provided in cubic centimeters (cc). Within each area, the maximum T value and its coordinate are provided.

A voxel-wise one sample z -test was performed from the correlation images of all the participants, thresholded at a z -level of 1.96. Figure 5 contains contiguity filtered, odd numbered slices 1, 3, ..., 37, 39 of the group correlation. Comparing Figure 5 with Figure 2 (SPM ANOVA), we see visual cortex “activation” not present in Figure 2.

The descriptions of the most highly and consistently correlated brain regions are listed in Table II.

Figure 6 shows the four cluster analysis of the auditory oddball group correlation image (Fig. 5) with the corresponding time courses. The end of the task shows a high spike in FMRI signal as displayed in two out of the four time courses (pink and blue), both of which include primary visual (occipital) and/or visual integration (parietal) areas. This spike corresponds to a visually novel stimulus, a box figure with the word “relax”, which was displayed at the end of the auditory oddball paradigm.

Simulation

In order to visualize the differences between the IPC and the GLM methods, we have also conducted an IPC analysis on simulated brain data. We generated an image

with dimensions of 30 by 30 pixels, and three areas on that image were selected to be the activated brain regions; 250 similar images were generated. The first area is a 5 by 5 pixels square that had data corresponding to the spm hemodynamic function (spm_hrf()) convolved in time by a vector of onsets 25 s apart. This was simulated using a row vector of size 250 that had value 1 at time instances corresponding to TR and zeros elsewhere. The second area was a normal random noise function convolved with the same onset vector; this area overlapped area 1. The third area is the same data as area one shifted in time by 10 scans. Random Gaussian noise was added to the simulated data such that the contrast to noise ratio (CNR) was either 1 or 5.

The results for CNR = 5 or 1 for the IPC (Fig. 7a,c) and GLM (Fig. 7b,d) are shown. Identified regions are color-coded and corresponding time courses are also shown for the IPC results. The three simulated region (two of which are overlapping) can be seen clearly in the results. For the IPC analysis, four regions were identified with the fourth region corresponding to voxels containing the overlap between the task-related and the Gaussian region. The GLM method revealed region 1 perfectly for both CNR

Figure 6.

Auditory oddball group cluster correlation: Voxels which survived the threshold in Figure 5 were entered into a k-means clustering algorithm. Time courses and regions corresponding to four clusters are shown in the figure.

levels and was also able to successfully identify the presence of task-related activity when overlapping with other unmodeled activity. This simulation illustrates two key points. First, the GLM outperforms the IPC approach in the region where the assumptions were correct, even when it was mixed with an additional source of variation. Secondly, the IPC approach is able to reveal additional regions which are consistently activated for all subjects, not necessarily in a way that corresponds to the modeled response.

DISCUSSION

IPC images are calculated via pair-wise participant correlations to identify the brain regions that were most consistently synchronized across participants in the auditory oddball task. High correlations indicate a similarity of activation across participants. The maximum correlation voxel provides an overview of the results and highlights participants who “activated” poorly relative to the other participants. This approach is distinct from the common GLM analysis approach in which a ‘predictor’ is correlated (or more generally multiple regression is used) with the data. The GLM approach is very powerful and enables specific and flexible hypothesis testing. However, such an approach is well complemented by a technique which provides information about the response which is consistently activated in each subject, although not necessarily in a task-related manner. The GLM will typically not reveal such regions, and they will be grouped into the error variance. In addition, the GLM approach makes no explicit requirement that subjects much be activating similarly; in the extreme case two subjects can diverge from the predic-

tor in opposite ways and have a low correlation for the same amount of residual error. This is especially true in the case where multiple regressors (such as temporal derivatives, or flexible basis function) are used. In contrast,

Figure 7.

Simulation results: Four time courses were generated in a simulation of twenty data sets with 250 time points each including task related (orange), delayed task-related (blue), random (red), and mixed task-related/delayed task-related (green). Gaussian noise was added such that the contrast-to-noise (CNR) level was either 1 or 5. The GLM approach outperforms the IPC approach for the task-related region; however, the IPC method was able to detect all regions which exhibited similarity between participants.

the IPC approach provides a direct measure of the average “similarity” of the time courses between subjects. We also include a clustering step in order to group the revealed regions into similar temporal patterns.

Recently in the study of natural vision, IPC was used in order to discover cortical areas in which participants displayed synchronized cortical activity (Hasson et al., 2004). The researchers discovered areas not previously associated with sensory processing but areas beyond the well known visual and auditory cortices. These novel high order association areas included the retrosplinal and cingulate cortex, the lateral sulcus, and along the superior temporal gyrus. However this study only involved five participants and its focus was to make discoveries about naturalistic vision. The focus of the current study is to develop the IPC analysis approach itself and to understand better the characteristics of the obtained results. The current analysis method was applied to fMRI data from an auditory oddball task gathered from 20 healthy participants.

Lange et al. (1999) demonstrated it is advantageous to use complementary analysis methods in order to potentially uncover results not found by one method alone. Furthermore, this pluralistic approach allows for the confirmation and consolidation of results (Lange et al., 1999). Their approach can both compliment a model-based approach and uncover results not found by other methods due to imperfect model specification. The IPC finds additional areas of activation that are different from traditional regression based techniques, in addition to corroborating the regression analysis. Therefore, it is able to consolidate and confirm results obtained from other analysis techniques.

The main strength of our approach is that it is a model free method of analyzing fMRI data. The technique does not rely upon assuming a canonical hemodynamic response function or time course. Furthermore, the maximum correlation voxel image allows for a quick summary of results and easy identification of participants whose “activation” was not consistent with the other participants. Limitations to the current approach is that it does not allow us to distinguish between different event types as with the targets, novel, and standard stimuli in the auditory oddball task. Although using a clustering algorithm we can identify different temporal “patterns” in the IPC maps. Because of its model free nature, the IPC approach is specifically designed to be sensitive to any type of inter-participant correlation. As such, there may be increased sensitivity to non-BOLD related changes (for example if all subjects moved in a similar manner, then this would result in a significant finding). In this case, a clustering of the resulting voxels and subsequent comparison with the predictive GLM model can be a useful way to assess this type of effect. In the case of motion, one could also use the standard approach of fitting the data to the estimated motion parameters as well as their squares (and perhaps the squares of their derivatives). Differences in hemodynamic lag differences among participants are not taken into consideration with this approach (although systematic lag differences between the brain regions are

accounted for since correlations are computed voxel by voxel). Another limitation to our approach, which is also one that the widely used GLM approach has, is the assumption that all the brains have been perfectly spatially normalized. Spatial smoothing, a common procedure in fMRI, will mitigate the impact of normalization errors to some degree. In the future, we hope to utilize further improvements in spatial normalization procedures. Finally, for comparison purposes, an empirical threshold was used instead of a statistical one (such as a t-test) due to dependence between individual correlation images (since two single participant’s data can have some impact on these measures). Future work will involve extending the IPC approach to handle delay differences and to partition the results by event type, as well as the incorporation of explicit distributional forms or bootstrapping approaches to improve thresholding.

Future studies may build upon the IPC technique and make it into an “intraparticipant” correlation as well as address the limitations discussed previously. Additionally, it may be a useful method for differentiating healthy controls from patient groups or even various subgroups in a patient population by examining how the mixed group of participants correlates in various tasks.

As shown in the analysis, IPC can corroborate and uncover additional information not shown by traditional fMRI analysis techniques. The IPC method minimizes assumptions about hemodynamics and its simple GLM basis makes for intuitive interpretation of results, thus making IPC a complementary and useful tool for fMRI analysis.

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