Combining Task-Related Activation and Connectivity Analysis of fMRI Data Reveals Complex Modulation of Brain Networks

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Abstract: Task-related effects in functional magnetic resonance imaging (fMRI) data are usually analyzed with local activation approaches or integrative connectivity approaches, for example, by psychophysiological interaction (PPI) analysis. While both approaches are often applied to the same data set, a systematic combination of the results with a whole-brain (WB) perspective is rarely conducted and the relationship between task-dependent activation and connectivity effects is relatively unexplored. Here, we combined brain activation and graph theoretical analysis of WB-PPI results in an exemplary episodic memory data set of $N = 136$ healthy human participants and found regions with congruent as well as incongruent activation and connectivity changes between task and control conditions. A comparison with large-scale resting state networks showed that in congruent as well as incongruent regions task-positively modulated connections were mainly between-network connections, especially with the default mode network, while task-negatively modulated connections were mainly found within resting state networks. Over all regions, the strength of absolute activation effects was associated with the tendency to exhibit task-positive connectivity changes, mainly driven by a strong relationship in negatively activated regions. These results demonstrate that task demands lead to a complex modulation of brain networks and provide evidence that task-evoked activation and connectivity effects reflect separable and complementary information on the macroscale brain level assessed by fMRI. *Hum Brain Mapp* 38:5726–5739, 2017. © 2017 Wiley Periodicals, Inc.

Key words: functional magnetic resonance imaging; psychophysiological interaction; task; resting state; default mode network; hippocampus; graph theory

INTRODUCTION

The human brain is a highly complex organ that can be conceptualized as a network that concurrently shows functional segregation and integration between its functional

modules [Deco et al., 2015; Sporns, 2013; Tononi et al., 1994]. When experimentally evoked effects in the human brain are assessed in functional magnetic resonance imaging (fMRI) research, they are typically studied with either a local perspective of changes in brain activation or with

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an integrative perspective of connectivity between brain regions. Interestingly, the topography of functional brain networks is generally similar during task and resting state conditions and task-evoked changes are small in comparison to the primary functional network structure [Cole et al., 2014; Gratton et al., 2016; Krienen et al., 2014], which has been linked to the anatomical structure of the brain [Greicius et al., 2009; Marrelec et al., 2016; van den Heuvel et al., 2009]. The small task-dependent connectivity changes evoked by an experiment are, however, of primary interest for investigating specific brain functions, and can be assessed for example by psychophysiological interaction (PPI) analysis [Friston et al., 1997; McLaren et al., 2012; O'Reilly et al., 2012].

While often both, task-dependent activation and task-dependent connectivity analysis are applied to the same data set, a systematic combination of the two analysis strategies with a whole-brain (WB) perspective is less often conducted. Therefore, the relationship between local brain activation and interregional connectivity changes in accordance with task demands hitherto remains an open question.

Early computational studies by Chawla et al. [1999, 2000] with two-region models suggest that mean activity and interregional synchronization are strongly related [Chawla et al., 1999], and that this relationship also holds when activity is integrated over time as in neuroimaging [Chawla et al., 2000]. Tomasi et al. [2013] used [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) and fMRI to measure local glucose metabolism and resting state signal fluctuations and connectivity and found that glucose metabolism was positively associated with both, fluctuation amplitude and the number of connections of regions (degree). Riedl et al. [2014] directly tested this relationship with simultaneous FDG-PET/fMRI in a resting state experiment where they contrasted periods with eyes closed and eyes open and found that local neuronal activity increases coincided with increased connectivity between the visual system and the and salience network.

However, when fMRI studies are considered that combined task-dependent activation and connectivity analysis, the relationship seems to be less direct. While some studies find connectivity increases between activated regions [Gazzaley et al., 2007; Spadone et al., 2015], other studies suggest that activity and connectivity effects can diverge. King et al. [2015] studied task-dependent connectivity changes during memory recollection by PPI with five seed regions in the “core recollection network” and identified a broadly distributed set of brain regions with increased connectivity. Importantly, they found overlapping as well as nonoverlapping task-modulated activation and connectivity effects, suggesting that both analyses to a certain degree provide complementary information. In a repeated viewing paradigm with short video clips, Andric et al. [2016] found that repeated viewing of the clips produced highly similar voxel time courses in left perisylvian

regions but changed global brain connectivity patterns of the same regions substantially, revealing large-scale network reorganization despite maintained local activity profiles. In a very comprehensive study, Gratton et al., [2016] found that the average absolute task-dependent change in functional connectivity of brain regions was positively associated with the average absolute task-dependent signal change, and that activated and more connected regions showed connection patterns related to cognitive control and task demands. Independent from this influence they found that whether regions were serving as hubs in the network was associated with network modulation. However, due to the existing but imperfect relationships they conclude that “while activation and correlation measures may be related, they appear to index separable aspects of brain function” [Gratton et al., 2016, p. 1284].

Our results provide further evidence to support this conclusion. We have recently adapted PPI analysis to a whole-brain manner (WB-PPI) [Gerchen et al., 2014; see also Cocchi et al., 2013; Cole et al., 2013; Fornito et al., 2012; Hearne et al., 2015; Minati et al., 2012; Sripada et al., 2014] and found in a subsample of the data presented here ($n = 41$, recall phase only) that brain regions can possess task-modulated connections even when they do not contain significant activation [Gerchen et al., 2014]. Here, we extend this approach in an exploratory study in which we apply graph theoretical approaches to WB-PPI results to characterize local integrative behavior. We first use the total nodal degree to identify regional contrast-specific connectivity changes and then integrate the information of the contrast directions to define brain regions with clear preferences in the direction of task-dependent connectivity. Through combination with activation effects, we are then able to explore and map brain networks with both, congruent as well as incongruent changes in activation and connectivity. Our results clearly demonstrate both, coinciding as well as dissociable activation and connectivity effects and thus demonstrate the complex modulation of brain networks during task execution.

MATERIALS AND METHODS

Participants

$N = 136$ healthy right-handed participants [age 31.99 ± 9.72 years ($\bar{O} \pm$ standard deviation (SD)), range 18–51 years, 65 ♀] eligible for MRI scanning and without a history of mental or neurological disorders were included in the analysis. The original sample consisted of 140 participants, but four participants were excluded due to excessive head motion during scanning (see below). Resting state data was available from 135 of the 136 participants. All participants provided written informed consent and received 50 € for participation. All procedures conformed to the Declaration of Helsinki and were approved by the local ethics committees of the Medical Faculties Mannheim and Heidelberg at the University of Heidelberg.

Figure 1.

Episodic memory task and task-dependent activation and connectivity results. **A:** Task conditions. The task had a simple ABAB block design and consisted of two separate scanning sessions (encoding and recall phases) that both used the same control condition. Button box symbols represent required button presses. **B,C:** Activation effects in the encoding and recall phase at $P < 0.05$ FWE corr. **D,E:** WB-PPI effects in the encoding and recall phase. t -Value matrices are sorted with respect to large

scale resting state networks. Maps indicating regions in the sensory-motor, fronto-parietal, and default mode networks are shown as small symbols on the axes. t -Values range from negative (control > task) to positive effects (task > control). For condition-specific connectivity results see Supporting Information Figure S5. [Color figure can be viewed at wileyonlinelibrary.com]

Materials and Procedures

MRI scanning was performed at two similar 3T Siemens Trio TiM magnets at the Central Institute of Mental Health Mannheim and the University of Heidelberg, Germany. Echo-planar imaging (EPI) during task execution was conducted with a TR of 1.8 s, TE 30 ms, 73° flip angle, a field of view of 192 mm, $3 \times 3 \times 3$ mm voxel size, 33 slices of 3 mm with 33% gap, and GRAPPA with iPAT = 2. Resting state EPI scanning was conducted with a TR of 1.37 s, TE 25 ms, 73° flip angle, a field of view of 192 mm, $3 \times 3 \times 4$ mm voxel size, 25 slices of 4 mm with 33% gap, and GRAPPA with iPAT = 2.

We used an episodic memory task [Erk et al., 2010] in which participants had to learn and recall associations between faces and professions that consisted of two separate phases. In the encoding phase (7:19 min) participants saw 16 face-profession pairs twice which they were instructed to remember. To promote deeper encoding they indicated by a right or left button press whether they had the subjective impression that face and profession were matching or not. In the subsequent recall phase (3:47 min) the same faces were presented and participants indicated, again by a right or left button press, whether job training or a university degree is a prerequisite for the associated

profession. Both phases used the same control condition in which schematic heads were presented and participants indicated by button press whether the right or left ear was larger. The experiment had a block design of alternating blocks of 4 experimental trials and 6 control trials with a block duration of 24 s (Fig. 1A). The resting state scan had a duration of 5:08 min and was acquired in the same scanning session as the task data.

fMRI Preprocessing

Analyses were performed with MATLAB (MathWorks, Sherborn, MA). Preprocessing of the functional images was conducted with SPM8 (v4667, Wellcome Department of Cognitive Neurology, London, UK). Images were slice time corrected, realigned, normalized to the MNI EPI template, rescaled to $3 \times 3 \times 3$ mm voxel size, and smoothed with a full width at half maximum of $6 \times 6 \times 6$ mm Gaussian kernel. To additionally account for deleterious effects of small head movements we used the ART toolbox (http://www.nitrc.org/projects/artifact_detect) to identify volumes with head movements >0.5 mm and/or a z -score of global mean intensity changes >6 . Four participants with more than 33% affected scans in any of the task conditions were excluded. In the remaining participants,

dummy variables marking the identified volumes were included in all first level analyses. In addition, the first eigenvariate from cerebrospinal fluid (CSF) was extracted and included as a covariate.

Conventional SPM Analysis

To identify task-dependent activation changes, one sample *t*-tests with age, sex, and scanner site included as covariates were conducted in SPM over the results of first level general linear models (GLMs) containing condition-specific box car functions of the experimental blocks convolved with the canonical hemodynamic response function (HRF), movement regressors, ART dummy variables, the CSF signal, and a constant. A high-pass filter cut-off of 128 s was used. A similar first level model without the experimental regressors was used for the resting state data analysis.

In the task data, each phase (encoding and recall) had a simple block design with alternating experimental and control conditions, and the contrasts task > control (encoding > control or recall > control) and control > task (control > encoding or control > recall) were constructed in both phases. A significance threshold of $P < 0.05$ FWE corr. was used for each contrast direction. Throughout this article, results for the contrasts task > control are referred to as being in the task-positive or positive direction, while results for the contrasts control > task are referred to as task-negative or negative. This naming was chosen solely to make the results easier to present. Because we label specifically our empirical results, differences to what is generally understood as task-positive and task-negative networks [e.g., Fox et al., 2005] do exist.

Clustering

Before WB-PPI analysis, the functional task data corrected for task effects, movements (standard & ART) and the CSF signal was parcellated by normalized cut spectral clustering (NCUT) [Craddock et al., 2012] into 944 spatially restricted and locally continuous regions of interest (ROIs). NCUT detects regions that are maximally similar within and maximally different between clusters based on the correlation of the BOLD time courses of neighboring voxels [Craddock et al., 2012]. The parcellation was restricted to gray matter voxels. For quantitatively investigating the relationship between regional activation and connectivity, first eigenvars of the activation effects were extracted from each ROI and absolute and directed activation estimates were correlated with connectivity effects (see Supporting Information Figures S6–S8).

Resting State Network Community Detection

To explore the relationship of task effects with the inherent functional architecture of the brain we estimated large-scale networks from the resting state data. We estimated a mean connectivity matrix over Fisher *z*-transformed Pearson

correlations between the eigenvariate time courses corrected for all nuisance variables of the same ROIs as in the task data, thresholded [4% density, selected with the objective of obtaining a well-defined default mode network (DMN) community] and binarized the matrix, and applied the Infomap community detection algorithm [Rosvall and Bergstrom, 2008; <http://www.mapequation.org>] to detect large-scale resting state networks. Networks comprising <15 ROIs were not considered separately in our analyses.

WB PPI Analysis

Following the procedures in Gerchen et al. [2014], first eigenvariate time series were extracted from the ROIs, and first level WB-PPI analyses were conducted from each ROI to each other ROI with generalized PPI GLM models (gPPI) [McLaren et al., 2012] including condition-specific regressors for the task and control conditions, the time course of the respective seed ROI, two interaction terms with task $\times$ seed and control $\times$ seed, and the aforementioned covariates. For constructing the gPPI interaction terms, the seed ROI time courses were first deconvolved, multiplied with the time course of the experimental conditions, and subsequently reconvolved with the canonical HRF [Gitelman et al., 2003]. After condition-specific WB task-dependent connectivity matrices of gPPI coefficients were obtained for each subject, the matrix for the control condition was subtracted from the matrix for the task condition to give a single ROI*ROI contrast matrix. These matrices were then tested by second level one-sided one sample *t*-tests at the group level in the positive (task > control) and negative direction (control > task) to assess task-dependent connectivity effects (Fig. 1D,E; see also Supporting Information Figure S5 for the results of second level analyses of the condition-specific connectivity estimates). It is important to note that the further analyses are based on the second level group results obtained at this step.

Thus, the WB-PPI analysis results in WB connectivity matrices reflecting task-dependent connectivity changes between ROIs (Fig. 1D,E). To characterize the topology of the detected effects we used the nodal degree, one of the simplest graph theoretical measures where the number of connections of the individual brain regions is counted. Because WB-PPI gives directed, asymmetric connectivity matrices but we wanted to avoid overinterpretation of this inherent directionality, the total nodal degree counting inward as well as outward connections was used. For estimating nodal degrees we thresholded and binarized the second level results matrices. Thresholding of the connectivity matrices was conducted at each contrast direction with a constant number of connections being selected to yield one-sided matrix densities of 1%. The largest *P*-values of selected connections were $P = 2.47 \times 10^{-8}$ (encoding positive), $P = 2.73 \times 10^{-8}$ (encoding negative), $P = 6.82 \times 10^{-7}$ (recall positive), and $P = 7.42 \times 10^{-6}$ (recall negative), while the Bonferroni corrected $P < 0.05$ threshold lies at $P = 5.62 \times 10^{-8}$.

Figure 2.

Total nodal degree maps. Regions with a high number of task-modulated connections in the encoding and recall phase. An overlap between the contrast directions is found mainly in regions of the DMN. The displayed maps are thresholded at the mean degree + 1 SD estimated over all brain regions for illustrative purposes. [Color figure can be viewed at wileyonlinelibrary.com]

The thresholding of connectivity matrices is a crucial factor influencing graph theoretical results, therefore we used additional density thresholds of 0.1, 0.5, 2.5, 5, 7.5, 10, and 12.5% and assessed which results were stable over the majority of thresholds (at least 5 out of 8; Fig. 7B).

Connectivity Bias

Because a brain region can have positively as well as negatively task-modulated connections, its nodal degree can be positive for both contrast directions (Fig. 2). To integratively characterize task-related behavior of brain regions we estimated a regional task-dependent connectivity bias d_b

$$d_b = \frac{d_p - d_n}{d_p + d_n}$$

with d_p being the total nodal degree for the contrast direction task > control and d_n being the total nodal degree for the contrast direction control > task. d_b ranges from -1 to 1 and is undefined for $d_p = d_n = 0$. A large negative d_b value means that a region possesses mainly negatively task-modulated connections, while regions with large positive values have mainly positively modulated connections. A value close to 0 means that a region has a balanced number of positively and negatively modulated connections (Fig. 3A,B). The calculation of d_b scores integrates the ROI*ROI connectivity information into a single regional representation, which makes it possible to combine it with spatially localized activation effects.

D_b Histogram Permutation Test

To characterize the empirical distribution of d_b scores we constructed histograms with bin sizes of 0.2 over brain

regions and compared them to histogram distributions obtained by 10,000 permutations generated under the assumption of constant regional numbers of connections but random distribution of positively and negatively modulated connections, effectively testing against a null hypothesis of random relationships between the connections of a region (Fig. 3C,D).

Combination of Activation and Connectivity Results

Regions with high absolute d_b values have a strong bias towards a specific direction in the task-dependent modulation of their connections. To examine whether this bias is consistent with task-dependent activation effects we constructed intersection maps between task-positive and task-negative activations and ROIs with positive $d_b > 0.8$ and negative $d_b < -0.8$ for the four combinations (activation $\cap$ connectivity) $\uparrow\cap\uparrow$, $\downarrow\cap\downarrow$, $\uparrow\cap\downarrow$, and $\downarrow\cap\uparrow$ (red, blue, green, and yellow, respectively, in Fig. 4). The significance of the effects was assessed with permutation tests with 10,000 permutations in which the signs of the first level activation and connectivity effects were randomly flipped at the single subject level, the chain of analyses was repeated, and the number of identified voxels was counted in each contrast direction. This procedure tests the significance of finding a combined activation and connectivity effect under the null assumption of no systematic task-dependent activation and connectivity effects.

To assess the relationship of the identified effects with the functional brain structure at rest we counted the number of connections involved (positive connections for $\uparrow\cap\uparrow$ and $\downarrow\cap\downarrow$, negative for $\uparrow\cap\downarrow$ and $\downarrow\cap\uparrow$) and plotted how they were

Figure 3.

Task-dependent connectivity bias. **A,B:** Maps of task-dependent connectivity bias (d_b score) for the encoding and recall phase. Red regions have positive d_b scores and predominantly positively task-modulated connections, blue regions have negative d_b scores and predominantly negatively modulated connections, magenta regions have d_b scores close to 0 and therefore balanced numbers of positively and negatively modulated

connections. **C,D:** Histograms of regional d_b scores (blue bars) and upper and lower limits (red lines, $P < 0.0001$) of a permutation distribution based on randomly shuffled positive and negative connections. The real data exhibits a tendency towards predominant regional directions in task modulation of connections. [Color figure can be viewed at wileyonlinelibrary.com]

distributed across networks (Fig. 5). For each effect and each network, we identified ROIs which contained a specific combined activation-connectivity effect and expressed the number of connections with each network as a percentage of all connections involved in the specific effect.

Medial Temporal Lobe/Hippocampus Effects

For a more fine-grained analysis, we explored the regions underlying the $\uparrow\downarrow$ effect in the hippocampus as a structure of special interest in our task. We selected ROIs that contained voxels with positive activation and negative connectivity and were located in the hippocampus as seed regions

and identified negatively connected regions contributing to the effect (Fig. 6). Because the selected seed ROIs can also include non-hippocampal voxels we refer to them as medial temporal lobe/hippocampus (MTL/HC) ROIs.

Reproducibility across Subsamples

To test for reproducibility and stability of the combined activation/connectivity findings we repeated the analysis in the two independent subsamples from the two scanning sites ($n = 54$ and $n = 82$) and constructed intersection maps of the results (Fig. 7A).

Figure 4.

Combined activation and connectivity results. Intersection maps of activation effects and high connectivity bias ($|d_b| > 0.8$) in the encoding and recall phase for the combinations (activation $\cap$ connectivity) $\uparrow\uparrow$ (red, upper left quadrants), $\downarrow\downarrow$ (blue, upper right

quadrants), $\uparrow\downarrow$ (green, lower left quadrants), and $\downarrow\uparrow$ (yellow, lower right quadrants). [Color figure can be viewed at wileyonlinelibrary.com]

Combined Activation and Connectivity Analysis with a t-Test Strategy (“Strategy 2”)

To further explore the combined analysis of task-dependent activation and connectivity effects we applied a second strategy to estimate the connectivity bias, which was not based on matrix thresholding and graph theory. In this strategy we estimated connectivity biases by applying one sample *t*-tests over the second level PPI contrast estimates of all connections of a region, and identified regions with mean task-dependent connectivity changes significantly higher (positive) or lower (negative) than zero at a threshold of $P < 0.05$, Bonferroni corrected for the number of regions. Maps of the detected regions were again intersected with activation effects to detect combined effects.

RESULTS

Task

Mean task accuracy was $73.73 \pm 11.81\%$ ($\bar{O} \pm SD$). The episodic memory task led to widespread and strong activations in the medial and lateral prefrontal cortex, the anterior insula, the precuneus and posterior cingulate cortex, the angular gyrus, the medial temporal lobe and middle temporal gyrus, the occipital pole, the caudate nucleus, and large parts of the cerebellum in the task-positive and in pericentral frontal and parietal regions, the right inferior frontal gyrus,

the posterior insula, the superior temporal lobe, the middle occipital lobe, the lingual gyrus, and the thalamus in the task-negative direction in the encoding as well as in the recall phase (Fig. 1B,C). While activation was largely overlapping between the encoding and recall phases, prominent differences existed in the medial and lateral prefrontal cortex where no activation was found during recall but during encoding, in the subgenual ACC where negative activations were detected during recall but not during encoding, and in the medial temporal lobe where activation was spatially more restricted during recall.

Resting State Network Community Detection

The Infomap algorithm lead to the identification of 7 large-scale networks in the resting state data which covered $\sim 70\%$ of all ROIs. We identified sensory-motor (SMN), fronto-parietal (FPN), DMN, cerebellar (CN), cingulo-opercular (CON), subcortical (SN), and anterior temporal (ATN) networks (Supporting Information Figure S1). The remaining ROIs, including those covering the hippocampus, were categorized as “other.”

WB-PPI

WB-PPI analysis identified strong task-dependent connectivity changes in both the task-positive and task-negative direction in the encoding and recall phase.

Figure 5.

Relative distribution of connections between and within resting state networks. Connections of regions with specific combined activation/connectivity effects in the resting state networks (y-axis) with regions in all networks (x-axis) are shown. Color intensity codes for the percentage of the amount of connections between specific networks from all connections involved in an effect. Only positively modulated connections of detected

regions are shown for $\uparrow\uparrow$ and $\downarrow\uparrow$ effects and only negatively modulated connections for $\downarrow\downarrow$ and $\uparrow\downarrow$ effects. Same colors as in Figure 4. Networks: SMN: sensory-motor; FPN: fronto-parietal; DMN: default mode; CN: cerebellar; CON: cingulo-opercular; SN: subcortical; ATN: anterior temporal. [Color figure can be viewed at wileyonlinelibrary.com]

Interestingly, a prominent role of the DMN is observable in the WB-PPI *t*-value matrices at first glance, with strong negative modulation of within-network connectivity and strong positively as well as negatively modulated between-network connectivity (Fig. 1D,E).

Nodal Degree

For a basic characterization of the topology of task-dependent connectivity, we constructed maps of the total nodal degree of the ROIs to display regions with a high number of task-modulated connections. When the effects for the different contrasts are overlaid it is directly visible that the posterior cingulate cortex, the precuneus, the ventromedial prefrontal cortex, the angular gyrus, the occipitotemporal cortex, and also the right inferior frontal gyrus in the recall phase have high numbers of task-modulated connections in the task-positive as well as the task-negative direction (Fig. 2). Correlations between nodal degree and activation showed that over all ROIs the absolute activation of a region was associated with the total number of positively and negatively modulated connections (encoding: $r = 0.41$, $P < 1 \times 10^{-8}$; recall: $r = 0.34$, $P < 1 \times 10^{-8}$).

Connectivity Bias

To define regions with task-specific connectivity we integrated the results of the contrast directions and estimated regional task-dependent connectivity biases (d_b ; Fig. 3A,B). The d_b scores are positive when a region has predominantly positively modulated connections, close to 0 when a region has balanced positively and negatively modulated connections, and negative when connections are predominantly negatively modulated. To characterize the distribution of d_b scores we performed permutation tests under the null hypothesis of random connectivity and found that our empirical results contained higher numbers of regions with high absolute d_b scores and less regions with d_b scores close to 0 than expected under random connectivity assumptions (Fig. 3C,D). Over all regions with a defined d_b score, absolute activation was positively correlated with d_b scores (encoding: $r = 0.17$, $P = 1.43 \times 10^{-6}$; recall: $r = 0.19$, $P = 2.34 \times 10^{-8}$). This effect was stable across matrix density thresholds and was mainly driven by a strong negative relationship between activation and d_b scores in regions with negative activation effects. Positively activated regions were only contributing to the effect at higher thresholds during encoding and did not exhibit

Figure 6.

Networks underlying hippocampal $\uparrow\downarrow$ results. ROIs exhibiting negative task-dependent connectivity (lower row) with $\uparrow\downarrow$ regions in the hippocampus/medial temporal lobe (upper row) during encoding and recall. ROIs with negatively modulated connections to more than one $\uparrow\downarrow$ region are shown. [Color figure can be viewed at wileyonlinelibrary.com]

this relationship during recall (Supporting Information Figure S6 and S7). An analysis based on “strategy 2” detected very similar relationships (Supporting Information Figure S8).

Combination of Activation and Connectivity Results

Having topographical information about local and integrative task effects at hand, we identified regions with strong task dependent connectivity bias ($|d_b| > 0.8$) and intersected this information with the results of the activation analysis. Permutation tests showed that the P -values of obtaining any voxel with an activation effect and a high connectivity bias by chance ranged between $P = 0.0016$ and $P = 0.0033$ over all 8 contrast directions. We identified brain regions with congruent as well as incongruent task-dependent activation and connectivity effects in all four possible combinations in both task phases (Fig. 4). In the encoding phase, regions with congruent positive effects ($\uparrow\uparrow$) were found in the dorsolateral and ventrolateral prefrontal cortex, the dorsomedial prefrontal cortex, the anterior insula, the posterior middle temporal gyrus, mainly left angular gyrus, right caudate, parts of the thalamus,

cerebellum, and the brain stem. Regions with congruent negative effects ($\downarrow\downarrow$) were found in pericentral frontal and parietal regions, the posterior insula, the superior temporal lobe, the middle occipital lobe, and the lingual gyrus. Regions with positive activation and negative connectivity bias ($\uparrow\downarrow$) were found in the dorsomedial prefrontal cortex, the inferior frontal gyrus, the orbitofrontal cortex, the medial temporal lobe including the hippocampus, the temporal pole, and the occipital pole. Regions with negative activation and positive connectivity bias ($\downarrow\uparrow$) were found in the supplementary motor area, the superior parietal lobe, in small clusters in the thalamus, and in the superior temporal gyrus. Again, the results were mainly overlapping between the encoding and the recall phase, with main differences in the recall phase being a stronger lateralization of $\uparrow\uparrow$ effects to the right angular gyrus, a small $\uparrow\uparrow$ cluster in the medial temporal lobe, $\uparrow\downarrow$ effects in right ventrolateral prefrontal cortex, and more widespread $\downarrow\uparrow$ effects in the right posterior parietal cortex.

With respect to the resting state network structure, positively modulated connections involved in $\uparrow\uparrow$ effects were distributed across networks, with the highest numbers of connections between fronto-parietal and “other” regions and the DMN. In contrast, negatively modulated connections

Figure 7.

Stability of the results. **A:** Reproducibility of the results in the two independent subsamples. Intersection maps of the results obtained by repeating the analysis in each subsample. **B:** Stability of the results over matrix density thresholds. Voxels, which were found with the majority of matrix density thresholds (at least 5 of 8), are shown for the different combinations. Same colors as in Figure 4. [Color figure can be viewed at wileyonlinelibrary.com]

constituting $\downarrow\downarrow$ effects were concentrated within the SMN. This also applies to a high number of negatively modulated connections leading to $\uparrow\downarrow$ effects, where some connections were also found between SMN and “other” networks and between “other” and the DMN network. High numbers of positively modulated connections constituting $\downarrow\uparrow$ effects were found between sensory-motor and “other” regions and the DMN and within the SMN in the recall phase (Fig. 5).

Medial Temporal Lobe/Hippocampus Effects

The MTL/HC showed activation but negatively modulated connectivity during encoding and, to a smaller extent, negative as well as positive connectivity bias during recall (Fig. 4). The networks underlying the detected effects for the $\uparrow\downarrow$ regions were mainly the posterior DMN and visual cortex in the encoding phase and the posterior and anterior DMN in the recall phase (Fig. 6).

Stability across Thresholds

To test for the stability of the results we repeated the analysis in the two independent subsamples and in the whole sample with different density thresholds. The results were spatially more restricted than with the whole sample and a single density threshold, but confirmed the overall pattern (Fig. 7A).

Combined Activation and Connectivity Analysis with a t-Test Strategy (“Strategy 2”)

To repeat our analyses with a method not based on arbitrary matrix thresholding and graph theory we used “strategy 2” to estimate connectivity biases based on *t*-tests over all connections of a region. With “strategy 2” we again were able to identify effects in all four directions in both parts of the experiment (Supporting Information Figure S3). The second strategy seemed to generally detect larger networks than the first strategy and found overlapping, but for some regions also diverging effects. Divergence between the two strategies was found especially in some parts of the prefrontal cortex where effects changed from $\uparrow\uparrow$ to $\uparrow\downarrow$ and in the DMN where “strategy 2” detected additional $\uparrow\uparrow$ effects.

DISCUSSION

In this study, we assessed the topography of WB task-dependent connectivity changes with graph-theoretical methods in an exemplary episodic memory data set and combined the results with the topography of task-dependent activation changes to explore whether activation and connectivity effects are tightly coupled or represent dissociable effects.

In a first step, we identified regions that had high numbers of task-modulated connections in both positive and negative contrast directions. They were found mainly in regions of the DMN (Fig. 2), replicating findings by Utevsky et al. [2014] who found overlapping task and rest connectivity effects in the precuneus. Interestingly, the same regions have also been reported to have high numbers of connections in resting state analyses [Buckner et al., 2009; Cole et al., 2010; Tomasi and Volkow, 2011], and it has been argued that the high degree reflects membership in large brain networks [Power et al., 2013]. However, network-specific changes in DMN connectivity suggest that in our case overlapping high task-dependent degrees might not be due to network size, but rather stem from the DMN flexibly switching the networks it is connected to in accordance to task demands, which further points towards a task-general role of the DMN as proposed, for example, by Utevsky et al. [2014]. Over all regions, the sum of positive and negative connections was associated with the absolute activation, showing a comparable relationship between activation and connectivity as found by Gratton et al. [2016].

In a second step, we aimed at characterizing specialized regions with task-specific connectivity changes. For this,

we combined the information of the contrast directions and set the degrees for the different directions into relation to calculate task-dependent connectivity biases (d_b). Because ROIs are roughly of the same size in NCUT parcellation [Craddock et al., 2012], our d_b scores effectively characterize regions by comparing the size of the networks they change their involvement with between experimental conditions.

To characterize the distribution of d_b scores over brain regions we used permutation tests over histograms and found more regions with preferred directions in connectivity changes and less with balanced numbers of modulated connections than expected under random connectivity assumptions, suggesting a tendency of brain regions towards specialization in task-dependent connectivity. Of note, also regions in the DMN with high overlapping degrees in both contrast directions exhibited slight tendencies in the preferred direction of connectivity changes (Fig. 3A,B). While the relative rarity of balanced regions does not exclude that they play important roles, we did not further focus on these regions because restricted spatial resolution in our approach could lead to balanced task-dependent connectivity due to the combination of different neural modules in a ROI. Instead, we used only unambiguous regions with strong contrast direction preferences of $|d_b| > 0.8$ in subsequent analyses. We applied a very strict threshold to binarize the matrices to calculate our main results because we wanted to focus on connections with strong statistical support in accordance with the FWE corrected activity analyses we combined them with. While this procedure selects statistically relevant connections, it can favor strong connectivity biases in regions with few consistently modulated connections. It is therefore important to consider the whole picture of the presented results including the stability across thresholds and threshold-free “strategy 2”. Of note, in our main results regions with $|d_b| > 0.8$ also included regions from the top 2% with the highest degree in all contrast directions, showing that the analyses were not exclusively detecting low-degree regions.

We then intersected the d_b maps with the activation maps to address our main question about the relationship of activation and connectivity effects. We detected congruent as well as incongruent activation and connectivity changes in large-scale brain networks, clearly demonstrating that local brain activation and task-dependent connectivity effects can be modulated in different directions at the same time. In contrast to the expectation from simple modeling approaches [Chawla et al., 1999, 2000] and FDG-PET/fMRI [Riedl et al., 2014; Tomasi et al., 2013], but in line with other fMRI research [Andric et al., 2016; Gratton et al., 2016; King et al., 2015] our results argue against a direct congruency between the modulation of activation and connectivity at the macroscopic WB level assessed by fMRI. The results rather suggest that in complex brain networks congruent and incongruent activation and connectivity changes are more likely a consequence of task demands than based on a simple physiological association.

The distribution of the task-modulated connections over large-scale resting state networks showed that a majority of positively modulated connections involved in $\uparrow\cap\uparrow$ and $\downarrow\cap\uparrow$ effects is found to cross network boundaries, especially to the DMN, while a high percentage of negatively modulated connections involved in $\downarrow\cap\downarrow$ and $\uparrow\cap\downarrow$ effects is found within the SMN (Fig. 5). This suggests that, generally speaking, in our analyses task-positive connectivity effects reflect an interaction of separate neural modules, while task-negative connectivity effects rely on commonly interacting modules, which is in accordance with the demands of the task conditions. Interestingly, in contrast the hippocampus $\uparrow\cap\downarrow$ effect, involving only a small percentage of such task-negative connections, is based on between-network connectivity (Fig. 6), suggesting that the hippocampus changed from a more integrated role towards a more specialized and segregated, but more active condition. This effect diverges from earlier reports on memory-related increases in hippocampus-DMN coupling [e.g., King et al., 2015; McLaren et al., 2014], but there the applied contrasts (encoding novel vs. repeated items, recollected vs. not recollected items) differed from our study. Interestingly, both the hippocampus and the DMN were activated by the task, and the detected task-related decoupling hints at a divergent change in the functional role of the regions. This illustrates that it is problematic to infer changes in regional coupling from coactivation patterns in a specific task, as the effects can be in opposite directions. While coactivation patterns over several experiments can be used to characterize cortical modules [e.g., Eickhoff et al., 2011], conclusions from a single experiment could be prone to errors.

Over all regions, the absolute change in activation was significantly, although not very strongly, correlated with a positive degree bias (Supporting Information Figure S6–S8). This effect was especially driven by a strong negative relationship between activation and d_b scores in regions with negative activation effects. This suggests that in our data the magnitude of local deactivations might to a certain amount reflect how coherently a region is becoming integrated with other regions during task execution.

It would be interesting to test our findings with complex WB computational modeling, as it has been applied to resting state data [e.g., Deco and Jirsa, 2012; Ritter et al., 2013], but it might be difficult to comprehensively model all task-specific processes and influences over the whole brain, although first steps in this direction have been taken [Cole et al., 2016; Deco et al., 2015; Senden et al., 2017].

While the analyses focused on the combination of detected effects, we were again able to identify regions that did not contain activated voxels but had significantly task-modulated connections in the recall phase (see Supporting Information Figure S4) as already shown in our previous work [Gerchen et al., 2014].

Notably, several limitations apply to our study. First of all, a major limitation is the restriction of the analyses to a single task which leaves the question of the generality of our

findings unanswered. However, even while our data likely contains highly specific patterns of effects, the clear and stable dissociation between activation and connectivity effects might reflect a more general principle of brain function. In future research it will be important to explore which effects are task-specific and which effects generalize over different tasks.

As in every study with complex analyses, we had to make several methodological decisions that limit the generality of the results, but were made with the goal to make the analyses more concise and accessible. We restricted our results to one relative fine-scaled parcellation which we think does provide a trade-off between spatial resolution and data complexity, but it is known that results are dependent on the parcellation scheme [Zalesky et al., 2010]. Therefore, we repeated the analyses with a coarser parcellation with 350 regions and obtained similar results (see Supporting Information Figure S2).

In our study, d_b scores were calculated based on thresholded binarized connectivity matrices, but the approach could be adapted to weighted connectivity matrices, which might or might not be thresholded. In addition, we did not further select or weight the d_b scores with regard to the number of connections involved, which could also be done for more specific analyses and could be used to alleviate the effects of strict thresholding. In addition, we used only second level group results, but it would also be possible to construct subject-specific combined results maps and use them to test for group differences or associations with external factors.

The results of “strategy 2” to estimate connectivity biases based on t -tests mainly confirmed our findings but diverged in some regions from the results of the graph theoretical approach. These discrepancies likely stem from a different point of view the two approaches are taking on the data. While our initial strategy focuses on connections with large effects and strong statistical support, strategy 2 focuses on the distribution of effects over all connections of a region, taking also effects with weak statistical support into account. When few strongly modulated connections exist on a background of many weakly modulated connections with effects in the opposite direction, such discrepancies can be expected.

Furthermore, our results are based on WB-PPI analysis, which is only one possibility to estimate task-dependent connectivity changes. We think that PPI is optimally suited to be combined with activation analysis because it allows application of the same contrasts, is estimated with the same GLM approach, and corrects for simple task co-activation effects. Nonetheless, it would be important to cross-validate our results with different approaches. As a validity check, we have compared our PPI results to differences of condition-specific correlations and found good correspondence (Supporting Information Figure S9).

The reported analyses are based on modeling task effects with the canonical HRF, which might neglect the influence

of regional differences in hemodynamic responses on connectivity estimates. However, when we included time and dispersion derivatives of the canonical HRF in the PPI GLM to adjust for more variable activation effects, the results were very similar (Supporting Information Figure S10). Nonetheless, it will be an important task in the future to better understand the influence of task correction on connectivity results and to test whether the detected effects hold true when more sophisticated methods to account for task effects are applied.

A method related to WB-PPI that could potentially be used to detect similar effects is the Task-related Edge Density approach [Lohmann et al., 2016]. Consistent with our results, Lohmann et al. [2016] detected regions that were involved in different contrast directions in a fingertapping task and also found differences between task-related activation and connectivity effects.

CONCLUSION

We have demonstrated that a combination of task-dependent activation and connectivity analysis can be used to detect and map the complex modulation of brain regions in accordance with task demands. The occurrence of brain regions with incongruent changes in activation and connectivity was tested by permutation tests, was replicable in the two independent subgroups, was stable over different matrix thresholds, and could also be obtained with an alternative strategy to estimate connectivity biases. These results suggest that local and integrative processes in the brain can be considered as separable brain functions with a complex relationship at the macroscale level assessed by fMRI.

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