Domain-general signals in the cingulo-opercular network for visuospatial attention and episodic memory

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Abstract

We investigated the functional properties of a previously described cingulo-opercular network (CON) putatively involved in cognitive control. Analyses of common fMRI task-evoked activity during perceptual and episodic memory search tasks that differently recruited the dorsal attention (DAN) and default mode network (DMN) established the generality of this network. Regions within the CON (anterior insula/frontal operculum and anterior cingulate/presupplementary cortex) displayed sustained signals during extended periods in which participants searched for behaviourally relevant information in a dynamically changing environment or from episodic memory in the absence of sensory stimulation. The CON was activated during all phases of both tasks, which involved trial initiation, target detection, decision and response, indicating its consistent involvement in a broad range of cognitive processes. Functional connectivity analyses showed that the CON flexibly linked with the DAN or DMN regions during perceptual or memory search, respectively. Aside from the CON, only a limited number of regions, including the lateral prefrontal cortex, showed evidence of domain-general, sustained activity, although in some cases the common activations may have reflected the functional-anatomical variability of domain-specific regions rather than a true domain-generality. These additional regions also showed task-dependent functional connectivity with the DMN and DAN, suggesting that this feature is not a specific marker of cognitive control. Finally, multivariate clustering analyses separated the CON from other fronto-parietal regions previously associated with cognitive control, indicating a unique fingerprint. We conclude that the CON's functional properties and interactions with other brain regions support a broad role in cognition, consistent with its characterization as a task-control network.

Introduction

Much research is concerned with identifying the neural mechanisms of cognitive control (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Cole & Schneider, 2007; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Niendam et al., 2012). These mechanisms are thought

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to maintain task control signals (E. K. Miller & Cohen, 2001) that specify how stimuli are mapped into responses and that flexibly select and configure the elemental cognitive processes necessary to perform a task (Rogers & Monsell, 1995). A previous meta-analysis of task-evoked activity across multiple mixed block/event experiments identified a cingulo-opercular network (CON) that showed three properties consistent with a role in implementing a task set (Dosenbach et al., 2006): i. significant start-cue activity at the beginning of a task block (task-set instantiation); ii. positive sustained activity across the block (maintenance); and iii. error-related feedback activity (adjustment). Further work expanded the CON to include the anterior prefrontal cortex (aPFC) and the thalamus (Dosenbach et al., 2007), and showed that the network was partially segregated from a second, fronto-parietal network that has also been associated with cognitive control (Dosenbach et al., 2008).

If the CON serves the broad role attributed by previous studies, then it should show sustained activity during the performance of different tasks that elicit very different spatial patterns of cortical activity. Here we provided a strong within-experiment test of this prediction by studying the response profile of the CON during two tasks that involved either attending to environment stimuli (i.e. perceptual search) or the retrieval of behaviorally relevant information from episodic memory (i.e. memory search). These tasks recruited respectively a dorsal attention network (or DAN, (Corbetta & Shulman, 2002; Kastner & Ungerleider, 2000)) and a default-mode network (or DMN, (Buckner, Andrews-Hanna, & Schacter, 2008; Raichle et al., 2001; Shulman et al., 1997)) that operated in a push-pull dynamic competition (Sestieri, Shulman, & Corbetta, 2010), paralleling their negative correlation in the resting state (Fox et al., 2005). By hypothesis, the CON should show positive sustained activity during the performance of each task, regardless of the pattern of activation/deactivation in domain-specific networks.

Previous studies have proposed that a larger set of fronto-parietal regions (Cole & Schneider, 2007; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008) is activated during both the execution of externally- and internally-oriented tasks (Gao & Lin, 2012; Smallwood, Brown, Baird, & Schooler, 2012; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010). For example, Spreng and colleagues (Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013; Spreng et al., 2010) found that an extensive set of regions in lateral and medial fronto-parietal cortex, including the CON, showed common activity during two planning tasks that activated the DMN and DAN, respectively. The relatively large extent of common activity, which included large portions of the occipital cortex, may have partly reflected the fact that both the DMN- and DAN-oriented tasks involved cognitive processes related to planning and visual sensory input. Here, by testing DMN- and DAN-oriented tasks that involved very different cognitive processes, we determined whether the set of regions commonly activated during the two types of tasks was more restricted and yet still included the CON. In line with this goal, our experimental design allowed us to separate different phases within the perceptual and memory tasks. This design feature enabled us to i) test for common activity during those parts of the two tasks that isolated very different processes, and ii) assess the generality of the CON across very different cognitive processes within each task. For example, we assessed the presence of sustained brain activity when subjects searched for an object in a dynamically changing display, prior to target detection and response execution, vs. when subjects retrieved information from episodic memory over an extended period of time while fixating a blank screen, again prior to reaching a final decision and making a response. In addition, whereas the original meta-analysis of Dosenbach et al. (Dosenbach et al., 2006) examined whether brain activity was sustained over a block in order to show that task set signals were present also during the inter-trial interval as well as during the trial, here we examined activity that was sustained within a prolonged phase of individual trials, i.e. an extended period of task performance. Therefore, while the present tasks do not

represent all the different elements of cognitive control, as in large meta-analytic approaches (Dosenbach et al., 2006), their features enabled a strong and novel test of the domain-generality of activity within the CON.

A second important property of a 'domain-general' network is the degree to which the network selectively interacts with domain-specific, task relevant networks. Prior studies that focused on whether the CON dynamically linked with domain-specific networks did not examine both externally- and internally-oriented tasks in a single experimental design (Chiong et al., 2013; Higo, Mars, Boorman, Buch, & Rushworth, 2011; Sridharan, Levitin, & Menon, 2008; Zanto, Rubens, Thangavel, & Gazzaley, 2011). In contrast, those studies that have investigated the presence of modulations of functional/effective connectivity with the DMN and the DAN during the execution of externally- and internally-oriented tasks (Gao & Lin, 2012; Smallwood et al., 2012; Spreng et al., 2010) have not explicitly focused on the CON, making it difficult to appreciate its particular relationship with domain-specific networks. Here we specifically measured the functional connectivity of the CON with the DMN and DAN as those networks were activated and deactivated during memory and perceptual search.

Therefore, in the present study, we first determined whether regions that exhibited sustained within-trial activity during both perceptual and memory search tasks included the CON [dorsal anterior cingulate/presupplementary cortex (dACC/preSMA) and anterior insula/frontal operculum (aINS/fO), as defined in (Dosenbach et al., 2006)]. We then characterized the full profile of task-evoked activity in the CON during the different phases of each task. Next, we analyzed the pattern of task-evoked and resting functional connectivity to investigate whether the CON flexibly coupled with domain-specific regions of the DMN and DAN according to task demands (Spreng et al., 2010; Sridharan et al., 2008). Finally, we examined whether the profile of task-evoked activity and functional connectivity for the CON distinguished that network from other cortical regions that showed any evidence for domain-general sustained activity.

Methods

This manuscript is based on a new analysis of an experiment that has been previously reported (Sestieri, Corbetta, Romani, & Shulman, 2011; Sestieri et al., 2010). Since stimuli, tasks, procedures and linear modeling of task-evoked activity have been extensively described in these publications, here we present a briefer description.

Subjects

Nineteen healthy right-handed subjects (mean age = 26.8 years, range 23–32 years; three males) gave informed consent in accordance with guidelines set by the Human Studies Committee of Washington University in St. Louis, MO, USA. Each participant performed a perceptual search and an episodic memory search task involving audiovisual material on different days, counterbalanced across subjects. Subjects were also scanned at rest for ~30 minutes (rs-FC scans).

Procedure

The experimental paradigm is illustrated in Figure 1A–B.

Perceptual search task—In the perceptual task, visually presented sentences instructed participants to search for a visual target that could be presented at any time during an upcoming 12 s video clip, while maintaining central fixation. Search time was manipulated by varying the time of onset of the target in order to separate the neural signals associated

with searching for the target (search), audiovisual constant stimulation (display) and target detection/motor response (detection) (Shulman et al., 2003). On each trial, a sentence was presented on the screen for 4s instructing subjects to search for a specific target in the next 12s video clip. The clips had a superimposed central fixation cross and were followed by a variable intertrial interval (ITI) (~4.1/6.2/8.3 s). Three kinds of clips were presented: clips with a target ('target'), clips with an oddball target ('oddball') and clips with no target ('non-target'). Trials were grouped according to target onset and the corresponding search time: early (0–4 s after sentence offset), middle (4–8 s) and late (8–12 s) trials. When either the target or the oddball target was detected, subjects had to press as quickly as possible one of the two 'Yes' keys with their left hand, rating their confidence (high, low). If a target was not detected, they had to press one of the two 'No' buttons with their right hand, depending on confidence, at the end of the clip. Responses were categorized in hits, misses, false alarms (FA) and correct rejections (CR) according to Signal Detection Theory (Green & Swets, 1966). Subjects knew that targets could appear only once during the clip and they were instructed to passively watch the end of the clip after a target had been detected. 'Catch' trials, in which the sentence was immediately followed by the ITI, were used to separate BOLD activity associated with sentence reading from subsequent phases of the trial (Ollinger, Corbetta, & Shulman, 2001b; Ollinger, Shulman, & Corbetta, 2001a; Shulman et al., 1999). Ten runs, each containing 25 trials, were administered.

Memory search task—In the memory task, subjects judged the accuracy of sentences describing specific details about one of two movies that had been previously encoded, while maintaining central fixation. In this task, the source of search duration variability was the subject's decision time, reflecting the time needed to retrieve the critical information and answer the question. This cued recollection task likely involves elaborative recall processes of imagery and scene reconstruction, in addition to a general sense of familiarity (Mendelsohn, Furman, & Dudai, 2010). Therefore, the term memory search is used here as a proxy for a broad range of processes that involve the retrieval of episodic information guided by the behavioral goal, the organization and evaluation of the retrieved information, and the accumulation of evidence that pointed to a particular response. At encoding, subjects watched two episodes from an English language television sitcom (Curb Your Enthusiasm, by Larry David; Home Box Office), separated by an hour break. The fMRI retrieval session was performed ~24 hours later. On each trial, a sentence describing memory for details and events across the two episodes was presented for 4s, followed by a black display with a white central fixation cross. Subjects were instructed to read the sentence, wait until it disappeared and then take the time they needed, up to 15 s, to retrieve the specific information and provide a yes/no judgment about the accuracy of the sentence (named detection for consistency with the perceptual task), with confidence rating (high, low). Judgments were made using four buttons with the same category-key mapping used for the perceptual task. Trials were grouped into early (0–4 s after sentence offset), middle (4–8 s) and late (8–12 s), representing different search times (trials between 12 s and 15 s were discarded due to low accuracy). Following subject's response, the fixation cross turned red, indicating the onset of a variable ITI (4.1 s, 6.2 s, 8.3 s). During catch trials, sentences were immediately followed by the ITI. Subjects were asked not to retrieve information following catch trial sentences. Five runs of twenty trials pertaining to the episode encoded first were presented, followed by five runs pertaining to the episode encoded second.

Imaging methods and preprocessing of BOLD images

Images were acquired with a Siemens Allegra 3T scanner. Structural images were obtained during the first scanning session using a sagittal MPRAGE T1-weighted sequence [Repetition Time (TR) = 1810 ms, Echo Time (TE) = 3.93 ms, flip angle = 12°, Time for Inversion = 1200 ms, voxel size = 1 × 1 × 1.25 mm) and a T2-weighted spin-echo sequence

(TR = 3800 ms, TE = 90 ms, flip angle = 90°). Blood oxygenation level-dependent (BOLD) contrast functional images were acquired using an gradient echo echoplanar sequence [TR = 2064 ms, TE = 25 ms, flip angle = 90°, 32 contiguous 4 mm axial slices, 4 × 4 mm in-plane resolution).

Analysis of task-evoked activity

Linear Modeling—Data were analyzed using two kinds of general linear models (GLMs) (Sestieri et al., 2011; Sestieri et al., 2010). The aim of the first model (process-GLM) was to separately estimate the BOLD signal for the different task processes that temporally overlapped in the course of a trial: sentence reading (sentence), sensory stimulation (display), perceptual search (search), target detection and response (detection) in the perceptual task; sentence reading (sentence), memory search (search) and response (detection) in the memory task. A multiple parameter regression model was created that specified the effects of the several task processes on the observed BOLD response. The model assumed that the BOLD response on each trial was the sum of the hemodynamic responses (HR) that were generated by the above processes, and was used to identify voxels activated or deactivated by each process. The assumed response shape for each process was generated by convolving a function representing the duration of the process (rectangle functions for sustained processes, delta functions for transient processes) with a standard hemodynamic response function (Boynton, Engel, Glover, & Heeger, 1996). The sentence-reading phase was separated using a catch-trial technique, in which on a random 20% of the trials, the trial ended following the sentence-reading phase. For the perceptual task, separate parameters modeled the search and the detection components of the task according to subject's accuracy [Hit, Miss, False Alarm (FA), Correct Rejection (CR)] and confidence [High (HC), Low (LC)]. Similarly, for the memory task, separate parameters modeled the search and the detection component of the task according to subject's accuracy [Correct (Corr), Incorrect (Inc)] and confidence [High (HC), Low (LC)].

To examine the overall time course of BOLD activity for different types of trials (e.g. early, middle, and late correct response trials), which reflects the sum of the BOLD signal for the processes operative on those trials, a second type of GLM was created that made no assumption about the shape of the hemodynamic response (frame-by-frame-GLM). This model provided an unbiased estimate of the time course for each trial type (Ollinger et al., 2001b; Ollinger et al., 2001a), generating separate delta function regressors for each MR frame up to ~30 s after trial onset. Time courses for 13 types of trials, all starting at sentence onset, were estimated for the perceptual task: sentence reading catch trials, three Hit-target, three Hit-oddball, and three Miss types of trials, depending on the interval of target presentation (early, middle, late), and CR, FA and trials in which subjects did not press any key. Time courses for 8 types of trials, all starting at sentence onset, were estimated for the memory task: sentence reading catch trials, three correct response trials (early, middle, late), three incorrect response trials (early, middle, late), and trials in which subjects did not press a key. One subject was removed from the time course analysis for the lack of early correct trials in the memory experiment.

Statistical Analyses—Although the two types of GLMs included regressors for correct and incorrect trials, all the statistical analyses have been conducted on correct trials only. Using the process GLM, we created group voxelwise statistical maps corresponding to each process in which subject was treated as a random effect. We used a standard method to correct for multiple comparisons based on a region size/z-score-criterion combination, determined by Monte-Carlo simulations. We employed the same combination (17 face contiguous voxels/z=3) used in our previous publications (Sestieri et al., 2011; Sestieri et al., 2010), which corresponds to a probability of falsely rejecting the null hypothesis of p<0.05.

In order to focus on optimal task performance, voxelwise maps of perceptual and memory search-related activity were obtained using high confidence correct trials. Regional one-sample t-tests were performed to test whether regions activated by sustained parameters also responded to other parameters in either task. Using the process GLM, we assessed the presence of significant activity for two additional parameters (sentence reading, detection) of the perceptual and the memory tasks. This approach allowed us to establish the full pattern of task evoked activity for each region of interest (ROI).

Definition of domain-general ROIs—ROIs showing sustained activity for both tasks were formed using a procedure to maximize consistency across subjects. While the memory task had a single sustained process (search), the sustained processes of the perceptual task included the display and the search parameters, which were averaged to create a voxelwise map (z=3, corrected). The display parameter was included since sustained signals in higher-level regions might be maintained after the subject's response while the meaningful audio-visual display continued. Therefore, including both the search and display parameters increased our ability to map sustained signals during the perception task.

Next, we formed a binary AND map between the memory and the perceptual maps to identify voxels positively activated by sustained process of both tasks at the group level. The same procedure was repeated for each subject to generate individual binary AND maps. These images were then summed to obtain a frequency map in which the value of each voxel represented the number of subjects showing sustained activity in both tasks. The frequency map and the group AND map were multiplied and the resulting image was used to form ROIs (6 mm radius, peaks separated by at least 12 mm). ROIs with less than 5 voxels were excluded. This method guaranteed that ROIs were centered on those voxels where domain-general sustained activity was most consistent across subjects and was present at the group level.

Definition of domain-specific ROIs—We also defined two sets of domain-specific ROIs showing sustained activity during the memory and the perceptual task, respectively, to examine whether the pattern of connectivity between networks was modulated by task execution. The memory set was extracted from the voxelwise map corresponding to the memory search parameter, masked to exclude eventual voxels showing domain-general activity. Four ROIs (6 mm radius, peaks separated by at least 12 mm) were selected, based on their proximity to posterior nodes of the DMN [bilateral angular gyrus (AG), bilateral posterior cingulate cortex/precuneus (PCC/PreCu)] (Sestieri et al., 2011). The perceptual set of ROIs was extracted from the voxelwise map corresponding to the average voxelwise map of the search and display parameters, masked to exclude potential domain-general activity. Four ROIs were selected, topographically corresponding to key fronto-parietal regions of the DAN [bilateral frontal eye-field (FEF), bilateral posterior intraparietal sulcus (pIPS) (Corbetta & Shulman, 2002; He et al., 2007)].

Functional Connectivity Analysis

Resting state and task-induced functional connectivity—We conducted six runs (~5 min each) in which the BOLD signal was measured while subjects maintained fixation on a central cross in an otherwise blank display. After standard preprocessing of BOLD images, data were passed through an additional series of specific processing steps for rs-FC (Fox et al., 2005; Vincent et al., 2006). First, the runs were concatenated. For each voxel, temporal filtering retained frequencies <0.1 Hz and data were spatially smoothed using a 6 mm full-width half-maximum Gaussian blur. Several sources of spurious or regionally nonspecific variance were removed by linear regression including: six parameters obtained by rigid body head motion correction, the signal averaged over the whole brain, the signal

averaged over the lateral ventricles, and the signal averaged over a region centered in the deep cerebral white matter. The analysis was also conducted without whole brain signal regression to test the stability of the results across different methods.

Functional connectivity was also assessed during the execution of the perceptual and the memory search tasks. The mean task-evoked response was removed by linear regression, adding a further set of regressors corresponding to the design matrix of the frame-by-frame GLM to the list of regressors for rs-FC preprocessing. We minimized the contribution of evoked responses associated with task structure, motor responses and perceptual stimulation by using a GLM that made no assumptions about the shape of the HRF. This procedure resulted in two task-induced functional connectivity datasets (Norman-Haignere, McCarthy, Chun, & Turk-Browne, 2011) for investigating potential changes in connectivity as a function of the task set. Compared to previously developed approaches for the analysis of task-related modulation of FC (i.e. based on regional betas (Chadick & Gazzaley, 2011) or partial least squares analyses (Spreng et al., 2010)), the present approach was relatively conservative and aimed at emphasizing the functional coupling associated with the maintenance of the task set, rather than the pattern of regional co-activation induced by transient evoked activity.

Regional FC—The connectivity between each of the three regions of the CON and each domain specific ROI (DMN, DAN) at rest and during the two task conditions was assessed in each subject. Pearson correlation coefficients were Fisher z-transformed. Significant changes of connectivity across tasks and networks were assessed by means of 2-way repeated measures ANOVA for each CON region, in which the dependent variable was the average Fisher-transformed correlation value between the CON ROI and the four domain-specific regions of each network. Post-Hoc analyses were performed using Duncan tests. The same procedure was used to compute measures of connectivity between domain-specific ROIs and each of the other domain-general ROIs identified in the present study. As a control analysis to test the extent to which modulations of FC were driven by the pattern of task co-activation, a within-network analysis was computed, averaging the correlation values of ROIs from the same network (CON, DMN, DAN). Significant changes of connectivity across tasks and networks were assessed by a 2-way repeated measures ANOVA with task and network as factors and Post-Hoc analyses.

Voxelwise rs-FC maps—Voxelwise connectivity maps were generated in each subject using domain-general ROIs as seeds. The BOLD time series from the rs-FC session was averaged over all voxels in the ROI, the voxelwise Pearson correlation coefficients between the seed time course and all other voxels were computed and the Fisher z-transform was applied. For the group statistical analysis, a one-sample t-test with subject as a random effect was computed on the Fisher z-transformed values and the resulting group maps were Monte Carlo corrected over the brain for multiple comparisons (voxel size, $3\times3\times3$ mm; cluster size, 17 voxels; z=3, corresponding to p<0.05).

Hierarchical clustering

A multivariate hierarchical clustering procedure was used to determine whether the 22 domain-general regions identified in the present study could be divided into different groups according to their functional properties (see (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Ploran et al., 2007) for a similar approach). This analysis was conducted on the following measures, averaged across subjects: 1. the pattern of task evoked activation for each task parameter using the process GLM; 2. the time courses of task evoked activity for each trial type using the frame-by-frame GLM; 3. the voxelwise pattern of rs-FC using a seed-based approach; 4. the regional pattern of connectivity with domain specific ROIs at

rest and during task execution. Matrices were created for each measure: a 22 (ROI) × 7 (BOLD % signal change for 7 parameters) for (i), a 22 (ROI) × 108 (BOLD % signal change for 18 time points by 3 conditions by 2 tasks) for (ii), a 22 (ROI) × 65523 (voxels in the brain mask) for (iii), a 22 (ROI) × 24 (4 domain-specific ROIs × 2 networks × 3 tasks). Using the correlation coefficient between pairs of regions, a weighted dissimilarity matrix was calculated combining the matrices of the individual measures and assigning equal value (1/4) to each measure to balance their weight. An agglomerative hierarchical cluster tree was created from the distances in the matrix. The threshold for the pruning of the cluster tree was calculated maximizing cluster size and two measures of clustering validity (searching for the local maximum value of the Dunn index and silhouette coefficient and for the local minimum value of the Davies-Bouldin index).

The inter-subject consistency of the clustering approach was tested by measuring the reproducibility across subjects of the dissimilarity matrix used for the hierarchical clustering. A dissimilarity matrix was created for a subgroups of individuals (N=9) on the basis of single subject parameters. One subject did not contribute to the analysis due to a lack of time courses relative to early correct trials in the memory experiment (see above). The procedure was repeated for different subgroup permutations (N=3000) to obtain a distribution of Pearson r correlation values between any possible pair of dissimilarity matrices. In addition, the clustering analysis was performed using only a subset (N=3) of the 4 measures used in the original analysis to test the consistency of the results across measures.

Results

A brief summary of the behavioral performance is presented in Figure 1C–E. A detailed assessment of behavioral performance has been reported in previous publications (Sestieri et al., 2011; Sestieri et al., 2010).

Domain-general sustained activity in the CON during memory and perceptual search

We first identified regions showing sustained activity in both tasks (Figure 2), using a procedure that searched for the presence of an overlap at the group and at the individual level (see methods), to test whether the CON exhibited domain-general activity. Overall, a large segregation between voxels showing sustained activity for the memory and the perceptual task was observed, with regions showing domain-specific activity located adjacent to one another in large portions of cortex (Figure 2A). This result extends previous findings of a topographical segregation in the parietal lobe (Sestieri et al., 2010) also to the organization of frontal and temporal lobes. Domain-general activity was sparse and was sometimes located at the boundary between extended, unambiguous regions of domain-specific activity. For example, the region in right IPL was bordered superiorly by a large extent of memory-task activity and inferiorly by a large extent of perception-task activity. One might argue that it would be efficient for domain-general regions to be interposed between domain-specific regions, as noted by a reviewer. But this topography also raises the possibility that the common activation in this and other areas with a similar topography resulted from variability in the functional-anatomy of domain-specific regions, spatial smoothing, and a lack of spatial resolution. Therefore, while these regions may in fact be domain-general, some caution is warranted.

A notable exception to this pattern, however, was observed in three regions that are anatomically consistent with the three main components of the CON: left aINS/fO (x: −29, y: +17, z: +2), right dACC/preSMA (x: +3, y: +6, z: +50) and right aINS/fO (x: +31, y: +15, z: +4). The peak of consistency (Figure 2B) of these regions was similar to the coordinates reported in previous studies (left aINS/fO= x: −35, y: +14, z: +5; dACC/preSMA= x: −1, y:

+10, z: +46; right aINS/fO= x: +36, y: +16, z:+4; indicated by black circles in the figure (Dosenbach et al., 2008; Dosenbach et al., 2006)). Importantly, domain-general activity in these regions was not sandwiched between two larger swaths of domain-specific activity. For example, the majority of voxels activated in the left and right anterior insula showed domain-general rather than domain-specific activity. In the anterior cingulate, the region showing common activity was bordered anteriorly by a region showing memory-task activity but was not bordered by any region showing only perception-task activity. Consistent with the sustained activation of the CON during the search phase of the visual search task, similar regions had shown the same pattern of within-trial, sustained activity in a previous experiment on visual search ((Shulman et al., 2003) cf. Figure 2) that involved a comparable analysis procedure. Domain-general activity was not found in regions (anterior PFC, thalamus) that showed sustained activity only for a subset of the tasks in the meta-analyses performed by Dosenbach and colleagues (Dosenbach et al., 2006) and that have been included in more recent formulations of the cingulo-opercular networks (Dosenbach et al., 2008; Dosenbach et al., 2007).

Other regions showing domain-general activity included the right retrosplenial cortex (RSC), left dorsal precuneus (dPreCu) and left prefrontal cortex (PFC). The complete list of domain-general clusters, sorted by consistency across subjects, is provided in Table 1. The domain-general activity found in multiple left prefrontal locations is consistent with previous reports of task-independent, cognitive control signals in these regions (reviewed in (Duncan & Owen, 2000; Sakai & Passingham, 2003)), while domain-general activity in the dorsal precuneus has been previously observed in the context of task-switching paradigms (Chiu & Yantis, 2009; Greenberg, Esterman, Wilson, Serences, & Yantis, 2010). However, partly because this paper is focused on the CON and partly because of the caution related to the 'sandwich' topography noted above, we do not make strong claims regarding the domain-generality of regions outside the CON. At the same time, however, since these regions exhausted the possible set of domain-general regions that showed sustained activations during the search phase of the perception and memory paradigms(i.e. sustained domain-general activity was not present outside of these regions), they provided a useful control for evaluating the degree to which the domain-general properties of the CON were unique.

Transient and sustained activity in the CON within the course of a trial

We examined the full profile of task-evoked activity in the three regions of the CON during the memory and the perceptual search tasks (Figure 3). BOLD activity relative to each transient and sustained task process was obtained for each ROI with a model that assumed a shape of the hemodynamic response function (Figure 3A). Since the regions were defined on the basis of their sustained activity in both tasks, we show the response for each of the sustained processes for display purposes only. A significant BOLD response was observed during i) the sentence reading phase that preceded the search phase in both the memory [left aINS/fO: t(18)=3.79, p<0.001; right dACC/preSMA: t(18)=4.28, p<0.001; right aINS/fO: t(18)=4.56, p<0.001] and the perceptual tasks [left aINS/fO: t(18)=4.16, p<0.001; right dACC/preSMA: t(18)=3.43, p<0.005; right aINS/fO: t(18)=2.70, p<0.05] and ii) the detection/response phase that followed the search phase in both the memory [left aINS/fO: t(18)=7.88, p<0.001; right dACC/preSMA: t(18)=4.17, p<0.001; right aINS/fO: t(18)=6.90, p<0.001] and the perceptual tasks [left aINS/fO: t(18)=15.98, p<0.001; right dACC/ preSMA: t(18)=13.36, p<0.001; right aINS/fO: t(18)=16.19, p<0.001]. Therefore, a significant BOLD response was observed during all the functionally distinct phases of the two tasks: an initial activation during sentence reading was followed by sustained activity over the entire duration of the search phase, which in turn was followed by transient activity evoked by detection/motor response. The robust response to the detection phase, especially

during the memory task, was a highly distinctive property that was observed in only a few regions showing domain-general sustained activity, as shown in Figure 4 (last two columns in each graph) and Table 2 (sixth column). These additional regions were located in left lateral prefrontal cortex (#5, 16, 17, 22) and dorsal precuneus (#7, 13). However, only the former group also exhibited significant activity for the sentence reading phase of both tasks, thus showing responses for all aspects of both task.

The sustained profile of activity observed in the CON was evident from the time course of BOLD activity, obtained with a model that did not assume a shape of the hemodynamic response and illustrated in Figure 3B. The peak of BOLD activity clearly shifted forward following the progressive increase of response times, and this shift was evident both during the memory (red) and the perceptual task (green). The reason the display parameter in the perceptual task was significantly positive is that the BOLD signal did not drop immediately to baseline following detection, but returned more gradually to baseline. Compared to the memory task, the CON exhibited a larger detection-related response during the perceptual task, which may be related to different task demands (see discussion).

Dynamic coupling between the CON and domain-specific networks depending on task demands

We next asked whether the pattern of functional connectivity between the CON and domain-specific regions was modulated by task demands. We first identified two set of regions (Table 3) that showed domain-specific sustained activity and corresponded to key nodes of the DMN and the DAN. These two networks are known to generate a pattern of dynamic competition both in terms of functional connectivity (Fox et al., 2005; Kelly, Uddin, Biswal, Castellanos, & Milham, 2008) and task evoked activity (Sestieri et al., 2010; Shulman et al., 2003). Then we assessed the strength of connectivity between the CON and these two sets of domain-specific regions at rest and during the memory and the perceptual task sets. The results are illustrated in Figure 5A (filled bars). At rest, the CON exhibited negative coupling with the DMN [p<0.001 for all the regions of the CON; one sample t-test] and positive coupling [p<0.005 for all the regions of the CON; one sample t-test] with the DAN. Among the regions that showed any evidence of domain-general sustained activity, only those of the CON showed significant negative coupling at rest with DMN regions, as illustrated in Figure 6 (left gray bars) and Table 4 (fourth column). The sign of the negative correlations during the memory task could have reflected the use of whole brain signal regression ((Murphy, Birn, Handwerker, Jones, & Bandettini, 2009) but see (Fox, Zhang, Snyder, & Raichle, 2009)). When the analysis was re-done without whole brain signal regression, the correlation coefficients were close to zero (empty bars in Figure 5A). However, irrespective of the true 'zero-point' of the correlation scale, the correlations during the perception task were considerably and significantly more positive than the correlations during the memory task. Therefore, at rest there was greater positive coupling between the CON and the DAN than between the CON and DMN.

The pattern of inter-network connectivity was strongly modulated by task execution. Importantly, the CON showed higher connectivity with the currently active task-relevant network (DMN for memory, DAN for perceptual task), compared to the task-irrelevant one. The task dependent dynamic coupling was assessed in each ROI through 2-way repeated measures ANOVAs with network (DMN, DAN) and task (rest, memory, perceptual) as factors, which revealed a significant network by task interaction [left aINS/fO: $F(2,36)=31.27$, $p<0.001$; right dACC/preSMA: $F(2,36)=16.61$, $p<0.001$; right aINS/fO: $F(2,36)=45.30$, $p<0.001$]. An even stronger result was obtained when inter-network connectivity during memory and perceptual tasks were directly compared in an ANOVA that excluded the resting state connectivity. Post-hoc analyses revealed that the CON-DMN connectivity was different across the two search tasks in all three CON regions (p<0.001),

whereas the CON-DAN was greater in the perceptual compared to the memory task in left (p<0.001) and right (p<0.001) aINS/fO but not in the right dACC/preSMA. However, this dynamic coupling was observed in almost all the other regions that putatively showed domain-general sustained activity, as shown by Figure 6 (red and green bars) and Table 4 (last column). Therefore, flexible task-dependent functional connectivity with domain-specific regions was not a distinctive property of the CON.

The analysis conducted without regression of the whole brain signal, while resulting in a general increase of connectivity regardless of network and task, provided evidence for a very similar pattern of task-induced modulations (the presence of a significant interaction effect is indicated in last column of Table 4, within parentheses). We also conducted a control within-network analysis to address whether task-induced modulations of FC always reflected the pattern of task-specific co-activation. The results are illustrated in Figure 5B. The 2-way ANOVA with network (CON, DMN, DAN) and task (rest, memory, perceptual) as factors showed a significant interaction effect [F(4,72)=18.47, p<0.0001]. Post-hoc analyses revealed no significant increases of FC from rest to task within any of the three networks, but the trend was in the direction expected based on the degree of activation. Therefore, the results are not conclusive concerning whether regions that are co-activated during task execution (e.g. DAN during the perceptual task) also tend to show an increase of task-dependent FC.

Distinctiveness of the CON among other regions showing domain-general sustained activity

To further investigate the functional distinctiveness of the CON, we conducted a multivariate hierarchical clustering procedure on the whole set of regions that putatively showed domain-general sustained activity. This analysis took several measures of task evoked activity and functional connectivity into account, assigning equal weight to each measure. The results of the clustering procedure are illustrated in Figure 7. Importantly, the three regions of the CON (purple) were not only grouped in the same cluster, but were also the only members of this cluster. The closest cluster (green), and thus the one exhibiting the most similar properties to the CON, included a region within the superior frontal sulcus and a region of the dorsal precuneus. Three other prefrontal regions were grouped in a more distant cluster (yellow). Many regions of the ventral parietal, retrosplenial and parahippocampal gyrus formed a distinct cluster (red) showing different functional properties. This analysis confirmed the common clustering of regions within the CON, and their segregation from other regions showing putative domain-general sustained activity.

Control analyses further tested the stability and reproducibility of the hierarchical clustering results across subjects and measures. The mean value of the correlation between dissimilarity matrices obtained creating different subgroup permutations was .94±.02, indicating a strong inter-individual consistency. The analysis was also repeated using a subset of the four functional measures. The regions of the CON were always in the same cluster, independent of the subset of parameters taken into consideration. However, for three out of four permutations this cluster also included the left SFS and left dorsal precuneus region, confirming their functional similarity to the CON. In general, the analysis confirmed that regions of the CON formed a cluster and that the regions showing the most similar characteristics to the CON were located in left SFS and left dorsal precuneus.

Discussion

The results demonstrated the generality of the cingulo-opercular network, both across two tasks that involved very different cognitive processes and across the different cognitive processes that occurred within each task. The CON was among a small number of regions

that showed sustained activity during extended periods in which people searched for behaviourally relevant information in the environment or from long-term episodic memory. This common activity was observed despite the fact that each task recruited a specific domain-specific network, the DAN and DMN, that show a mutual competitive relationship (Fox et al., 2005; Sestieri et al., 2010). Consistent with a role in cognitive control, within each task, the CON was significantly activated by all of the sustained and transient processes that were operative within a trial, from the initial sentence reading phase to the final transient response phase. The CON was dynamically coupled with task-specific networks, but this property was shared by almost all regions that showed any evidence of sustained, domain-general activity. A multivariate clustering procedure, which combined measures of task-evoked activity and functional connectivity, demonstrated the functional distinctiveness of the CON from lateral fronto-parietal regions that are also thought to be involved in task control.

Domain-general signals in the cingulo-opercular network

In the present study, very limited portions of cortex showed domain-general, sustained activity, compared to the large extent of regions that exhibited sustained activity within a single domain. Domain-specific activity for memory and perceptual tasks showed a striking topographical relationship characterized by spatial contiguity, which was previously described within the parietal cortex (Sestieri et al., 2010), but here was extended to frontal and temporal cortex. Sustained activity in the CON was observed during periods in which subjects searched through dynamically presented scene episodes for the presence of a particular object or in which they retrieved information from episodic memory while fixating a blank screen. The common, sustained activation of the CON under these very different circumstances confirmed its general involvement across highly disparate cognitive processes that were distinguished by the presence or absence of sensory stimulation and perceptual processing, and whether attention was directed toward external/on-line or internal/off-line representations. Moreover, this common sustained activity was observed during tasks that produced domain-specific activity in one or the other of two brain networks, the DAN or the DMN, that show a competitive relationship.

In addition, the experimental design allowed us to separately assess the involvement of the CON across a variety of processes that occurred within each task, from the reading of the cue sentence through to the motor response or end of sensory stimulation. The CON was significantly activated across all of these processes, again attesting to its general involvement across different cognitive processes. Although the CON was activated during all task phases, however, the magnitude of activation also depended on specific task demands. For example, the transient activity related to the detection/response phase was considerably more pronounced in the perceptual search than episodic memory task. This result may reflect the fact that the memory task was self-paced, whereas in the perception task, the timing of the response was dictated by the abrupt target onset.

Several previous studies have suggested that the CON is part of a Salience Network (SN) that facilitates the detection of behaviorally important or salient environmental stimuli (Seeley et al., 2007), and triggers a cascade of cognitive control signals (Menon & Uddin, 2010). The current results indicate that this description may be incomplete. The sustained involvement of the CON over the extended course of a trial adds support to the idea that the network is involved in maintaining a task set (Dosenbach et al., 2006), coordinating or sequencing task processes, or maintaining sustained effort (Sterzer & Kleinschmidt, 2010), perhaps coupled with transient processes related to error and salience detection.

Finally, we did not find evidence for the presence of sustained domain-general activity in regions that appeared in later definitions of the cingulo-opercular network based on resting

state FC analyses (Dosenbach et al., 2008; Dosenbach et al., 2007), namely the anterior PFC (BA10) and the anterior thalamus. Whereas Dosenbach and colleagues also did not observe sustained activity in the thalamus, they did observe sustained activity in BA10 for a subset of the tasks included in their meta-analysis (Dosenbach et al., 2006). It is possible that BA10 only responds to tasks requiring more complex forms of cognitive control, such as relational integration, planning, or multi-tasking, with respect to our tasks (Badre & D'Esposito, 2007; Gerlach, Spreng, Gilmore, & Schacter, 2011)). However, the present tasks were not chosen to cover all the possible elements of cognitive control, but were selected to show minimal functional overlap and strongly activate either the DAN or DMN. The lack of anterior prefrontal sustained activity may also reflect the direct contrast of the BOLD task-related response against the baseline. It has been shown that fixation can be accompanied by complex forms of internally-directed thought processes (i.e. mind-wandering), which have been associated with the activity of medial anterior prefrontal regions (Christoff, Gordon, Smallwood, Smith, & Schooler, 2009). It is possible that common activity during tasks and fixation might have obscured some patterns of domain-general brain activity.

Dynamic coupling between domain-general and domain-specific regions

Previous studies have proposed that fronto-parietal regions regulate the competition between the DMN and the DAN. Several studies have analyzed functional and effective connectivity across different tasks (Gao & Lin, 2012), including externally- or internally-oriented tasks (Smallwood et al., 2012; Spreng et al., 2010) that activated the DAN or DMN, respectively. However, these studies did not focus on the CON but examined changes in the pattern of connectivity within a larger network of fronto-parietal regions, making it difficult to examine the specific relationship between the CON and domain-specific regions. Conversely, previous analyses of task-related changes in the functional and effective connectivity of specific components of the CON have only been conducted separately using either externally-oriented (Higo et al., 2011; Sridharan et al., 2008; Zanto et al., 2011) or internally-oriented tasks (Chiong et al., 2013). The present study demonstrates the presence of robust, task-specific changes of connectivity between regions of the CON and other higher-order regions belonging to the DMN and the DAN, indicating flexible interactions across networks that depend on task demands (see also (Chadick & Gazzaley, 2011)). Such inter-network functional interactions may be mediated by anatomical connections between key nodes of the CON and relevant fronto-parietal networks. Although the pattern of anatomical connectivity of the dACC/preSMA and aINS/fO in humans has not been comprehensively characterized (see (Beckmann, Johansen-Berg, & Rushworth, 2009; Menon & Uddin, 2010)), a recent study has provided evidence that the structural integrity of the cingulo-opercular connection is necessary for the efficient regulation of activity in the DMN, both in terms of functional connectivity and behavioral performance (Bonnelle et al., 2012).

However, we found a similar pattern of flexible task-dependent functional connectivity in almost all regions that exhibited any evidence of domain-general sustained activity. While the functions of regions outside the CON were not the main focus of the present report, it seems unlikely that they all involved cognitive control. For example, both tasks may have activated regions involved in representing scenes, either during on-line perception or during episodic memory retrieval (Chun & Johnson, 2011), see below. Following this logic, the modulation of task-related functional connectivity of domain-general regions with domain-specific networks is not a unique marker of cognitive control.

Caution also should be exercised in interpreting task-dependent increases in functional connectivity as enhanced functional communication between regions (Spreng et al., 2010). First, the pattern of task-dependent functional connectivity matched the pattern of mean activity across regions and tasks. Therefore, although the present study adopted a

conservative approach aimed at minimizing the contribution of the mean event-related activity on the time series, it is still possible that residual trial-to-trial variations in the magnitude of the task signal biased measures of functional connectivity. In addition, the neurophysiological basis of BOLD functional connectivity remains controversial at best, both at rest and during task performance. Current models emphasize that resting-state BOLD connectivity reflects either fluctuations of slow cortical potentials (He, Snyder, Zempel, Smyth, & Raichle, 2008) or slow band-limited fluctuations of signals in alpha and beta bands between distant regions of cortex (Brookes et al., 2011; de Pasquale et al., 2010; Hipp, Hawellek, Corbetta, Siegel, & Engel, 2012). In contrast, cortical activations as measured electrophysiologically are characterized by decrements of alpha/beta power/coherence and increases in power/coherence at higher frequencies (e.g. gamma, (Fries, 2005; K. J. Miller, 2010; Siegel, Donner, Oostenveld, Fries, & Engel, 2008). Independent measures of fMRI functional connectivity coupled with electrophysiological measures (Daitch et al., 2010) may provide useful constraints on interpretation.

Functional distinctiveness of the CON

Several studies have proposed that regions of the CON are part of a larger fronto-parietal control network (FPCN) that also includes regions in lateral prefrontal (e.g. MFG, IFG) and inferior parietal cortex ((Vincent et al., 2008), see also (Cole & Schneider, 2007; Falkenberg, Specht, & Westerhausen, 2011) for alternative versions of the network topography). The FPCN is thought to be anatomically interposed between the DMN and the anticorrelated DAN (Fox et al., 2005), and thus well-positioned to facilitate functional integration between these two networks (Spreng et al., 2013; Spreng et al., 2010; Vincent et al., 2008). However, the present study showed that while many lateral fronto-parietal regions showed memory-specific sustained activity, they were poorly recruited by the perceptual task. The region in the superior frontal sulcus (SFS) that showed domain general activity was clearly more dorsal than the lateral prefrontal regions of the FPCN (Figure 2). The ventral lateral prefrontal regions that showed evidence of domain-general activity are likely located in the FPCN, although the correspondence was not exact (see Figure 2). Overall, however, a fair number of regions in the FPCN were likely not involved in regulating the competition between the DMN and DAN or coordinating the two networks. The lack of activation in these FPCN regions during the perceptual search task was not because that task was easy or automatic. The perception task was quite demanding, producing long reaction times and relatively low accuracy. Moreover, the perception task resulted in very sustained, domain-specific signals in IPS, FEF and other regions putatively involved in top-down control of sensorimotor cortex (Corbetta & Shulman, 2002), as well as sustained activity in the CON. It is the case that the domain-general activity observed here reflected the particular perception and memory tasks that were studied, which did not cover the entire spectrum of processes associated with cognitive control. Nonetheless, for these two tasks we observed a differential response between the CON and many fronto-parietal regions, and we are not aware of studies showing a converse dissociation in which fronto-parietal regions of the FPCN are commonly activated across very different tasks in the absence of common activation in the CON.

The CON was also distinguished from most fronto-parietal regions that showed evidence in the current study for domain-general activity, as the multivariate hierarchical clustering analysis indicated that these regions and the CON formed separate clusters. The two domain-general regions that were most similar to the CON, according to the clustering analysis, were located in the dorsal precuneus and superior frontal sulcus (SFS). The dorsal precuneus has been associated with the domain-independent function of shifting between task sets (Chiu & Yantis, 2009; Greenberg et al., 2010). Consistent with this characterization, the dorsal precuneus showed no activation, or even a significant

deactivation (see Table 2 and Figure 4) during the sentence reading phase of both tasks. Therefore, the dorsal precuneus did not respond during the transition from a resting state to a task state, but only during the course of a trial in which transitions likely occurred between different active task processes (e.g. the transition from visual search to target detection, see (Shulman et al., 2009; Yantis et al., 2002)). In contrast, the CON was significantly activated during the sentence reading phase of both tasks, consistent with a role in instantiating a task set (Dosenbach et al., 2006) during a transition from rest to a task state. These considerations suggest that although the dorsal precuneus showed some functional similarity with the CON, as indicated by the multivariate clustering procedure, it nevertheless has some distinguishing characteristics. In contrast, the current results did not clearly distinguish the CON from the SFS region.

Finally, the cluster of domain-general regions showing a functional profile that differed the most from the CON contained many regions that have been associated with scene perception, including bilateral retrosplenial and left posterior parahippocampal cortex (Epstein, 2008; Vann, Aggleton, & Maguire, 2009; Walther, Caddigan, Fei-Fei, & Beck, 2009). The common activation in these regions may have reflected the recruitment of the same 'representational' regions, in terms of on-line scene perception and off-line scene reconstruction during the perceptual and memory tasks, respectively. A representational function related to scene processing is consistent with the task-evoked fingerprint of these regions, which were strongly activated by the display component of the perception task but showed significantly less activation during the detection/response components of both tasks relative to the CON.

Overall, the present results support the idea that the CON is a network with distinctive properties (Dosenbach et al., 2006), functionally separate from other frontal and parietal regions (Dosenbach et al., 2008). Additional support for this conclusion has been provided in a recent study on the dynamics of large-scale brain functional networks during recollection (Fornito, Harrison, Zalesky, & Simons, 2012), which reported a functional distinction between the CON and fronto-parietal systems, as well as between left- and right lateralized components of the FPCN. In particular, each of these networks displayed diverse modes of context-dependent interaction with the DMN and a different relationship with behavioral performance. Taken together, these findings indicate the functional specificity of the CON with respect to other frontal and parietal regions putatively involved in task control.

Acknowledgments

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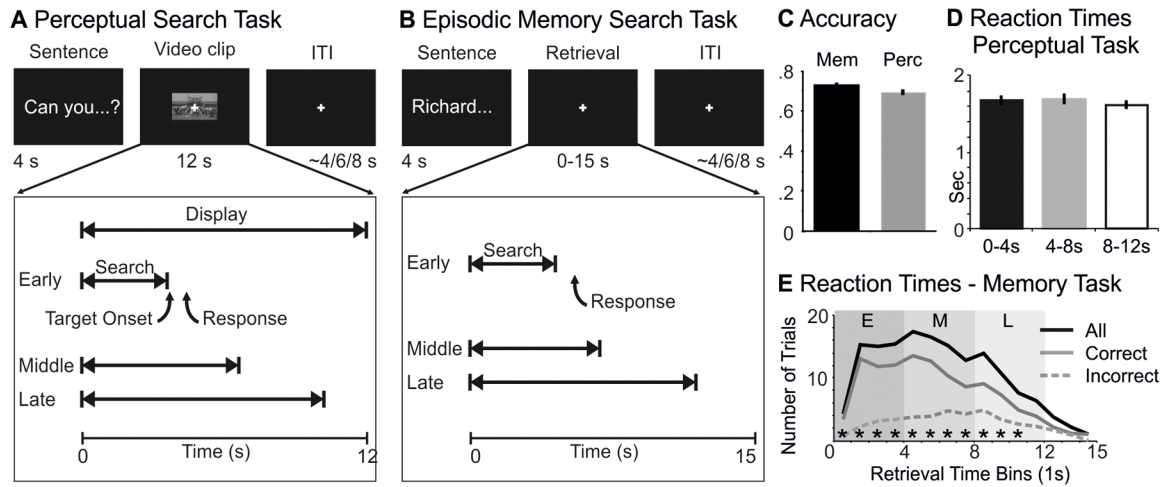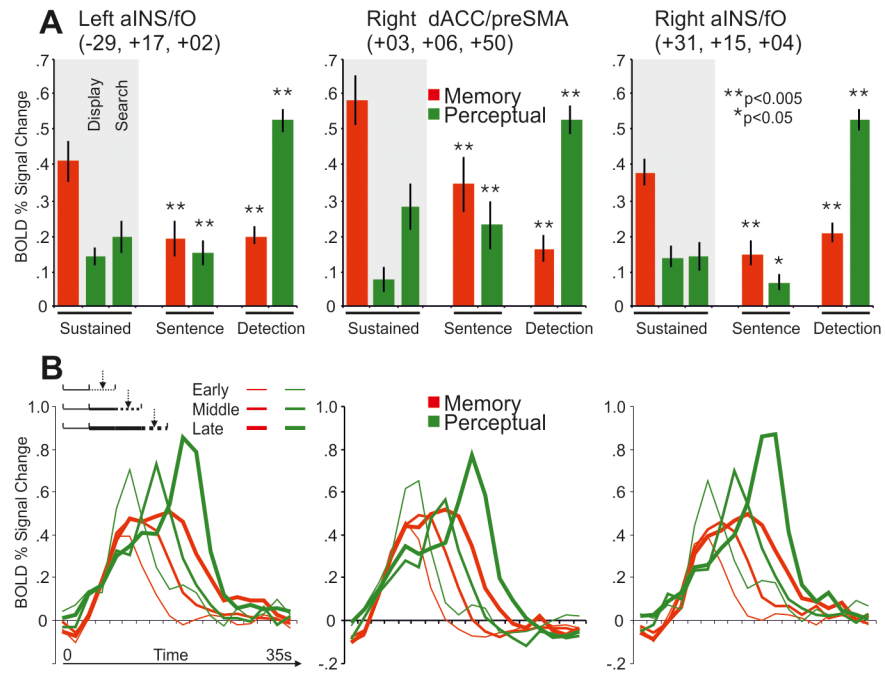
Figure 1.
(A) Trial structure in the perceptual search task. A sentence instructed participants to search for a specific target (object or character) that could appear at any time in the upcoming 12-sec video clip. Participants searched for the target while fixating a central cross and pressed a button as soon as the target was detected, depending on their confidence (high, low). Search duration was varied (early, middle, late) by manipulating the time at which the target was presented. After display offset, a variable ITI was interposed before the onset of the next sentence. (B) Trial structure in the episodic memory search task. Participants read a sentence describing a specific detail of a previously encoded episode from a TV show. They then retrieved information from episodic memory to judge the accuracy (i.e., true, false) of the sentence, which they indicated by pressing one of four buttons, depending on their confidence (high, low). Participants were given up to 15 sec to provide the judgment on each trial. An example of early, middle, and late search trials are provided. After participants' response, a variable ITI was interposed before the onset of the next sentence. (C) Mean accuracy for the memory and the perceptual (oddball target excluded) task. Vertical bars indicate *SEM*. (D) Mean RTs from target onset in the perceptual task, divided into early (1.678 sec), middle (1.691 sec), and late (1.615 sec) interval. Vertical bars indicate *SEM*. (E) Trial distribution (mean across participants) for each time bin (1 sec) of the allowed RT (15 sec). The graph shows the distribution of all trials (solid black), correct trials (solid gray), and incorrect (broken gray) trials. The asterisks indicate the time bins in which performance was significantly different from chance (one-sample *t* test against the chance level of 0.5). Different shades of gray on the graph illustrates the subdivision into early (E = 0–4 sec), middle (M = 4–8 sec) and late (L = 8–12 sec) trials for time course analysis. Trials in the 12- to 15-sec interval were discarded because of poor performance.
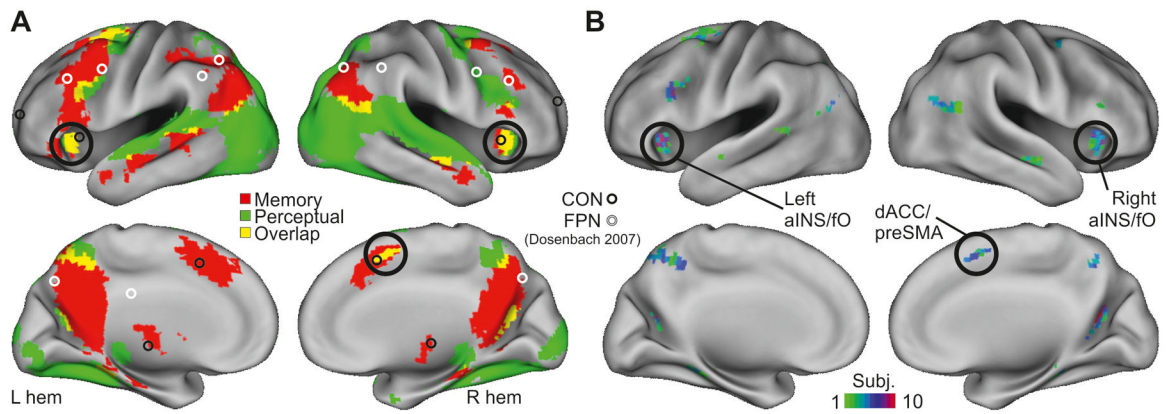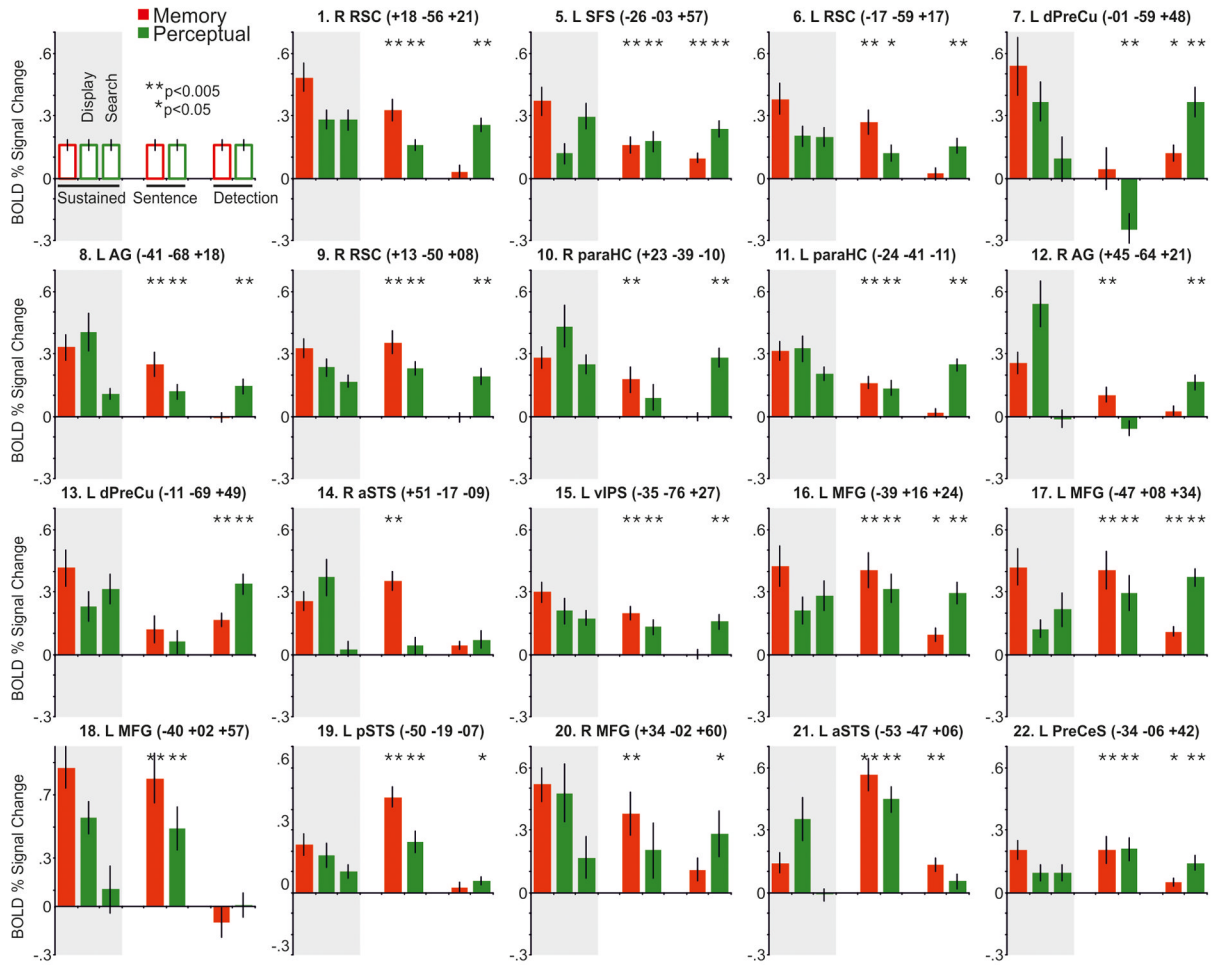
Figure 2.
(A) Voxelwise map of sustained activity during the memory task (red, multiple-comparison corrected group *z* map of the memory search process) and the perceptual task (green, multiple-comparison corrected group *z* map of the average of search and display processes). Voxels in yellow represent regions of overlap at the group level. The map is superimposed on the lateral and medial view of the bilateral inflated representation of the PALS Atlas (Caret 5.5 software; Van Essen, 2005, p. 56). Black and white circles have also been superimposed to indicate the nodes location of the CON and frontoparietal network (FPCN), respectively, based on the coordinates reported by Dosenbach and colleagues (2006, 2007, 2008). The node corresponding to the dorsal ACC/pre-SMA has been represented in both hemispheres because of its proximity to the midline ($z = -1$). Note the good spatial consistency between the three key regions of the CON (bilateral aINS/fO, dACC/pre-SMA) and regions showing sustained domain activity in this study. Domain-general activity was not observed in proximity of the additional CON regions (anterior pFC and thalamus) described by Dosenbach and colleagues (2007, 2008) and regions of the FPCN. (B) Map representing the number of individual participants showing overlap of sustained activity across tasks for each domain-general voxel identified in A. Individual maps were created with the same procedure of the group analysis.
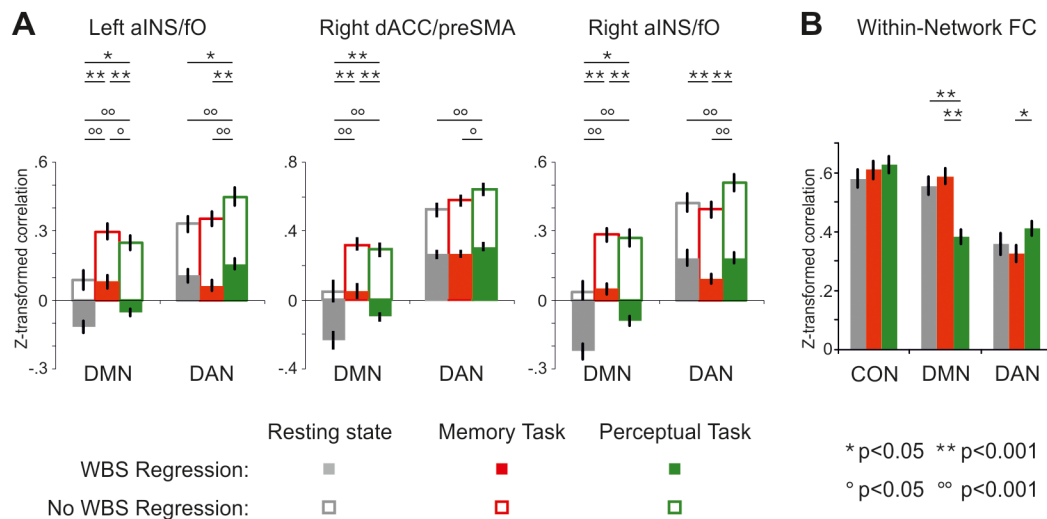
Figure 3.
(A) The complete pattern of task-evoked activity for the three regions of the CON. The BOLD percent response change is relative to each transient and sustained process of the memory (red) and the perceptual (green) tasks obtained with a model that assumed a shape of the hemodynamic response function (process-GLM). Processes were grouped into sustained processes that led to ROI definition (left bars on gray background), processes related to the early reading of the sentence indicating the target of the search (center bars), and those related to the final transient detection/response phase (right bars). Two sustained processes were estimated for the perceptual task, corresponding to stimulus (display) and search duration. Asterisks indicate a significant response compared with the baseline. Error bars represent *SEM*. The statistical significance of the sustained parameters was not calculated, as domain-general regions were defined on the basis of this criterion. (B) Time courses of BOLD activity for trials of different duration (early, middle, and late correct response trials) in each task, starting at sentence onset. Trials of increasing duration are represented by lines of increasing size. The time courses reflect the sum of the BOLD signal for the processes operative on each trials and were obtained with a model that made no assumption about the shape of the hemodynamic response (frame-by-frame GLM). The approximate trial duration for the three intervals (top) and the temporal scale (bottom) are indicated in the left graph.

Figure 4.
The pattern of task-evoked activity for each of the other regions showing domain-general sustained activity in both tasks (*n* = 19). The BOLD percent response change is relative to each transient and sustained process of the memory (red) and the perceptual (green) tasks obtained with the process-GLM. Processes were grouped into sustained processes, sentence-reading phase, and final transient detection/response phase. Asterisks indicate a significant activation/deactivation compared with the baseline for the additional processes. Error bars represent *SEM*.

Figure 5.
(A) The pattern of functional connectivity between the CON and domain-specific regions of the DMN and DAN that were selectively activated by sustained processes of the memory and perceptual task, respectively. The measure of functional connectivity was assessed at rest and during each task after the removal of the event-related activity by averaging the *z*-transformed correlation values between the region of the CON and the four representative ROIs of each domain-specific network. Filled and empty bars represent the *z*-transformed correlation values obtained with and without regression of the whole brain signal, respectively. Error bars represent *SEM*. Asterisks and circles represent significant differences across conditions. (B) The pattern of within-network connectivity in the three networks identified in this study (CON, DMN, DAN) as a function of task. No increase of within-network connectivity was observed compared with the resting state, supporting the hypothesis that task-induced modulations did not simply reflect the task-specific pattern of coactivation.
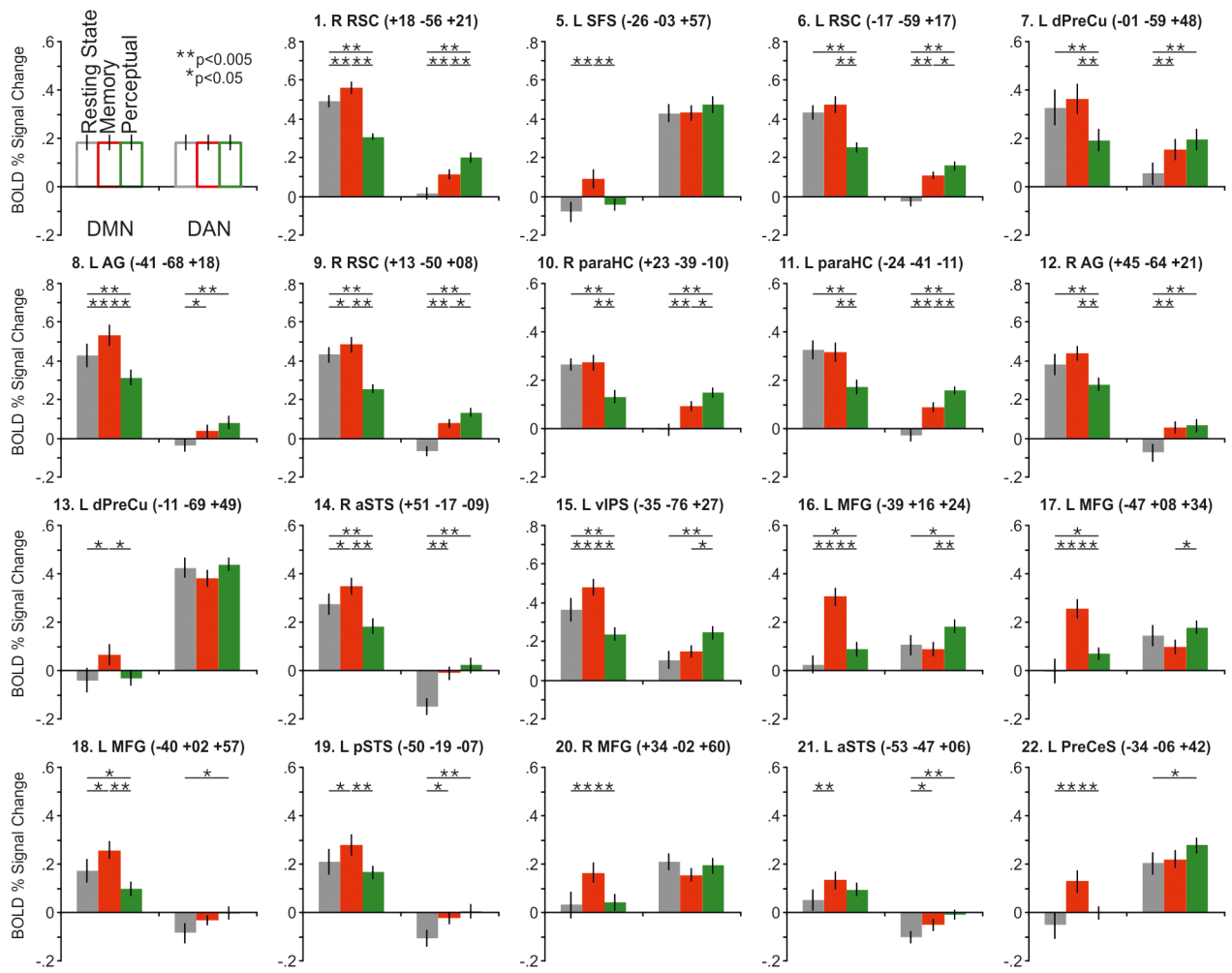
Figure 6.
The pattern of functional connectivity between each of the other regions showing domain-general sustained activity and domain-specific regions of the DMN and DAN. Error bars represent *SEM*. Asterisks represent significant differences across conditions calculated with Duncan *t* tests.
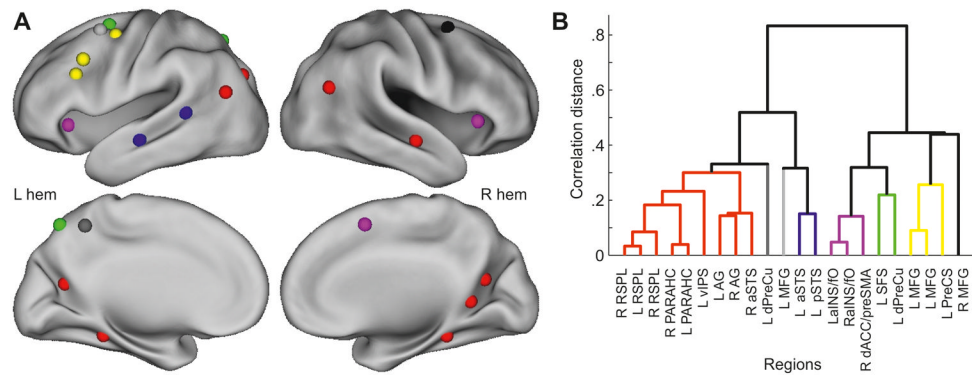
Figure 7.
(A) Anatomical location of the cortical regions showing domain-general sustained activity. Regions with the same color were grouped in the same cluster according to the multivariate hierarchical clustering analysis conducted on measures of task-evoked activity and functional connectivity. (B) Graph representing the correlation distance between each region illustrated in A. The threshold for the pruning of the cluster tree was calculated maximizing cluster size and measures of clustering validity (see <u>Methods</u>).

Table 1

Domain-general ROIs.

#	Side	Region	x	y	z	voxels
1	R	Retrosplenial cortex (RSC)	+18	−56	+21	24
2	L	Anterior insula/frontal operculum (aI/fO)	−29	+17	+02	26
3	R	Dorsal anterior cingulate/presupplementary motor area (dACC/preSMA)	+03	+06	+50	15
4	R	Anterior insula/frontal operculum (aI/fO)	+31	+15	+04	23
5	L	Superior frontal sulcus (SFS)	−26	−03	+57	27
6	L	Retrosplenial cortex (RSC)	−17	−59	+17	11
7	L	Dorsal precuneus (dPreCu)	−01	−59	+48	11
8	L	Angular Gyrus (AG)	−41	−68	+18	14
9	R	Retrosplenial cortex (RSC)	+13	−50	+08	17
10	R	Parahippocampal gyrus (paraHC)	+23	−39	−10	11
11	L	Parahippocampal gyrus (paraHC)	−24	−41	−11	22
12	R	Angular Gyrus (AG)	+45	−64	+21	12
13	L	Dorsal precuneus (dPreCu)	−11	−69	+49	15
14	R	Anterior superior temporal sulcus (aSTS)	+51	−17	−09	12
15	L	Ventral Intraparietal sulcus (vIPS)	−35	−76	+27	13
16	L	Middle frontal gyrus (MFG)	−39	+16	+24	14
17	L	Middle frontal gyrus (MFG)	−47	+08	+34	19
18	L	Middle frontal gyrus (MFG)	−40	+02	+57	11
19	L	Posterior superior temporal sulcus (pSTS)	−50	−19	−07	5
20	R	Middle frontal gyrus (MFG)	+34	−02	+60	17
21	L	Anterior superior temporal sulcus (aSTS)	−53	−47	+06	5
22	L	Precentral sulcus (PreCeS)	−34	−06	+42	5

Cortical regions showing domain-general sustained activity, listed according to the consistency across individual subjects. The table indicates hemisphere, name, Talairach Coordinates and voxel size.

Table 2

Response profile of domain-general ROIs.

#	Side	Region	Memory task		Perceptual task	
			Sent.	Det.	Sent.	Det.
1	R	RSC	6.40**	1.20	6.30**	7.57**
2	L	aI/fO	3.79**	7.88**	4.16**	15.98**
3	R	dACC/preSMA	4.28**	4.17**	3.43**	13.36**
4	R	aI/fO	4.56**	6.90**	2.69*	16.19**
5	L	SFS	4.01**	3.96**	3.58**	6.20**
6	L	RSC	4.60**	0.64	3.01*	4.38**
7	L	dPreCu	0.44	2.91*	−3.16**	5.16**
8	L	AG	4.39**	−0.38	3.39**	4.07**
9	R	RSC	6.48**	−0.17	7.15**	4.89**
10	R	paraHC	2.83*	−0.18	1.45	6.21**
11	L	paraHC	5.13**	0.74	3.82**	8.35**
12	R	AG	2.85*	1.20	−1.77	4.82**
13	L	dPreCu	1.83	4.72**	1.07	6.88**
14	R	aSTS	7.88**	1.99	0.95	1.70
15	L	vIPS	6.54**	−0.14	3.61**	4.67**
16	L	MFG	4.89**	2.89*	4.53**	5.78**
17	L	MFG	4.52**	5.37**	3.41**	8.54**
18	L	MFG	5.24**	−1.08	3.58**	0.17
19	L	pSTS	9.56**	1.10	4.51**	2.86*
20	R	MFG	3.65**	1.97	1.52	2.59*
21	L	aSTS	7.16**	4.01**	7.11**	1.51
22	L	PreCeS	3.20**	2.82*	3.83**	3.94**

BOLD response for the two additional processes of the memory and perceptual tasks obtained with the Process-GLM in each of the regions showing domain-general sustained activity listed in Table1. The table indicates the result of the one sample t-test against the baseline for each process and the corresponding significance level (*p<0.05; **p<0.005). Data for the sustained processes of both tasks are not reported since they were used for region definition.

Table 3

Selected domain-specific ROIs.

Side	Region	x	y	z	voxels
	Memory set				
L	Angular gyrus (AG)	−43	−65	+25	31
R	Angular gyrus (AG)	+39	−70	+40	31
L	Posterior cingulate/precuneus (PCC/PreCu)	−04	−64	+24	32
R	Posterior cingulate/precuneus (PCC/PreCu)	11	−63	+25	29
	Perceptual set				
L	Precentral sulcus (FEF)	−22	−06	+51	24
R	Precentral sulcus (FEF)	+36	−07	+46	35
L	Posterior intraparietal sulcus (pIPS)	−19	−72	+44	29
R	Posterior intraparietal sulcus (pIPS)	+23	−74	+42	28

Cortical regions showing domain-specific sustained activity during the memory and the perceptual task selected as representative of the DMN and the DAN, respectively.

Table 4

Resting state and Task-evoked connectivity between domain-general ROIs and domain-specific ROIs.

#	Side	Region	Resting state		Memory		Perceptual		3×2 ANOVA
			DMN	DAN	DMN	DAN	DMN	DAN	Interaction
1	R	RSC	0.49**	0.01	0.56	0.11	0.31	0.20	** (**)
2	L	aI/fO	−0.12**	0.11**	0.08	0.06	−0.05	0.16	** (**)
3	R	dACC/preSMA	−0.24**	0.26**	0.05	0.27	−0.10	0.30	** (**)
4	R	aI/fO	−0.22**	0.18**	0.05	0.09	−0.09	0.18	** (**)
5	L	SFS	−0.08	0.43**	0.09	0.43	−0.04	0.47	** (*)
6	L	RSC	0.44**	−0.02	0.48	0.11	0.25	0.16	** (**)
7	L	dPreCu	0.33**	0.05	0.36	0.15	0.19	0.19	** (**)
8	L	AG	0.43**	−0.04	0.53	0.04	0.31	0.08	** (**)
9	R	RSC	0.43**	−0.07*	0.48	0.08	0.26	0.13	** (**)
10	R	paraHC	0.26**	−0.01	0.27	0.09	0.13	0.15	** (**)
11	L	paraHC	0.33**	−0.03	0.32	0.09	0.17	0.16	** (**)
12	R	AG	0.38**	−0.07*	0.44	0.05	0.28	0.07	** (**)
13	L	dPreCu	−0.04	0.43**	0.07	0.38	−0.03	0.44	* (n.s.)
14	R	aSTS	0.27**	−0.15**	0.35	−0.01	0.18	0.02	** (**)
15	L	vIPS	0.36**	0.11*	0.48	0.15	0.24	0.25	** (**)
16	L	MFG	0.03	0.11*	0.31	0.09	0.09	0.18	** (**)
17	L	MFG	0.00	0.14**	0.26	0.10	0.07	0.18	** (**)
18	L	MFG	0.17**	−0.09*	0.26	−0.03	0.10	0.00	** (*)
19	L	pSTS	0.21**	−0.11**	0.28	−0.02	0.17	0.00	** (*)
20	R	MFG	0.03	0.21**	0.16	0.16	0.04	0.19	** (*)
21	L	aSTS	0.05	−0.10**	0.13	−0.05	0.09	−0.01	n.s. (n.s.)
22	L	PreCeS	−0.05	0.20**	0.13	0.22	0.00	0.28	** (**)

Pattern of connectivity between each of the regions showing domain-general sustained activity and the four representative regions of the DMN and the DAN as a function of task demands (rest, memory task, perceptual task). Connectivity is reported in terms of z-transformed correlation values. For the resting state condition, the asterisks indicate whether a significance difference against null correlation was observed (*p<0.05; **p<0.005; one sample t-test). The last column indicates whether the 2-way ANOVA showed a significant interaction effect between task and network. The symbol in parentheses indicates a significant interaction effect when the analysis was repeated without regression of the whole brain signal.