

## Effective connectivity during working memory and resting states: A DCM study

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### ABSTRACT

Although the relationship between resting-state *functional* connectivity and task-related activity has been addressed, the relationship between task and resting-state directed or *effective* connectivity – and its behavioral concomitants – remains elusive. We evaluated effective connectivity under an N-back working memory task in 24 participants using stochastic dynamic causal modelling (DCM) of 7 T fMRI data. We repeated the analysis using resting-state data, from the same subjects, to model connectivity among the same brain regions engaged by the N-back task. This allowed us to: (i) examine the relationship between intrinsic (task-independent) effective connectivity during resting ( $A_{\text{rest}}$ ) and task states ( $A_{\text{task}}$ ), (ii) cluster phenotypes of task-related changes in effective connectivity ( $B_{\text{task}}$ ) across participants, (iii) identify edges ( $B_{\text{task}}$ ) showing high inter-individual effective connectivity differences and (iv) associate reaction times with the similarity between  $B_{\text{task}}$  and  $A_{\text{rest}}$  in these edges. We found a strong correlation between  $A_{\text{rest}}$  and  $A_{\text{task}}$  over subjects but a marked difference between  $B_{\text{task}}$  and  $A_{\text{rest}}$ . We further observed a strong clustering of individuals in terms of  $B_{\text{task}}$ , which was not apparent in  $A_{\text{rest}}$ . The task-related effective connectivity  $B_{\text{task}}$  varied highly in the edges from the parietal to the frontal lobes across individuals, so the three groups were clustered mainly by the effective connectivity within these networks. The similarity between  $B_{\text{task}}$  and  $A_{\text{rest}}$  at the edges from the parietal to the frontal lobes was positively correlated with 2-back reaction times. This result implies that a greater change in context-sensitive coupling – from resting-state connectivity – is associated with faster reaction times. In summary, task-dependent connectivity endows resting-state connectivity with a context sensitivity, which predicts the speed of information processing during the N-back task.

### Introduction

The human brain at rest exhibits highly structured spontaneous or endogenous fluctuations in functional MRI signals (Biswal et al., 1995; Greicius et al., 2003; Lowe et al., 1998; McGuire et al., 1996; Raichle and Snyder, 2007). The temporal correlations between these fluctuations serves as a basis for estimating (resting-state) functional connectivity among distributed brain regions (Fox and Raichle, 2007) – an approach that has attracted much interest from the imaging neuroscience community. One important question about resting-state connectivity is its relationship with connectivity induced by performing a task. Previous studies have suggested a tight link between the resting-state connectivity

(or distributed patterns of endogenous activity) with task-related brain activation or connectivity (Biswal et al., 1995; Cole et al., 2014, 2016; Krienen et al., 2014; Park et al., 2014; Smith et al., 2009; Tavor et al., 2016; Yeo et al., 2015). For example, Cole et al. (2016) showed that functional connectivity from resting-state fMRI (rsfMRI) could explain the interaction among brain areas during task performance. Tavor et al. (2016) also showed that task-evoked activation could be predicted by (task-free) features of rsfMRI and DTI data. According to these studies, resting-state connectivity may serve as a potential ‘scaffold’ that underwrites diverse configurations subserving the pertinent functions of a given task (Fox and Raichle, 2007). In doing so, task-induced neural activity may not engage resting-state networks directly but may

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contextualize them and selectively engage the components of resting-state or intrinsic networks. Accordingly, previous studies have focused on the reconfigurations or reorientations of task-dependent (or flexible) functional connectivity from that of resting state (or intrinsic) network architecture (Corbetta et al., 2008; Elton and Gao, 2014; Hermundstad et al., 2013; Medaglia et al., 2015; Mill et al., 2017).

However, it is not still clear whether resting-state connectivity is simply recapitulated or reconfigured to perform a task. Moreover, previous studies of the relationship between resting-state functional connectivity and task-related activity have been largely based on temporal synchrony between regional activities (quantified using Pearson correlation coefficients), which does not provide information about the directed causal coupling among brain regions (for review, see Park and Friston, 2013). Inferences about directed coupling call for effective connectivity analyses that identify network architectures in terms of causal relationships. Therefore, the relationship between effective connectivity during the task state and effective connectivity in the resting state is unresolved.

In the current study, we characterized the relationship between task and resting-state coupling in terms of effective connectivity. To estimate effective connectivity for both states, we used dynamic causal modelling (DCM), which assumes a bilinear model of neural dynamics and a hemodynamic response model of fMRI data (Friston et al., 2003). In particular, stochastic DCM (Friston et al., 2011; Li et al., 2011) can estimate effective connectivity from both task and resting-state time series (with and without experimental inputs) using the same model inversion scheme. Using stochastic DCM, we examined the relationship between task and resting-state connectivity, within the context of an N-back task, for which many neuroimaging studies have identified the key brain regions involved (Barch et al., 2013; Honey et al., 2002; Manelis and Reder, 2014; Owen et al., 2005) – and for which a few DCM studies are available (Brodersen et al., 2014; Deserno et al., 2012; Dima et al., 2014; Schmidt et al., 2014). In this paper, we will use the phrase *intrinsic connectivity* to refer to the effective connectivity underlying task-free intrinsic brain networks in rsfMRI – and the effective connectivity that is intrinsic to a task set during task fMRI, having modeled any changes in effective connectivity due to task-related processes (i.e., extrinsic or modulatory connectivity), such as working memory.

We further note that task performance may not be supported by a single configuration of connectivity. In other words, there may be a many-to-one (i.e. *degenerate*) mapping between connectivity and function (Edelman and Gally, 2001; Friston and Price, 2003; Price and Friston, 2002; Tononi et al., 1999). This means, to perform a given task, people may engage different connectivity architectures. Although direct evidence for this *network degeneracy* hypothesis has not been established, it may explain the weak group average effective connectivity observed in previous DCM studies on N-back working memory tasks (Deserno et al., 2012; Dima et al., 2014; Fonville et al., 2015). Furthermore, the plurality of plausible dynamic causal models in group studies of 2-back tasks (Dima et al., 2014) may reflect the possibility that multiple patterns of effective connectivity support the same task. Brodersen et al. (2014) identified three subgroups using DCM, which showed significant differences in positive and negative symptom severity in schizophrenia. This clustering was taken as evidence of subtypes; not only in terms of behavioral performance but also at the level of effective connectivity engaged by the task.

The purpose of this study was to investigate the relationship between task-related effective connectivity and resting-state effective connectivity, to examine phenotypes of task-related effective connectivity across participants and to associate behavioral measure (particularly for reaction times) with the divergence of task-related changes in effective connectivity from resting-state intrinsic connectivity. Crucially, we were concerned with establishing the construct validity of effective connectivity, in relation to behavior – and the predictive validity of resting-state intrinsic connectivity, in relation to task-related effective connectivity. We therefore conducted independent DCM analyses of the task and

resting-state fMRI data to: (i) test for similarities between the respective intrinsic connectivity estimates (using correlations over connections) and (ii) to quantify the divergence of task-related effective connectivity changes from the resting-state intrinsic connectivity. This should be contrasted with a complementary approach, in which both task and resting-state fMRI data were modeled within a single DCM. Although this would have allowed us to model the differences between task, baseline and resting connectivity, it would not have enabled us to demonstrate their similarity or predictive validity (i.e., the ability to predict intrinsic connectivity under a task set from independent resting-state effective connectivity estimates).

## Methods

### Participants

24 healthy right-handed participants (13 males; age =  $22.9 \pm 2.7$  years) underwent N-back task and resting-state fMRI during contiguous sessions. All participants had no history of neurological illness and were right-handed according to the Annett's handedness questionnaire (Annett, 1970). This study was carried out under the guidelines established by the Institutional Review Board of Korea Basic Science Institute, and all participants provided written informed consent before participating.

### N-back task design

Prior to their visit, participants practiced N-back tasks with a training video (lasting 8 min) that was created specifically for this experiment – and administered via email. The video consisted of examples for 0-back, 1-back, 2-back, and 3-back trials that were similar to the trials they had to perform during the experiment. After training, they completed an online questionnaire to report the subjective level of easiness and understanding of the task on a 5-point scale. Only participants that scored 4 or 5 on the questionnaire were recruited. Upon their visit for the fMRI experiment, participants were subject to an additional training session on a computer – to ensure that they thoroughly understood the N-back task.

The N-back task was presented in a block design, alternating between experimental and baseline conditions. The design conformed to a previous study (Dima et al., 2014). A series of digits, in black font, were displayed on a white background for 1.7 s each, which then disappeared for 0.3 s. The 0-back condition was used to control for task engagement and vigilance. In the 0-back condition, participants were instructed to respond by pressing a button whenever the target digit “3” was displayed. In the working memory conditions (1-, 2-, and 3-back), the target was defined as any digit that was identical to the digit presented 1, 2, or 3 trials back. There were 12 epochs in all, each lasting 30 s, and comprising 10 digits. The entire N-back experiment lasted for 360 s, with a total of 34 targets and 134 non-target stimuli. The reaction time (RT) was measured for correct hits. To avoid any systematic order effects, all conditions were pseudo-randomized.

### Image acquisition and processing of N-back and resting-state fMRI

Functional and structural MRI data were acquired using a 7-Tesla scanner (Intera Achieva; Philips Medical Systems, Best, The Netherlands). fMRI blood oxygenation level dependent (BOLD) signals were obtained using a T2\*-weighted gradient echo-planar imaging (EPI) sequence (repetition time (TR) = 2000 ms; echo time (TE) = 17 ms; flip angle = 70°; matrix =  $128 \times 128$ ; voxel size =  $1.5 \times 1.5 \times 3.6 \text{ mm}^3$ ; field-of-view (FOV) = 192 mm; 30 interleaved slices without slice gap). High-resolution structural images were acquired using a three-dimensional T1-weighted sequence (TR = 4.3 ms; TE = 1.93 ms; flip angle = 8°; matrix =  $320 \times 320$ ; voxel size =  $0.75 \times 0.75 \times 0.75 \text{ mm}^3$ ; FOV = 240 mm; 320 slices).

Preprocessing of N-back task and resting-state fMRI was performed

using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>, Wellcome Trust Centre for Neuroimaging, London, UK). The first 5 scans of fMRI were discarded to ensure magnetic equilibration. The 183 EPIs for N-back and the 300 EPIs for resting state (eye-closed) were pre-processed by correcting for acquisition delays over different slices. Correction for head motion involved realignment of all consecutive volumes to the first image of the session. The realigned images were then co-registered to T1-weighted images, which were used to spatially normalize the functional data into a template space using standard nonlinear transformations. Finally, all normalized images were smoothed using a 6 mm full-width half-maximum Gaussian kernel. Low-frequency drifts were removed using a high-pass filter with a cut-off frequency of 1/128 Hz. Group-level activation was assessed using the usual random effect analysis at the second (between-subject) level. Activation at the group level – among four conditions (0-back, 1-back, 2-back and 3-back) – was tested using a factorial general linear model to generate statistical parametric maps (SPM).

For the group level inference of SPM results for contrasts (2-back vs. 0-back and 3-back vs. 0-back), we set a cluster level criterion with a voxel level threshold  $p < .001$  and the extent threshold  $k > 175$  voxels, which was equivalent to  $p < .05$  corrected by cluster level for multiple comparisons (for full-width half maximum 11.7 mm) as estimated by 10,000 Monte Carlo simulations using the 3dClustSim in AFNI\_17.2.17 (Forman et al., 1995).

To summarize time-series in task-related areas in each individual, we first determined group level effects from the local maximum in second-level SPMs of the conjunction of 2-back and 3-back versus 0-back effects (uncorrected  $p < .01$ ) (Friston et al., 2005; Price and Friston, 1997). The conjunction analysis used SPMs of the minimum  $t$ -statistic over two orthogonal contrasts (2-back vs. 0-back and 3-back vs. 0-back). Inference was based on  $p$ -values adjusted for the search volume using random field theory (Friston et al., 2005). We conducted a conjunction analysis based on the conjunction null hypothesis (i.e., a logical AND analysis) (Nichols et al., 2005) with a combined threshold of  $p < .0001$  over two individual contrast thresholds of  $p < .01$  (i.e.,  $0.01 \times 0.01 = 0.0001$ ).

These maxima were located in the bilateral superior parietal lobule (SPL), bilateral superior frontal gyrus (SFG), bilateral middle frontal gyrus (MFG), left para-cingulate gyrus (PrCG), and the right insula (INS). Individual (subject-specific) 5 mm volumes of interest (VOI) were centered on the nearest local maximum – around the group level maxima – on the first-level conjunction SPM of 2-back and 3-back versus 0-back effects (uncorrected  $p < .001$ ); each with an extent threshold of 100 continuous voxels. The principal eigen variate of all voxels within each VOI was then used to summarize regional activity in both the task and resting-state time series for subsequent DCM.

### Dynamic causal modelling

In order to estimate effective connectivity, we used DCM for fMRI (Friston et al., 2003), which formulates neuronal dynamics in terms of bilinear approximations and hemodynamic responses using an extended balloon model (Buxton et al., 1998; Friston et al., 2003). The neuronal model for a deterministic DCM can be expressed as the following ordinary differential equation:

$$\dot{x} = \left( A + \sum_{j=1}^J B_j u(j) \right) x + Cu \quad (1)$$

Here,  $x$  represents the hidden neural state for each region with dimension  $n \times 1$  and  $u$  represents a  $j \times 1$  vector of experimental inputs. The weighted undirected adjacency matrix  $A$  is  $n \times n$  matrix for an intrinsic connectivity and  $B_j$  is the  $j$ -th  $n \times n$  condition-specific connectivity matrix that is added to the intrinsic connectivity in an input or task-dependent fashion.  $C$  denotes an  $n \times j$  matrix encoding the influence of experimental input on the hidden neural states. The neural state then passes through a hemodynamic response function  $h(x, u, \theta_h)$  with hemodynamic

parameters  $\theta_h$  (Stephan et al., 2007). Finally, the BOLD signal,  $y$ , can be modeled as a mixture of the predicted response and observation error:

$$y = h(x, u, \theta_h) + e \quad (2)$$

Here,  $e$  is a normally distributed error term. Stochastic DCM differs from deterministic DCM (Eq. (1)) in that it includes endogenous or random fluctuation  $\omega$  (Chang and Lin, 2011; Daunizeau et al., 2012). Under a stochastic DCM, Eq. (1) can be rewritten as

$$\dot{x} = \left( A + \sum_{j=1}^J B_j u(j) \right) x + Cu + \omega \quad (3)$$

The driving input matrix  $C$  was specified to assign each item presented – in all conditions – as an input to the bilateral SPLs according to a previous study (Ma et al., 2012), where the driving input on the parietal cortex for working memory task showed an exceedance probability, using Bayesian model selection. A condition specific  $B$  matrix was assigned to all connections and modeled the effects of N-back items presented during either 2- and 3-back conditions. In this setting, the  $A$  matrix of the N-back task is not resting-state effective connectivity but effective connectivity intrinsic to the whole task, in the absence of modulatory 2-back or 3-back working memory effects. We used a fully connected model for an intrinsic connectivity matrix  $A$  and modulatory connectivity matrix  $B$ . We first inverted a deterministic DCM, to evaluate the initial parameters of the stochastic DCM (using the same connectivity model).

For a resting state, the neuronal dynamics in Eq. (3) can be simplified, to a stochastic differential equation with an intrinsic connectivity matrix  $A$ , and a hidden state  $x$ , driven by endogenous stochastic fluctuations  $\omega$ .

$$\dot{x} = Ax + \omega \quad (4)$$

In this setting, the adjacency matrix  $A$  corresponds to intrinsic brain connectivity. To initialize the parameters for stochastic DCM of the rs-fMRI data, we used a spectral DCM as the deterministic homologue (Friston et al., 2014b). Spectral DCM estimates effective connectivity using the observed complex cross spectral density among regions. In other words, instead of fitting the fMRI time series, the DCM is used to explain spectral responses in the frequency domain; however, these data features do not contain information about condition specific effects. We therefore used spectral DCM to initialize the parameters for a more comprehensive estimation of both intrinsic and task specific responses using stochastic DCM. Stochastic DCM uses the same neuronal model (and variational inversion scheme) but accommodates endogenous fluctuations by estimating them explicitly (as opposed to estimating their spectral form). By starting with spectral DCM estimates for  $A$  matrix in Eq. (1) as priors for  $A$  matrix in Eq. (2) in stochastic DCM, we were able to ensure rapid convergence and suppress local minima problems (as evidenced by the number of fitting iterations and the accuracy of the fits). We now turn to inferences about differences in effective connectivity within and between subjects.

### Parametric empirical Bayesian (PEB)

We conducted group (between-subject) level inference for DCM using the parametric empirical Bayesian scheme in SPM12. This allows one to specify between-subject linear models at the second level. A detailed explanation can be found in (Friston et al., 2015, 2016). Briefly, the first (within-subject) estimates are summarized in terms of posterior expectations and covariances and are passed to a second (between-subject) level to estimate posterior expectations and covariances of group means and other between-subject effects. At the second level, we used a general linear model with between-subject effects  $\beta$  on within-subject effects  $\theta = \{A, B, C, \theta_h\}$  encoded by a design matrix  $X$ .

$$y_i = \Gamma(\theta_i) + \varepsilon_i^{(1)}$$

$$\theta = (I \otimes X)\beta + \varepsilon^{(2)} \quad (5)$$

Here,  $\Gamma$  is a function that returns the predicted observations as a function of the model parameters (corresponding to Eqs. (2) and (3) for task fMRI and Eqs. (2) and (4) for rsfMRI). This hierarchical or parametric empirical Bayes model means that the parameters  $\theta_i$  of the  $i$ th subject are modeled as a group average, plus a random effect  $\varepsilon^{(2)}$ . In the current study, we used a simple between-subject design matrix  $X = [1 \dots 1]^T$ , rendering  $\beta$  group means. Note that this PEB model furnishes estimates of group means and subject-specific (connectivity) parameters  $\theta_i$  that are optimally shrunk to the group mean.

### Post hoc analyses of connectivity

To define *similarity* between the effective connectivity induced under the N-back task and resting state in each individual, we used the Pearson's correlation coefficient for three pairs of connectivity matrices; 1) the correlation between intrinsic connectivity A under N-back task ( $A_{\text{task}}$ ) and resting state ( $A_{\text{rest}}$ ) 2) the correlation between changes in connectivity B under the N-back task ( $B_{\text{task}}$ ) and intrinsic resting-state connectivity A ( $A_{\text{rest}}$ ) and 3) correlation between the task related connectivity  $A_{\text{task}} + B_{\text{task}}$  under the N-back task and intrinsic resting-state connectivity  $A_{\text{rest}}$ . The correlations were calculated for each subject—both including and excluding self or recurrent connections (effective connections on the leading diagonal of connectivity matrices).

Because the A matrix encodes intrinsic connectivity and the B matrix encodes changes in connectivity (induced by condition or working memory effects), the sum of the A and B matrix can be associated with the effective connectivity expressed during the (working memory) conditions. Furthermore, note that the intrinsic (within-region) connections, along the leading diagonal of the A matrix, are log scale parameters in DCM for fMRI. This contrasts with the extrinsic (between-region)

connections on the off-diagonal elements, which parameterize effective connectivity directly in terms of Hz. In other words, the within and between node connections have slightly different parameterizations (i.e., the log of a negative self-connection versus the connectivity between different regions). However, both have a prior expectation of zero and, in the absence of any structured connectivity, should show no correlation when estimated from independent data.

To characterize systematic between-subject variability in responses to the working memory tasks, we clustered individuals according to cross-subject similarity (correlation coefficient) matrix of  $B_{\text{task}}$ , using a modularity optimization function in the brain connectivity toolbox (Leicht and Newman, 2008; Rubinov and Sporns, 2010), from which the maximum modularity (indexed as Q) was obtained (Newman and Girvan, 2004). We performed modularity optimization to search for the most optimized community structure for 100 iterations. All Qs and groupings (into three subgroups for  $B_{\text{task}}$  and into two subgroups for  $A_{\text{rest}}$ ) were identical. For each subgroup or cluster, we performed *post hoc* PEB of the N back DCM. For completeness, this *post hoc* subgroup analysis was also applied to the resting-state connectivity.

For the evaluation of the relationship between the similarity of  $A_{\text{rest}}$  versus  $B_{\text{task}}$  matrices and reaction times across individuals, we first identified  $B_{\text{task}}$  edges that showed large inter-subject variability in order to emphasize individual differences (i.e., to ensure high between-subject experimental variance). To identify these connections, we divided edges into two groups; according to standard deviation (variation across subjects) of  $B_{\text{task}}$  using a k-means algorithm ( $k = 2$ ). For the high variance edges, Fisher Z-transformation of Pearson's correlation coefficients between the pattern of  $B_{\text{task}}$  and  $A_{\text{rest}}$  were used as a measure of similarity. These rest-task connectivity similarities (of high variance edges) were correlated with the RTs of 2-back tasks.

Fig. 1 summarizes the procedures entailed by the current study.

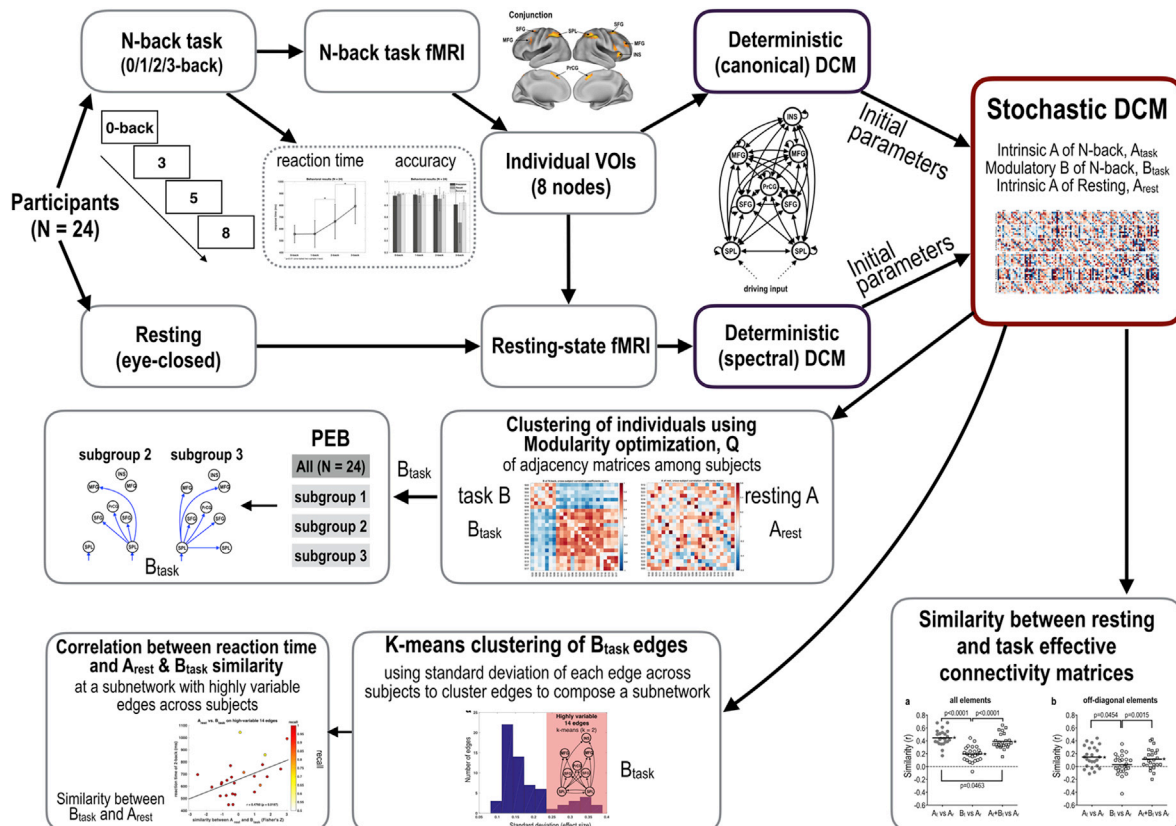


Fig. 1. Procedure for DCM of resting-state and N-back task fMRI.

## Results

### Different performance by N-back task difficulty

Mean and standard deviation of the RTs during 0-, 1-, 2-, and 3-back trials were 556.48 (74.27), 557.79 (113.98), 662.21 (146.39), and 792.24 (149.95) ms, respectively. The differences between group mean RTs were significant ( $p$  of 0-back vs. 2-back = .0012,  $p$  of 0-back vs. 3-back < .0001,  $p$  of 1-back vs. 2-back = .0007,  $p$  of 1-back vs. 3-back < .0001,  $p$  of 2-back vs. 3-back = .0059) except for the mean RT of 0-back vs. mean RT of 1-back. The accuracy, recall, and precision for all conditions were over 90%, except recall of 3-back condition (Table 1).

### Regions-of-interest for N-back task

Figure 2a, b, and 2c show brain regions activated during the N-back task (2-back versus 0-back, 3-back versus 0-back (2a) and conjunction analysis of 2-back and 3-back versus 0-back (2b and 2c), which were subsequently used as nodes in the DCM analysis. The regions engaged by the task were the left superior parietal lobule (SPL;  $-42, -50, 56$ ), right SPL (38,  $-52, 50$ ), left superior frontal gyrus (SFG;  $-28, 2, 60$ ), right SFG (28, 2, 58), left middle frontal gyrus (MFG;  $-44, 28, 30$ ), right MFG (42, 38, 32), para-cingulate gyrus (PrCG; 0, 16, 50), and the right insula (INS; 34, 20, 0). Based on these coordinates, we summarized regional activity in both task-state and resting-state fMRI time series using (subject-specific) principal eigen variates.

### Stochastic DCM

Fig. 3 shows the estimated stochastic DCMs for the N-back and resting state of all participants. In the present study, three types of effective connectivity matrices were estimated, A matrix (intrinsic) of N-back, B matrix (modulatory effects) of N-back working memory tasks, and A matrix of resting state.

### Similarity of effective connectivity between task and resting states

Similarities between the resting-state A matrix and three other matrices were calculated: N-back A matrix ( $A_{\text{task}}$  vs.  $A_{\text{rest}}$ ), N-back B matrix ( $B_{\text{task}}$  vs.  $A_{\text{rest}}$ ), and the sum of A and B matrices of N-back ( $A_{\text{task}} + B_{\text{task}}$  vs.  $A_{\text{rest}}$ ). The similarity were significantly positive when averaged across subjects (one sample  $t$ -test) and showed a significant main effect (one-way ANOVA,  $p < .0001$ ) (Fig. 4a). These positive correlations were preserved even when omitting self-connections: positive correlations between resting-state and N-back off-diagonal elements were significant across all subjects except for the case of B matrix of N-back versus A matrix of resting state (Fig. 4b). Similarities on off-diagonal elements of  $A_{\text{task}}$  vs.  $A_{\text{rest}}$ ,  $B_{\text{task}}$  vs.  $A_{\text{rest}}$ , and  $A_{\text{task}} + B_{\text{task}}$  vs.  $A_{\text{rest}}$  were also significantly different (one-way ANOVA,  $p = .0402$ ) and similarities of  $A_{\text{task}}$  vs.  $A_{\text{rest}}$  and  $A_{\text{task}} + B_{\text{task}}$  vs.  $A_{\text{rest}}$  were significantly higher than that of  $B_{\text{task}}$  vs.  $A_{\text{rest}}$  (Fig. 4b). Lower similarities between B matrix of N-back

**Table 1**

Reaction time, accuracy, recall, and precision for each condition. Significance was assessed by paired  $t$ -tests (significance level = 0.05).

| conditions | reaction time (ms)                | accuracy         | recall           | precision        |
|------------|-----------------------------------|------------------|------------------|------------------|
| 0-back     | 556.48 (74.27)                    | 0.996<br>(0.007) | 0.995<br>(0.018) | 0.979<br>(0.036) |
| 1-back     | 557.79 (113.98)                   | 0.992<br>(0.023) | 0.980<br>(0.059) | 0.990<br>(0.034) |
| 2-back     | 662.21 (146.39) <sup>a</sup>      | 0.987<br>(0.027) | 0.954<br>(0.105) | 0.986<br>(0.049) |
| 3-back     | 792.24<br>(149.95) <sup>a,b</sup> | 0.921<br>(0.059) | 0.752<br>(0.171) | 0.906<br>(0.131) |

<sup>a</sup> Significantly longer than 0-back and 1-back.

<sup>b</sup> Significantly longer than 2-back.

and A matrix of resting state ( $B_{\text{task}}$  vs.  $A_{\text{rest}}$ ) were also evident in the analysis of off-diagonal elements.

### Differences among N-back task and resting-state connections

PEB estimates of effective connectivity in the N-back task showed that the group connectivity differed from zero for every connection (at 95% posterior confidence). A subsequent cluster analysis of subject-specific connectivity reveals three different clusters or subgroups. Fig. 5a shows an optimized community structure based on the B connectivity matrix during the N-back task. The modularity  $Q$  of the optimized community structure was 0.3922. PEB estimates of connectivity within each subgroup revealed different intrinsic connectivity patterns (Fig. 5b). The connectivity in subgroup 1 did not reach the confidence level (95%). In subgroup 2, however, 4 edges from the right SPL to bilateral SFG, PrCG, and left MFG were significant. Subgroup 3 had also 6 significant connections, which were from the left SPL to bilateral SFG, bilateral MFG, PrCG, and right SPL (see graphical illustrations of Fig. 5c). There was no significant differences of recall and RTs among the subgroups. For subgroups 1, 2, and 3, the means and the standard deviations of recall of 2-back were 0.960 (0.070), 0.962 (0.100) and 0.917 (0.167), respectively. For 3-back, the means and the standard deviations of recall for three subgroups were 0.737 (0.132), 0.716 (0.166) and 0.893 (0.214). RTs of 2-back of the three subgroups were 663.5 (162.9), 640.5 (155.9) and 730.3 (113.5) ms. RTs of 3-back of the three subgroups were 736.2 (126.8), 823.6 (181.6) and 788.5 (64.5) ms (Fig. 5d).

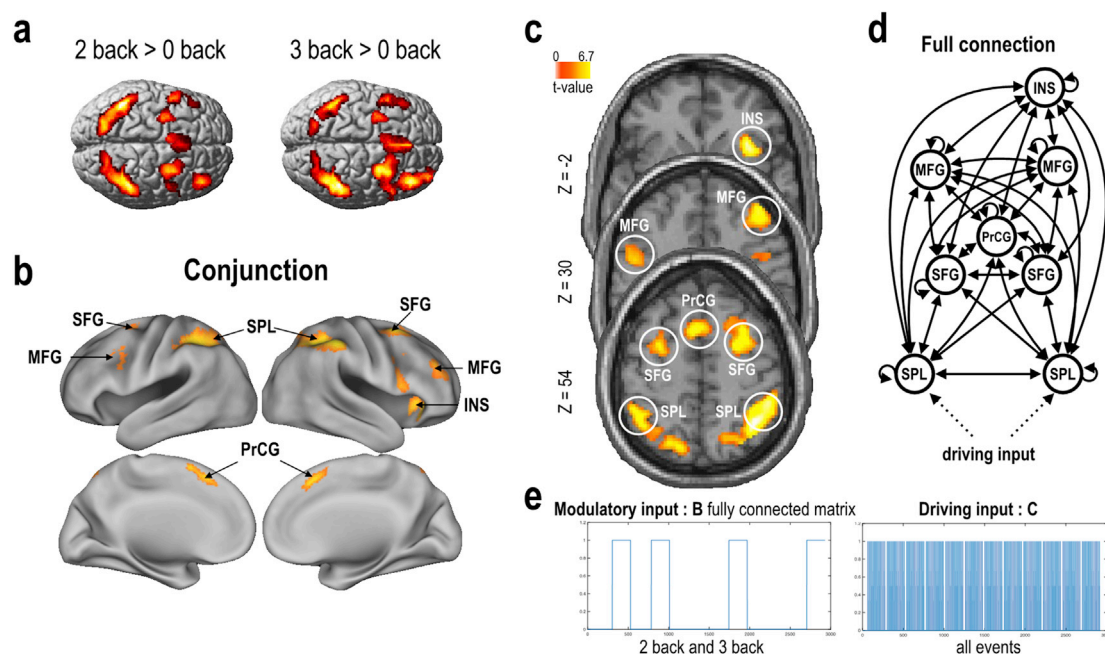
The community structure for resting-state DCMs, based on the between-subject similarity of the off-diagonal elements of A matrix of resting state is shown in Fig. 6. We found two clusters or subgroups but with low modularity ( $Q = 0.1871$ ). Their corresponding PEB results are shown in Fig. 6b. There was no significant difference in mean RT between the two subgroups based on resting-state effective connectivity estimators.

Subgroup differences between pattern similarities of  $A_{\text{task}}$  vs.  $A_{\text{rest}}$ , and  $B_{\text{task}}$  vs.  $A_{\text{rest}}$  were also computed. In the case of N-back, although the similarities of all elements showed a significant difference between  $A_{\text{task}}$  vs.  $A_{\text{rest}}$  and  $B_{\text{task}}$  vs.  $A_{\text{rest}}$  (1-way ANOVA;  $p = .003$  for the subgroup 1,  $p < .001$  for the subgroup 2, and  $p = .015$  for the subgroup 3), the similarities of the off-diagonal elements did not show any significant difference ( $p = .111$ ,  $p = .247$ , and  $p = .108$  for the subgroups 1, 2, and 3, respectively).

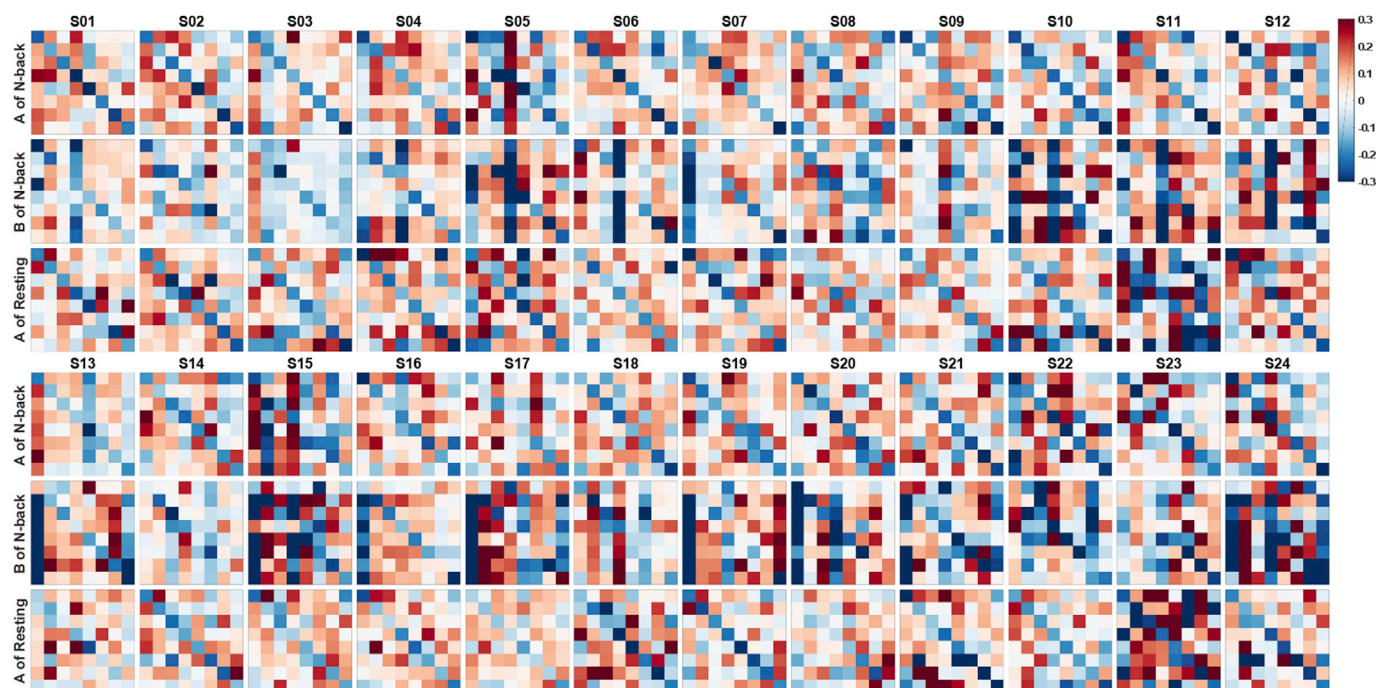
### Association between pattern similarity and behavior

To find out relationship between pattern similarity and behavior, correlation between similarity (between B of N-back and A of resting state) and RTs of N-back task was tested. For similarity on all edges, 2-back was not significantly correlated with the similarity ( $r = 0.252$ ,  $p = .235$ ). In the case of 3-back, it was also not significant ( $r = 0.298$ ,  $p = .157$ ). For similarity on off-diagonal edges, 2-back was not significant ( $r = 0.341$ ,  $p = .10$ ) and 3-back was also not significant ( $r = 0.329$ ,  $p = .117$ ).

To emphasize individual differences (i.e., ensure high between-subject experimental variance), we chose edges that showed high standard deviations of each edge for N-back task ( $B_{\text{task}}$ ) over subjects. Fig. 7a shows that a histogram of standard deviations of B of N-back task ( $B_{\text{task}}$ ) has a bimodal distribution with low and high variance edges (across participants). We found that high variance edges were mostly connections from the parietal to the frontal lobes. The similarities of high variance edges (14 edges) between the N-back B and resting-state A connectivity matrices ( $B_{\text{task}}$  and  $A_{\text{rest}}$ ) were positively correlated with RTs during the 2-back task ( $r = 0.476$ ,  $p = .019$ ; see Fig. 7b). We applied the same analysis to the 3-back, but it was not significant ( $r = -0.080$ ,  $p = .709$ ).



**Fig. 2.** DCM model construction. (a) Group-level (positive) SPM of 2-back and 3-back effects against 0-back ( $N = 24$ , voxel-level uncorrected  $p < .001$ , cluster size  $> 175$  voxels, corresponding to  $p < .05$  adjusted for the cluster-level multiple comparison). (b and c) Group-level SPM evaluated by a conjunction analysis of 2-back and 3-back versus 0-back effects ( $N = 24$ , uncorrected  $p < .01$ , clusters over 100 voxels). Individual activations, corresponding to the group-level activations, were visually identified in the conjunction SPM of 2-back and 3-back versus 0-back effects. From individual VOIs, both task-based and resting-state fMRI time series were extracted. (d) The graph shows the fully connected DCM with 8 VOIs or nodes. (e) Driving inputs from stimuli in all conditions were assigned to the bilateral SPL and task-dependent (working memory) effects of 2-back and 3-back conditions were assigned to every connection. SPL: superior parietal lobule, SFG: superior frontal gyrus, MFG: middle frontal gyrus, PrCG: para-cingulate gyrus, and INS: insula.

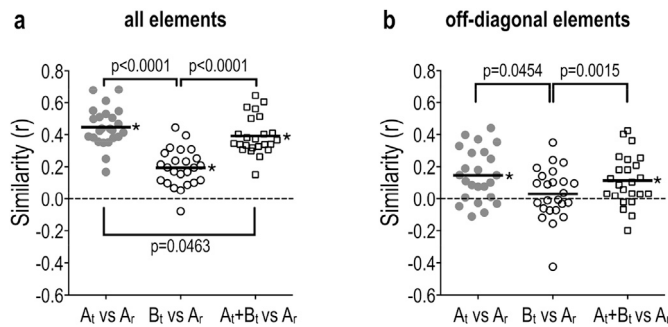


**Fig. 3.** Subject specific effective connectivity matrices following stochastic DCM of the N-back and resting-state fMRI. ‘A’ and ‘B’ matrices correspond to intrinsic and condition related changes (modulatory effect) in effective connectivity. Each matrix element represents effective connectivity among 8 nodes in the following order: left SPL, left SFG, left MFG, right SPL, right SFG, right MFG, PrCG, and right INS. Directions are represented from columns to rows, meaning that the direction of an element  $(n, m)$  of the connection matrix is effective connectivity from the  $m$ -th region to the  $n$ -th region.

## Discussion

The main purpose of this study was to explore the relationship

between effective connectivity during resting state and task performance. In contrast to most previous studies that have associated functional connectivity during the resting state with task-related activity patterns



**Fig. 4.** Similarity of effective connectivity between N-back and resting state. (a) Correlation coefficients between all elements of the connection matrices are displayed. ‘ $A_t$  vs.  $A_r$ ’ represents similarity of effective connectivity between intrinsic connectivity (A matrix) of N-back task and resting state. ‘ $B_t$  vs.  $A_r$ ’ indicates similarity of effective connectivity between modulatory changes (B matrix) of N-back and A matrix of resting state. ‘ $A_t + B_t$  vs.  $A_r$ ’ represents similarity between the effective connectivity during 2-back and 3-back conditions and A matrix of resting state. These similarities on all elements were significantly different (one-way ANOVA,  $p < .0001$ ). (b) As a complementary result, this panel shows the same format that tests for correlations among off-diagonal elements of the connectivity matrices. The three kinds of similarities on off-diagonal elements were significantly different (one-way ANOVA,  $p = .0402$ ). Significant differences in correlations over subjects were tested using paired t-tests. Except for off-diagonal correlations between  $B_t$  and  $A_r$ , all correlations were significantly positive (using a one sample t-test against a null hypothesis of zero correlation). Asterisks (\*) indicate significant positive correlations according to Tukey’s multiple comparisons test ( $p < .05$ ).

(Biswal et al., 1995; Cole et al., 2016; Smith et al., 2009; Tavor et al., 2016; Yeo et al., 2015), we explored both resting-state and task ‘connectivity’ among the same brain regions involved in a specific task, cf. Cole et al. (2014) and Krienen et al. (2014). Furthermore, instead of examining correlation-based functional connectivity, we used effective connectivity for both resting and task states. By utilizing stochastic DCM of resting-state and N-back task fMRI data, from the same brain regions, we observed a strong correlation between intrinsic effective connectivity of resting and task states but a marked divergence of task-related effective connectivity from resting-state intrinsic connectivity. Crucially, when task-related increases in connectivity correlated with the intrinsic connectivity in the N-back task – or the intrinsic connectivity during resting state – reaction times increased. In other words, participants whose effective connectivity (within the working memory related regions) diverged more from baseline or resting-state connectivity reacted more slowly on working memory tasks. Finally, we found a strong clustering of individuals in terms of effective connectivity during the N-back task, which was not found in the resting-state connectivity.

#### Brain activity and connectivity during the N-back tasks

In the current study, we constructed DCM networks of brain regions engaged by the N-back tasks to relate resting-state and task-state effective connectivity. In general, the N-back task is known to recruit the parieto-frontal circuitries (Deserno et al., 2012; Dima et al., 2014; Owen et al., 2005; Park et al., 2011; Schmidt et al., 2014) including the bilateral SFG, bilateral MFG as well as other brain regions; such as right INS, and left PrCG (Barch et al., 2013; Manelis and Reder, 2014). Activations detected during the N-back tasks in the current study were consistent with the findings of these previous studies (Fig. 2).

The current results are also consistent with Dima et al. (2014), who reported effective connectivity from the parietal regions to the frontal regions that differed across conditions (1-, 2-, and 3-back tasks). This previous study pre-specified several hypothesized models with a single effective connectivity of the parieto-frontal lobe and conducted a model comparison of the hypothesized models. The present study differs from

Dima et al. (2014) in that we found effective connectivity from the parietal lobe to the frontal lobe, based on a full connection model.

#### Divergence of task-related effective connectivity from the resting-state intrinsic connectivity

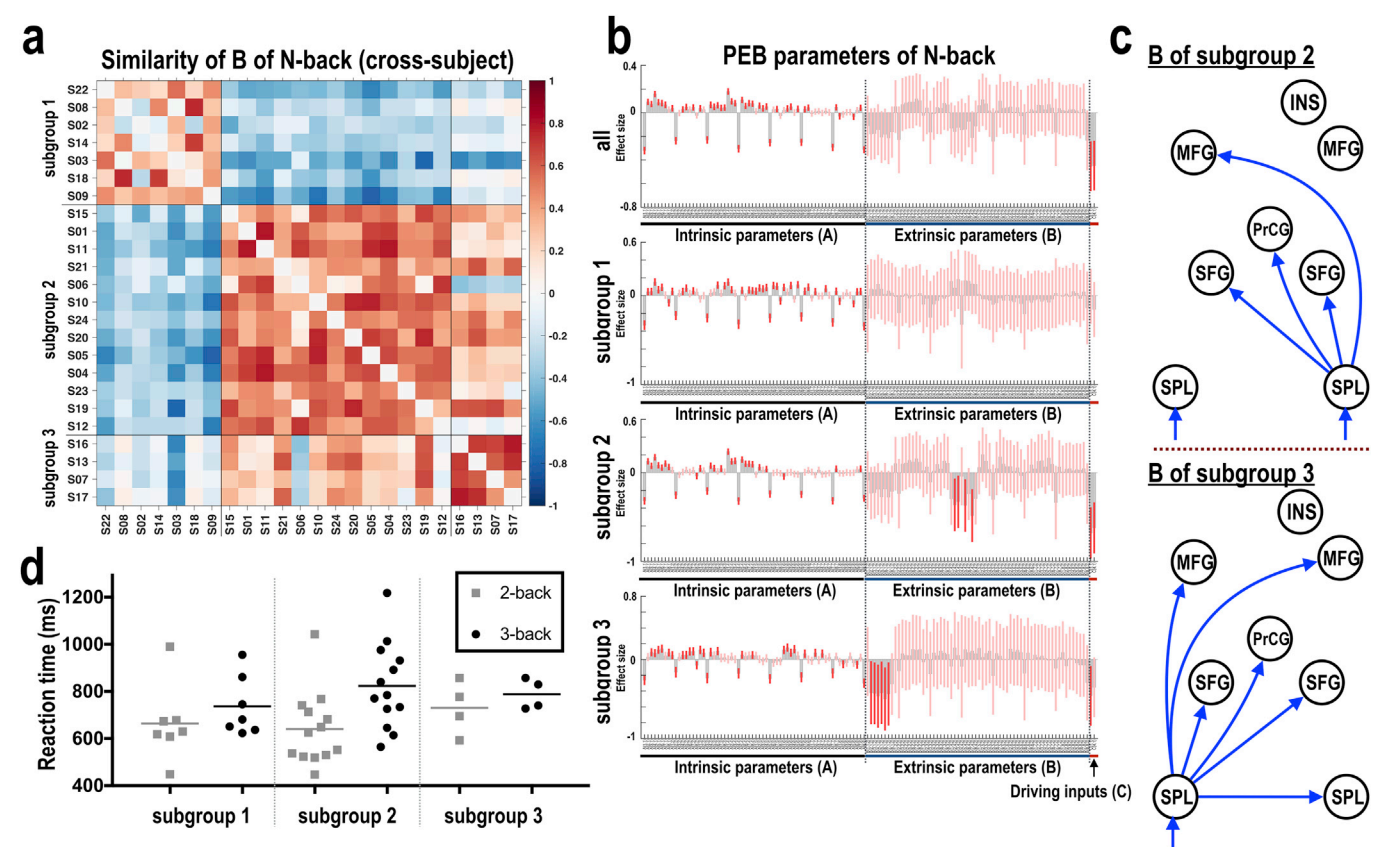
As shown in Fig. 4, the modulatory effective connectivity during the task-state (2-back and 3-back,  $B_{task}$ ) diverges greatly from the intrinsic effective connectivity of resting state ( $A_{rest}$ ), whereas the intrinsic effective connectivity of N-back ( $A_{task}$ ) manifests a similar pattern to that of the A matrix of resting state ( $A_{rest}$ ). Since 0-back task used in this study is not an absolute resting state but a baseline (incidental) task, the A matrix of N-back ( $A_{task}$ ) is not the same as the A matrix of resting state ( $A_{rest}$ ). However, according to previous studies, most regions involved in the 0-back task do not overlap with the regions for 2- or 3-back conditions. Although an increased activation for 0-back task compared to resting state were found in the right MFG (Papma et al., 2012), no activations were found in the left MFG during 0-back condition (Harvey et al., 2005). The similarity between A matrix of N-back condition and A matrix of resting state might be interpreted in this respect. Therefore, we can consider the A matrix of N-back as an intrinsic effective connectivity during N-back task, that is very similar to the intrinsic effective connectivity of resting state. The similarity between A matrix of N-back and A matrix of resting state serves as a reference for interpreting changes in connectivity during N-back task in relation to the intrinsic effective connectivity during resting state.

We found a smaller similarity (i.e. correlation coefficient) between task-related effective connectivity changes (modulatory effect,  $B_{task}$ ) and intrinsic effective connectivity of resting state ( $A_{rest}$ ), which reflects task-dependent and context-sensitive modulations of effective connectivity. Although a strong relationship between the intrinsic connectivity (or distributed spontaneous activity patterns) and task-related functional connectivity (or task-evoked activity patterns) across large-scale whole brain networks has been reported (Cole et al., 2014, 2016; Krienen et al., 2014; Park et al., 2014; Smith et al., 2009; Tavor et al., 2016; Yeo et al., 2015), intrinsic connectivity during the resting state appears not to be recapitulated but modulated or ‘repurposed’ to perform a N-back working memory task.

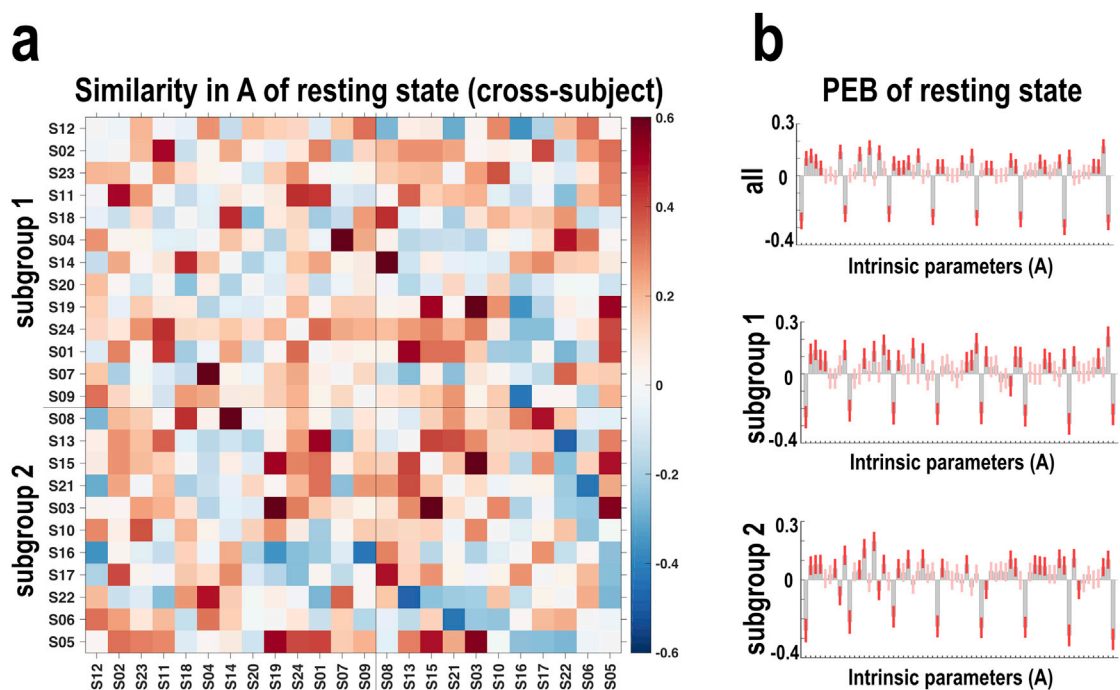
This interpretation of the current results is consistent with previous studies suggesting divergence of task-related connectivity from that of the resting state. Corbetta et al. (2008) reviewed that the brain can reorient an attentive state via a deactivation of brain regions for default network from resting state. Elton and Gao (2014) showed divergence between a network of selective attention task and that of resting state. Moreover, functional connectivity changes during attention and memory tasks appear to facilitate diverse cognitive functions and disclose their context-sensitivity (Hermundstad et al., 2013). The current study further shows that task-related connectivity during the N-back task diverges from the resting-state intrinsic connectivity and that the divergence was positively correlated with reaction times.

#### Group heterogeneity in N-back task effective connectivity

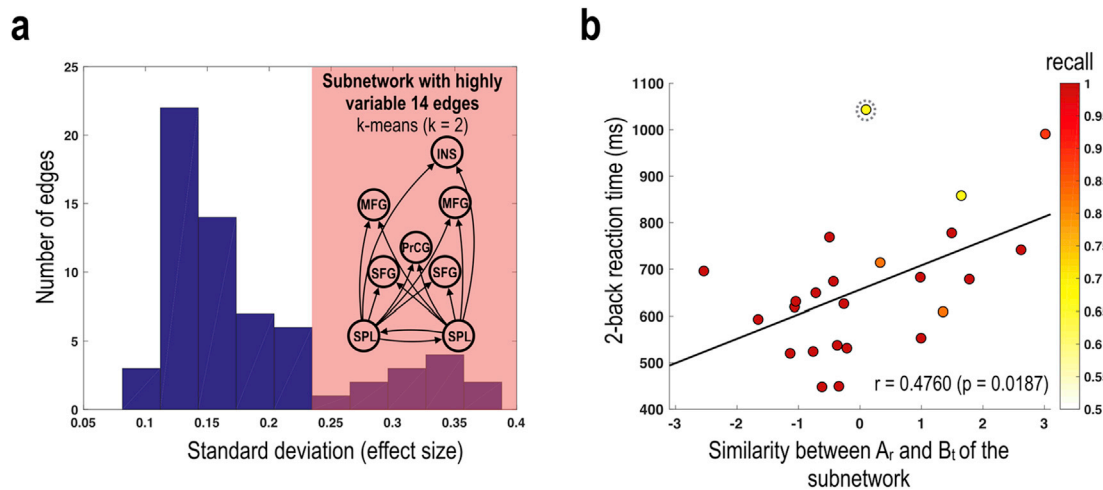
Behavioral performance in working memory tasks is known to vary substantially across individuals (Parasuraman and Jiang, 2012). Each individual can adopt a different strategy to solve a task-problem, which is revealed in distinct brain activity patterns (Tavor et al., 2016). Individuals utilize different brain circuits, not only during working memory tasks but also during general cognitive tasks, and the degree to which this heterogeneity emerges is particularly pronounced for tasks involving higher-level cognitive functions (Barch et al., 2013; Jang et al., 2017). The results of PEB for all participants (Fig. 5b) show that posterior estimates of B matrix of N-back have larger confidence intervals than estimates of A matrix of the task. This result implies that participants may share a common scaffold or backbone of intrinsic effective connectivity but exhibit very different task related changes in connectivity from



**Fig. 5.** Three different subgroups were identified by modularity optimization of the adjacency matrix based on the between-subject similarity of the B matrices of N-back ( $Q = 0.3922$ ). (a) Off-diagonal elements of the B matrix of each individual were used for computing pattern similarity. (b) Subgroup level effect sizes of N-back DCMs for all the subjects and for the PEB estimates of the three subgroups. (c) Significant connectivity B and C (to the bilateral SPL) during the N-back task for subgroup 2 and subgroup 3 are displayed (confidence interval  $p < .05$ ). There was no significant effective connectivity in subgroup 1. Blue arrows indicate negative effective connectivity. (d) The reaction times of 2-back and 3-back tasks in the three subgroups. There were no significant differences of reactions times among subgroups (ANOVA;  $p$  of 2-back = .597;  $p$  of 3-back = .497).



**Fig. 6.** Modularity optimization of the adjacency matrix based on the between-subject similarity of the resting-state A matrix (off-diagonal part). The very low modularity index indicates weakly separable clusters ( $Q = 0.1871$ ). Effective connectivity in the resting-state DCMs for each subgroup was estimated by PEB.



**Fig. 7.** The relationship between the reaction times and coupling between intrinsic ( $A_r$ ) and modulatory ( $B_t$ ) effective connectivity for N-back tasks. (a) Histogram of standard deviations (across subjects) of edges in  $B_t$  reveals a bimodal distribution. Highly variable edge group (14 edges) clustered by the standard deviation of  $B_t$  across subjects using a K-means algorithm corresponded to connections from the parietal lobes to the frontal areas. We chose highly variable edges as a subnetwork for the correlation analysis with reaction times. (b) Similarity between effective connectivity  $A$  of resting state ( $A_r$ ) and  $B$  of task ( $B_t$ ) was computed on the subnetwork with highly variable 14 edges. Correlation between the RT of 2-back and the similarity was significant and positive ( $r = 0.476$ ,  $p = .0187$ ; without an outlier (gray dotted circle) detected using Tukey's fences with  $k = 1.5$  for reaction times,  $r = 0.567$ ,  $p = .0048$ ).

subject to subject.

This inter-subject heterogeneity was more prominent in the task-driven effective connectivity than the resting-state intrinsic connectivity. In contrast to low modularity  $Q$  of  $A$  matrices during the resting state (0.1871), the modularity  $Q$  of similarity matrix of  $B$  matrices of N-back tasks was 0.3922; in the range from 0.3 to 0.7, which is typically known to form a strong community structure (Newman and Girvan, 2004). Participants exhibit three network phenotypes when performing the N-back task, speaking to the *network degeneracy* hypothesis introduced above. For example, the changes in connectivity in subgroup 2 are primarily from the right SPL, while subgroup 3 shows a selective enabling of effective connectivity primarily from the left SPL (see PEB estimates extrinsic parameters from subgroups 2 and 3 in Fig. 5c). This diversity was also evident in the high variation across individuals in the modulatory effective connectivity from the parietal to the frontal lobes (Fig. 7a). Note that the behavior performance was not significantly associated with the phenotypes of effective connectivity pattern, i.e., each group shows no significant differences in the recall or reaction times. Therefore, we interpret this finding to reflect that individuals adopt different strategies and engage different neural networks when performing a task.

In a previous study by Dima et al. (2014), there were several DCM architectures that could explain fMRI data for the 2-back tasks. This study implies involvement of distinct functional networks across individuals – for the working memory tasks studied here. A sub-typing of working memory circuits was also found in the study of Brodersen et al. (2014), who showed three subgroups of schizophrenia following DCM of the N-back task, having significantly different symptom scores on standard (schizophrenia research) instruments.

Finally, the modularity of similarity matrix of intrinsic effective connectivity during the resting state did not show a strong community structure. This finding may be attributable to the conservation of intrinsic effective connectivity across individuals as a characteristic of intrinsic human brain networks.

#### Relation between connectivity changes and reaction times

The relationship between the task-related and the resting-state networks has been studied by many to explain or predict behavioral performance. Sala-Llanch et al. (2012) found that participants who exhibit a stronger negative correlation between the resting-state default mode network and working memory networks perform better in behavioral

tasks. Elton and Gao (2014) also showed that the dissociation between a network in the resting state and the connectivity from a selective attention task was positively correlated with task accuracy. In line with these studies, we found that similarities between the intrinsic effective connectivity during the resting state and the task-related effective connectivity were positively correlated with RTs during the 2-back condition. This result implies that faster responses are associated with a greater divergence of task-related connectivity from the intrinsic connectivity of resting state. This relationship was not significant during the 3-back condition, which may be attributable to performance failures in this condition (8 out of 24 participants did not attain a recall rate of 70%).

It should be noted that the correlation coefficient between reaction times for 1-back and 2-back conditions across individuals was very high ( $r = 0.7151$ ,  $p = .0001$ ). This high correlation suggests that the inter-individual differences in reaction times under high recall rates can be attributable to the characteristic of each individual (e.g., speed) in information processing (for example, decision processes (Pearson et al., 2014)) that is not exclusively governed by task loads. In this respect, the amount of task-induced reconfiguration in the effective connectivity can be neuronal underpinnings for individualized characteristic of information processing, which is reflected in the reaction times. This strong correlation was not found in reaction times between the 2-back and the 3-back conditions, implying heterogeneous causes of reaction times across individuals in the 3-back condition (diverse recall-rates). The cognitive processes reflected in the accuracy and reaction times and dissociation of these measures in the N-back task are not fully resolved (Meule, 2017). Therefore, the implication of task-induced effective connectivity changes in association with reaction times remains to be resolved in future studies.

#### DCM in 7 T MRI

The data sets of task and resting-state fMRI were acquired at a relatively high magnetic field strength, 7 T MRI. The activated regions during the N-back tasks were similar to the regions identified in previous studies that used the same experimental paradigm with the magnetic field of 1.5 T (Dima et al., 2014) or 3 T (Deserno et al., 2012). The modulatory or task-specific effect of N-back tasks on the connectivity from the parietal lobe to the frontal lobe observed in the current study was equivalently observed by the previous studies of N-back tasks performed at 1.5 T (Dima et al., 2014). This suggests that DCM can consistently identify

neural architectures underlying cognitive tasks regardless of different magnetic field strengths. We expect the differential effects of 3 T and 7 T on DCM will be explored further in future studies.

In this study, the driving input parameter C had a negative value. This means that the driving input reduces overall activity in the target regions; presumably through interactions between excitatory (e.g., spiny stellate) and inhibitory interneurons, in receipt of afferent driving input. Interestingly, the negative effective connectivity from the parietal regions to the frontal regions means that the frontal regions are effectively disinhibited by driving input. In other words, the input inhibits the inhibitory influences mediated by extrinsic (between-region) connections between the parietal and prefrontal regions.

In the current study, we considered both diagonal and off-diagonal elements in the effective connectivity matrix (both intra-regional and inter-regional connectivity). The diagonal (self-connections) are an important aspect of effective connectivity and correspond to self-inhibition that determines a nodes response to all afferent input (i.e., excitability). This contrasts with functional connectivity analyses, in which coupling is restricted to the correlation between the nodes. We therefore supplemented our characterization by restricting the comparison to off-diagonal (between nodes) connectivity for readers who more are familiar with inter-regional functional connectivity. The diagonal elements encode recurrent connectivity (intra-regional local connectivity), which reflects canonical micro-circuitry mediated largely by inhibitory interneurons. In analysis of effective connectivity, both inter-regional and intra-regional coupling needs to be modeled.

Finally, we modeled task-related effective connectivity changes in both 2-back and 3-back condition; to ensure more reliable parameter estimation. Thus, the effective connectivity described in this paper reflects a common circuit involved in both 2-back and 3-back processing.

### Limitations

In this study, we used effective connectivity, defined in terms of a DCM, to offer a proof of principle that task-state functional networks are reconfigured in a context-sensitive fashion during task performance. However, there are several limitations of our study, in terms how this proof of principle generalizes. First, we have assumed that intrinsic networks are isomorphic with resting state networks; as opposed to network configurations that are common to all possible brain states. To establish the validity of an intrinsic network – that was conserved under multiple tasks – one would need to evaluate effective connectivity under multiple cognitive tasks, rather than just one (e.g., the N-back task). In this context, the resting state becomes another brain state that may, or may not, have a special role in defining intrinsic brain networks. This approach has already been established in the context of functional connectivity (Elton and Gao, 2014; Sala-Llonch et al., 2012; Schultz and Cole, 2016) – and it would be interesting to pursue using effective connectivity.

Secondly, the relatively small number of nodes in our models may mean that we did not characterize some edges recruited by the task. We restricted our effective connectivity analysis to the nodes that have been shown to be actively engaged by the task by previous fMRI studies; primarily, because we did not want task-independent edges to bias the similarity measures between resting and task effective connectivity matrices. However, we cannot preclude the possibility that edges not considered in our models may have been recruited for the N-back task. Indeed, functional connectivity analyses of rest-task relationships generally use large-scale brain networks with more than 100 nodes (Cole et al., 2014, 2016; Krienen et al., 2014; Park et al., 2014; Smith et al., 2009; Tavor et al., 2016; Yeo et al., 2015). We note that whole brain networks, not just task activated nodes, may be reconfigured for (and thus directly or indirectly involved in) the task. Future studies using large-scale DCMs (Frassle et al., 2017; Razi et al., 2017; Seghier and Friston, 2013) could, in principle, address the question of rest-task effective connectivity in terms of large-scale networks and provide a

complementary perspective on functional connectivity.

Another limitation of our study is that the sample size was relatively small. Although the current sample size ( $N = 24$ ) is within the range of most fMRI studies, a larger sample size would have provided more efficient estimates of between subject variability (Yarkoni and Braver, 2010).

Finally, our conclusions are conditioned on the particular model considered. In contrast to functional connectivity analyses (Mill et al., 2017; >Smith et al., 2011; Wang et al., 2014), current conclusion is based on the effective connectivity analysis. Effective connectivity is defined in relation to a model of directed coupling that – in the context of dynamical systems like the brain – corresponds to a dynamic causal model (Friston, 2011; Friston et al., 2014a; Valdes-Sosa et al., 2011). However, there is still an issue of plurality; not in terms of the analysis but in terms of the models that are compared. We considered a stochastic dynamic causal model to address our hypotheses. It may be interesting to revisit this question with other sorts of DCMs (for example, deterministic models). It would be also interesting to compare task-rest relationship in the effective connectivity with that estimated in functional connectivity analysis. As functional connectivity analysis has strong advantages for large scale networks and has been widely used in diverse applications, it would be promising to integrate both model-driven (effective connectivity) and data-driven (functional connectivity) approaches, from analysis to interpretation.

In summary, we have (i) explored context-sensitive divergence of task-related effective connectivity from the intrinsic resting-state effective connectivity, (ii) examined phenotypes of effective connectivity across participants during tasks and (iii) have found association between reaction time and the degree to which intrinsic effective connectivity is reconfigured, regardless of the phenotypic connectivity. This suggests that the degree to which a task-dependent coupling in the brain diverges from task-free intrinsic coupling is associated with task performance.

### Acknowledgement

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