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Technical Note

A generalized form of context-dependent psychophysiological interactions (gPPI): A comparison to standard approaches

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A B S T R A C T

Functional MRI (fMRI) allows one to study task-related regional responses and task-dependent connectivity analysis using psychophysiological interaction (PPI) methods. The latter affords the additional opportunity to understand how brain regions interact in a task-dependent manner. The current implementation of PPI in Statistical Parametric Mapping (SPM8) is configured primarily to assess connectivity differences between two task conditions, when in practice fMRI tasks frequently employ more than two conditions. Here we evaluate how a generalized form of context-dependent PPI (gPPI; http://www.nitrc.org/projects/gppi), which is configured to automatically accommodate more than two task conditions in the same PPI model by spanning the entire experimental space, compares to the standard implementation in SPM8. These comparisons are made using both simulations and an empirical dataset. In the simulated dataset, we compare the interaction beta estimates to their expected values and model fit using the Akaike information criterion (AIC). We found that interaction beta estimates in gPPI were robust to different simulated data models, were not different from the expected beta value, and had better model fits than when using standard PPI (sPPI) methods. In the empirical dataset, we compare the model fit of the gPPI approach to sPPI. We found that the gPPI approach improved model fit compared to sPPI. There were several regions that became non-significant with gPPI. These regions all showed significantly better model fits with gPPI. Also, there were several regions where task-dependent connectivity was only detected using gPPI methods, also with improved model fit. Regions that were detected with all methods had more similar model fits. These results suggest that gPPI may have greater sensitivity and specificity than standard implementation in SPM. This notion is tempered slightly as there is no gold standard; however, data simulations with a known outcome support our conclusions about gPPI. In sum, the generalized form of context-dependent PPI approach has increased flexibility of statistical modeling, and potentially improves model fit, specificity to true negative findings, and sensitivity to true positive findings.

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Introduction

Functional MRI allows one to study task-related regional brain responses and task-dependent connectivity analysis using psychophysiological interaction (PPI) methods. The latter affords the additional opportunity to understand how brain regions interact in a task-dependent manner (Chee et al., 2010; Dodel et al., 2005; Kim and Horwitz, 2008; Minnebusch et al., 2009; Schmitz and Johnson, 2006; Snijders et al., 2010). From 1998 to 2003 there were 81 studies citing Friston and colleagues' initial paper describing psychophysiological interactions compared to 299 citations from 2004 to 2009 (Friston et al., 1997). Likewise, the important paper from Gitelman and colleagues (2003), which enabled psychophysiological interactions to be applied to event-related designs by incorporating the hemodynamic response, has spurred a similar increase in citations; between 2004 and 2006 there were 29 citations compared to 57 citations from 2007 to 2009. However, despite the increasing use of PPI and its potential role for advancing our knowledge regarding the functional integration of brain activity, the standard implementation

Abbreviations: PPI, psychophysiological interactions; sPPI, SPM PPI; gPPI, generalized form of context-dependent PPI; N, novel condition; PV, previously viewed condition; sem, semantic condition; self, self-appraisal condition.

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in SPM8, where the psychophysiological term is formed by the interaction of neural activity and a difference vector of two tasks (e.g. A–B), has two major limitations. Currently, a single PPI can only identify regional effects related to differences between psychological contrasts and not similarities between contrasts. Second, the standard implementation described by Friston et al. (1997) and Gitelman et al. (2003), using a psychological vector of A or a psychological vector of A–B, does not span the space of all conditions and as such is potentially limited to simple experiments with only one or two conditions, respectively, or experiments that can be collapsed into two conditions for analysis. Here we utilize a generalization of the existing PPI methods that address these limitations (Higo et al., 2011; McLaren et al., 2008).

The initial framework for psychophysiological interactions was to identify regions that differ in connectivity by context or condition in block-designed fMRI studies (Friston et al., 1997; from here forward, we will refer to the modulation of connectivity by a psychological or behavioral context as "context-dependent connectivity"), thereby enabling inference regarding condition-specific functional integration. However, in block or event-related task designs with two or more experimental conditions, one may be interested not only in condition-specific functional integration, but also where functional integration may be similar across conditions. When Gitelman et al. (2003) extended PPI to event-related designs by incorporating a deconvolution of the BOLD response step into forming the psychophysiological interaction, they started with the notion that psychophysiological interactions occur at the neural level, which results in a change in the BOLD signal, rather than at the level of BOLD signal, which is an indirect and downstream measure of neural activity. Since, mathematically, the interaction of BOLD signal is not the same as the interaction of neural signal convolved with the canonical HRF, Gitelman et al. (2003) implemented a deconvolution step to arrive at an estimate of neural signal on which interaction analyses are performed. In a study of simulated neural activity, the BOLD signal, and PPI, Kim and Horwitz concluded that PPI parameters are robust and generally agree with the underlying neural interactions (Kim and Horwitz, 2008). Their conclusion bolsters the use of PPI as non-invasive tool to investigate the dynamics of functional connectivity.

Both Gitelman et al. (2003) and Kim and Horwitz (2008) demonstrated the importance of properly modeling the underlying neural activity. However, the standard implementation of PPI in SPM8, using a psychological vector of A or a psychological vector of A–B, is still limited to models of only one or two conditions, respectively, or experiments that can be collapsed into two conditions for analysis, as only a single PPI regressor is created per first level analysis, whereas experiments often contain more than two conditions. For example, in an event-related design with two conditions, there are at least 3 discrete neuronal states defined by the experimenter: (i) activity during the processing of the stimulus for condition 1; (ii) activity during processing of the stimulus for condition 2; and (iii) activity while there is no stimulus being processed (e.g. "baseline" periods or null events). These states may all potentially differ from each other and collapsing two to test against the third is less desirable than modeling each condition separately, as this leads to a model that does not span the full space of the conditions. The generalized form of context-dependent PPI (gPPI) spans the full space of the experimental design.

In this paper we describe the theoretical framework for the generalized form of context-dependent PPI (gPPI; Higo et al., 2011; McLaren et al., 2008). Following this description we use simulations to show, based on a gold standard, that gPPI consistently estimates psychophysiological interactions with greater accuracy. Additionally, we also use simulations to show that between-subject PPI effects can be both over and underestimated when gPPI is not utilized. Finally, we demonstrate some strengths of this approach using empirical data from an fMRI study of face recognition (Xu et al., 2009).

Materials and methods

Statistics of PPI approaches

The modeling of each condition independently is already standard practice when investigating fMRI activation patterns (Friston et al., 1995a, 1995b). The generalized form of context-dependent PPI (gPPI) applies this principle to PPI analysis and is available in the automated gPPI toolbox (http://www.nitrc.org/projects/gppi). The Statistical Parametric Mapping (SPM8; Wellcome Department of Imaging Neuroscience, University College London, UK) PPI (sPPI) approach and gPPI approach are both based on the same underlying concepts and use the following models (Friston et al., 1997; Gitelman et al., 2003):

$$\boldsymbol{Y_k} = \boldsymbol{H}(\boldsymbol{x_a}) \tag{1}$$

$$\boldsymbol{Y_i} = \left[\boldsymbol{H}\left(\boldsymbol{x_a} * \mathbf{g_p}\right)\right] * \beta_{\boldsymbol{i}} + \left[\boldsymbol{Y_k}\boldsymbol{H}\left(\mathbf{g_p}\right)\mathbf{G}\right] * \beta_{\boldsymbol{G}} + \mathbf{e_i} \tag{2}$$

where $\boldsymbol{H}$ is the HRF in Toeplitz matrix form; $\boldsymbol{Y_k}$ is the BOLD signal observed in the seed region; $\boldsymbol{x_a}$ is the estimated neural activity from the BOLD signal in the seed region (Gitelman et al., 2003); $\boldsymbol{Y_i}$ is the BOLD signal observed at each voxel in the brain; $\beta_{\boldsymbol{i}}$ is a matrix of the beta estimates of the psychophysiological interaction terms; $\beta_{\boldsymbol{G}}$ is a matrix of the beta estimates of the seed region BOLD signal ($\boldsymbol{Y_k}$), covariates of no interest ($\mathbf{G}$), and task regressors that are the convolution of psychological vectors $\boldsymbol{H}(\mathbf{g_p})$; and $\mathbf{e_i}$ is a vector of the residuals of the model. In the sPPI approach, $\mathbf{g_p}$ is a vector formed by multiplying the condition ON times (onset times plus stimulus duration — when the stimulus or psychological state is presented to the participant or when the participant experiences a defined psychological/experimental state) by a weighting vector (see Figure 5B of Gitelman et al., 2003). As of revision 3270 in SPM5, the weighting vector does not need to have a mean of zero as the psychological vector is no longer mean-centered before convolution (ftp://ftp.fil.ion.ucl.ac.uk/spm/spm5_updates/Updates_README.txt). This change removed the requirement of weighting the conditions based on the number of trials. In the gPPI approach, $\mathbf{g_p}$ is a matrix of N columns, where N is the number of conditions in the experiment and formed by separating the condition ON times into separate columns. This is the only difference between the two methods, but is sufficient to account for the different neuronal states in both the psychological regressors and the interaction regressors. Eq. (2) is the general linear model for the PPI first-level statistics.

In Fig. 1 we graphically compare the standard PPI (sPPI) with the generalized form of context-dependent PPI (gPPI). In both sPPI and gPPI, the analyses start with identifying the condition ON times (Fig. 1A). In sPPI, the condition ON times for conditions A, B, and C are multiplied by a weighting vector (e.g. in this data [-1 1 1]) and are then convolved with the canonical hemodynamic response function (HRF; Fig. 1B) to form the task regressor (Fig. 1C). However, in gPPI, the condition ON times for conditions A, B, and C are separately convolved with the HRF (Fig. 1B) for each condition to form a set of task regressors (Fig. 1D). This step forms the task/psychological regressor(s) for the model ($H(g_p)$ in Eq. (2)). The latter is similar to the approach taken by Dodel et al. (2005) to address context-dependent connectivity by separately computing the correlations between regions for each condition. However, their method analyzes the correlations rather than the interaction of the neural signal and experimental conditions. Next, both sPPI and gPPI approaches extract the BOLD signal from an ROI and remove the effect of noise covariates, if any (matrix $\mathbf{G}$, e.g. motion regressors). This adjusted signal is deconvolved (Fig. 1E, matrix $\mathbf{Y_k}$) to obtain an estimate the neural activity (Gitelman et al., 2003). In the sPPI approach, the estimated neural activity is multiplied by the product of condition ON