Deconstructing the Default: Cortical subdivision of the Default Mode/Intrinsic System During Self-Related Processing

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Abstract: Recent brain imaging research has highlighted a new global system of areas termed the Default Mode network (DM), which appears to specialize in intrinsically oriented functions. However, it is still unresolved to what extent this system contains functional subsystems as in the better known sensory and motor cortices. Here, we report that functional subdivisions can be revealed within individual nodes of the DM, such as the Inferior Parietal Lobule (IPL), through the use of different categories of self-oriented tasks. Subjects underwent BOLD fMRI scans during which they were asked to recall self-related positive and negative information in the categories of people and food. These tasks elicited distinct regions of activation within the DM. Importantly, the observed activations were above the activity level in the baseline, no-task condition for these regions. The main subdivision within the DM was observed in the inferior and posterior parietal cortex. Analysis of coherent resting state fluctuations (functional connectivity analysis) revealed that these regions of activation were part of a distinct network of regions within the DM. These results argue against viewing the DM as a unitary system, and are compatible with the notion that, similar to the rest of the cerebral cortex, the DM consists of distinct, functionally specialized subregions. *Hum Brain Mapp* 35:1491–1502, 2014. © 2013 Wiley Periodicals, Inc.

Key words: cortical specialization; fMRI; functional connectivity; rest; self-referential processing

INTRODUCTION

A fundamental property of the human cerebral cortex is its mosaic-like segregation into functionally distinct regions. Such segregation can be found at all levels of anatomical detail - from the properties of single neurons, through groups or “columns” of neurons [Malach, 1994; Tanaka, 2003], through areas and “streams of areas” [Grill-Spector and Malach, 2004; Ungerleider and Haxby, 1994]. Recent human brain imaging research has provided evidence for an even broader cortical specialization into global cortical systems that span all cortical lobes. This potential specialization is suggested by the discovery of a set of cortical regions, including frontal, parietal and temporal areas, collectively termed the “default mode” network (DM) [Buckner et al., 2008; Raichle et al., 2001].

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Intriguingly, DM areas reduce their activity during externally oriented tasks compared with the no-task baseline [Greicius and Menon, 2004]. We have proposed that these functional responses reflect a fundamental, bi-partite organization of the human cortex into two global systems [Fox et al., 2005; Golland et al., 2008]. One system, termed the “Extrinsic” system, is oriented externally and specializes in processing information derived from the external environment. This system consists of the entire constellation of sensory-motor and language areas. The complementary system, termed the “Intrinsic” system (corresponding to the DM), is oriented internally, to the organism itself. Although the precise functionality of this system is still unclear, a growing number of studies indicate that it indeed deals with various aspects of self-related information. Such information is processed during self-related evaluations [Buckner and Carroll, 2007; Goldberg et al., 2006; Gusnard et al., 2001a; Northoff et al., 2006; Salomon et al., 2009], voluntary actions [Goldberg et al., 2008; Preminger et al., 2010], episodic memory [Buckner et al., 2008; Sestieri et al., 2011; Spreng et al., 2009; Spreng and Grady, 2010] and planning. Central component nodes of the DM/Intrinsic system consist of medial frontal regions, inferior parietal lobe, precuneus, and anterior temporal regions. Importantly, the set of cortical regions associated with this system tend to fluctuate in a coherent manner (a phenomenon termed functional connectivity, FC) which further supports the notion that it constitutes a network of functionally related processing areas [Fox et al., 2005; Golland et al., 2008; Greicius et al., 2003].

The extrinsic system has been amply documented with regards to its multiscale mosaic organization, with evidence for such specialization at all levels of processing—from single cells, to specialized cortical areas, and all the way to different modality representations. The discovery of the DM raises the intriguing question whether this principle of multiscale mosaic organization observed in the extrinsic system is a global cortical principle, i.e., should manifest itself also in the organization of the DM. Alternatively, it is possible that the functional organization of the DM is fundamentally different, and therefore shows a more homogeneous organization across different cortical sites.

Since the precise functional properties of the DM are not fully established, and particularly because this system is less amenable to external stimulation [Preminger et al., 2010], delineating functional subdivisions of the DM has been challenging. Previous studies revealed divisions of the DM network [Andrews-Hanna et al., 2010; Sestieri et al., 2011; Uddin et al., 2009a] using either data driven parcellation methods (e.g., ICA, graph-analysis), or using specific tasks such as episodic memory retrieval. These studies have proven successful in mapping functional subdivisions of the network at the level of entire nodes [Andrews-Hanna et al., 2010], by showing, for example, a dissociation between the “dorsal medial prefrontal cortex subsystem” and the “medial temporal lobe subsystem” [Andrews-Hanna et al., 2010]. However, these have not

addressed the question whether functional subdivisions may exist within each of the DM nodes. A strategy that proved successful in identifying such within-region functional specializations in previous research of the extrinsic system was to search for tuning for different exemplars belonging to a single category. For example, using different angles of orientation within the category of elongated lines has uncovered the existence of orientation columns within the visual cortex [Hubel and Wiesel, 1962]. More recently, the use of different categories within the range of visual objects revealed the presence of cortical specializations for faces, houses, tools, etc. [Grill-Spector and Malach, 2004]. Here, we applied this strategy to the DM in an attempt to search for functional subdivisions within individual component nodes of this system.

In the present study, we looked for distinct representations of two different categories (people and food) within the broader category of self-related items. The people category was chosen because the DM has been shown to be involved in self-referential social cognition [Mitchell et al., 2005, 2006; Ochsner et al., 2004], especially in the medial prefrontal regions. The second category, food, was selected as we predicted that it would elicit strong self-referential activations while, due to its markedly different content, it would likely produce a nonoverlapping activation with the people category. It is important to emphasize that the aim of the present study was not to make claims about the exact functional selectivity of DM subdivisions, which is unrealistic using only two broad and complex categories. These categories were chosen merely as a tool that could potentially uncover possible functional subdivisions within the DM.

Our results show that when subjects evaluated the people and food categories distinct regions within individual nodes of the DM were activated, as well as some regions of the Extrinsic system. Importantly, the observed activations in the DM were above the baseline, no-task activity for these areas. A functional connectivity analysis, using these functionally defined regions as seeds in a separate resting state scan, revealed segmentation within the DM—with each seed correlating with a different subsystem of the DM. Our results reveal the presence of within-region functional subdivisions in the DM organized in parallel networks, and hence are compatible with the notion that mosaic organization is a general cortical phenomenon. This conjecture raises the intriguing prospect of self-related columns and even single neuron specializations within the DM system.

METHODS

Subjects

Our study included 17 healthy subjects (7 females; ages, 22–36; 2 left handed) recruited primarily from the Weizmann Institute of Science student population. Among them, two were excluded due to extensive head-movements during the experiment (above 2 mm). Nine subjects participated

Figure 1.

Experimental design: Three functional scans were run on each subject. Top: self-referential (people/food) scan; subjects were requested to recall a mental list of people and foods they like and dislike. Each block was 15 s long with 15 s of rest between blocks. Middle: categorization scan; subjects were presented with pictures of faces, objects, and houses and were asked to categorize them. Bottom: rest scan; subjects were asked to relax and not think of any specific content.

in all experiments and runs. All participants had normal hearing and normal or corrected-to-normal vision and provided written informed consent to participate in the experiments. The Sourasky medical center ethics committee approved the experimental protocols.

at the back end of the MRI tunnel, and viewed through a tilted mirror positioned over the subject's forehead. Button presses were recorded during the fMRI experiments via a response box (Current Designs MR safe fiber optic response pad, bimanual 8 models).

Imaging Setup

The scans were performed on a 3T Trio Magnetom Siemens scanner at the Weizmann Institute of Science, Rehovot, Israel. Three-dimensional T1-weighted anatomical images were acquired with high-resolution 1-mm slice thickness (3D MP-RAGE sequence, TR = 2,300 ms, TE = 2.98 ms, $1 \times 1 \times 1 \text{ mm}^3$ voxels). BOLD contrast was obtained with gradient echo planar imaging (EPI) sequence, TR = 3,000 ms, TE = 30 ms, flip angle = 90° , FOV 240 mm, matrix size 80×80 , scanned volume - 46 axial slices of 3mm thickness (no gap, $3 \times 3 \times 3 \text{ mm}^3$ voxel).

Presentation software (Neurobehavioral systems) was used to deliver the stimuli and record subjects' responses. Stimuli were generated on a PC, projected via an LCD projector (Epson PowerLite 74c) onto a screen positioned

Tasks and Stimuli

The experiment consisted of three functional runs of ~10 min in length each: categorization task, self-referential task, and rest scan (Fig. 1). At the beginning of each block/rest period, subjects received a relevant auditory cue via headphones. The order of all the scans was counter-balanced between subjects.

Each subject performed a categorization task on three different picture categories (faces, houses, and objects). The subjects were instructed to press a button relevant to the category of the picture presented in the center of the screen. The pictures appeared for one second each, in blocks of one minute, separated by resting periods of similar length. This categorization task was used in order to define the DM network through the pattern of bellow

baseline activations [Sestieri et al., 2011]. In the self-referential task, subjects were asked to recall a list of four to five items that were either people or eatable dishes they especially liked or disliked (cue word: people/food; cue duration: 1,500 ms). The choice of items was individual for each subject allowing highly self-relevant stimuli of both positive and negative valence to be used. The number of positive and negative valence stimuli was balanced across subjects. All subjects were instructed not to visually imagine the items in order to avoid visual imagery related activations. Subjects were given a few minutes to think of relevant items before entering the scanner. When analyzing the results, we excluded the first TR in each block corresponding to the time in which the cue word was heard. This was done in order to prevent the auditory-related activation from affecting the data. Finally, in the rest scan, the subjects were asked to lie still in the scanner with their eyes closed and try not to think of any specific subject, experience or feeling.

Following the scans, subjects completed a questionnaire rating the levels of difficulty of the tasks and vividness of the imagery process. A 10-point scale was used for this rating (1 = very easy/not vivid at all; 10 = very difficult/very vivid). In addition, subjects provided a brief description of their thoughts during the different runs. The most commonly reported thoughts included thinking of boyfriend/girlfriend, family members, political leaders, and fast food.

Data Analysis

The ratings of vividness and difficulty were analyzed using paired *t*-tests comparing the reported vividness and difficulty between the people and food conditions. fMRI data were analyzed using "Brain-voyager" software package (Brain Innovation, Maastricht, Netherlands) and complementary in-house software. The first two images of each functional scan were discarded. The functional images were superimposed on 2D anatomic images and incorporated into the 3D data sets through trilinear interpolation. The cortical surface in a Talairach coordinate system [Talairach and Tournoux, 1988] was reconstructed for each subject from the 3D-spoiled gradient echo scan. Preprocessing of self-referential and categorization scans included 3D motion correction and filtering out of low frequencies up to 2 cycles per experiment (slow drift). In the preprocessing of the rest scan, a high-pass filter of 0.006 Hz was used.

All data were spatially smoothed using a Gaussian filter full width of half maximum values of 8 mm. Statistical analysis/mapping was based on the general linear model (GLM) [Friston, 1995], with a regressor for each condition in the experiment. All regressors were modeled as box-car functions convolved with a canonical hemodynamic response function. A hemodynamic lag of 6 s was assumed and verified for each subject. The analysis was performed independently for the time-course of each individual voxel.

Multisubject analysis was based on a random-effect GLM [Friston et al., 1999]. The multisubject functional maps were projected on an inflated or unfolded Talairach normalized brain. Significance levels were calculated, taking into account the minimum cluster size and the probability threshold of a false detection for any given cluster. This was accomplished by a Monte-Carlo simulation (AlphaSim by B. Douglas Ward) using the combination of individual voxel probability thresholding. The probability of a false positive detection per image was determined from the frequency count of cluster sizes within the entire cortical surface and corrected to $P < 0.05$ for multiple comparisons. Color scales indicate the statistical level ranging from $P < 0.05$ (darker colors) up to at least $P < 2.92e^{-07}$ (brighter colors) corrected.

Definitions of ROIs

Regions of interest (ROIs) were defined for each subject individually in the following manner: In order to map the DM network we used a targeted functional connectivity analysis based on the rest scan. Multisubject activity mapped for the categorization>rest ($P < 0.05$, corrected for multiple comparisons) was identified and the top deactivated cluster within the left inferior parietal lobule (lIPL) area was defined as the ROI. From this region, a seed region of ~300 contiguous voxels was defined for each subject. For each subject, the time-course of the lIPL seed activity during the rest scan was extracted and used in a random effect multisubject analysis of functional connectivity analysis. The resulting FC map of the DM system was used to define the regions of interest: bilateral posterior cingulate cortex - precuneus (IPCUN, rPCUN), bilateral superior frontal gyrus (ISFG, rSFG), bilateral inferior parietal lobule (lIPL, rIPL), bilateral dorsal-medial prefrontal cortex (lDMPFC, rDMPFC), bilateral ventral medial prefrontal cortex (lVMPFC, rVMPFC) and left pre-central cortex (lPreC).

To verify the consistency of the resulting DM map from the lIPL seed analysis, we repeated the analysis, but this time using the PCUN as a seed. This region was chosen as the PCUN is considered a hub region of the DM network, with strong connectivity with the other nodes of this system. This was done by anatomically selecting a square of 1,000 voxels extending bilaterally in the PCUN region (TAL: $x: -1.5, y: -49.5, z: 30.5$) in each subject (Fig. 7). For each subject, the time-course of the PCUN seed activity during the rest scan was extracted and used in a random effect multisubject analysis of functional connectivity. The resulting FC map of the DM system was used to verify the regions of interest found in the previous analysis, independently of the task negative activations from the categorization task. ROIs for the self-referential run were defined as regions of significant activation or deactivation ($P < 0.05$ corrected for multiple comparisons) which overlapped the ROIs of the DM maps. We employed an internal localizer approach using

half of the trials to define the ROI and the other half to calculate the time-course. The time-course graphs presented in this study represent the average temporal pattern of activation in the ROIs for each task.

Functional Connectivity During Rest

The ROIs from the self-referential task (IPL for food > rest, IPCUN for people > rest) were used as seed regions for a FC analysis during rest. For each seed region we extracted the time-course during rest for every subject. The time-courses of these regions were correlated with the time-courses of all brain voxels in each subject and then averaged across subjects in a multisubject random effects analysis. The resulting maps show the regions correlated with each seed region for all subjects, and these were corrected for multiple comparisons using a Monte-Carlo simulation as described above.

RESULTS

Our study was based on fMRI scans in 15 subjects who were engaged in two different categories of self-related tasks with the aim of uncovering potential subdivisions within the DM network. Specifically, our design consisted of three experiments: A visual categorization task in which subjects were presented with pictures from three different categories (faces, houses, and objects). The subjects were required to indicate the category to which each picture belonged (Fig. 1A). The second task was a self-referential task in which subjects recalled people and food which they liked or disliked (Fig. 1B). Finally, in the third part of the experiment, a rest scan was performed in which the subjects were scanned while lying in a relaxed awake state in the scanner (Fig. 1C).

As task difficulty is known to affect the activity of the DM, it was important to verify that the two self-referential tasks were of similar difficulty level. Analysis of the ratings of vividness and difficulty indicated that the participants found the people and food tasks to be quite simple. The mean difficulty rating for the people task ($M = 3.7$, $SD = 2$) and for the food task ($M = 2.9$, $SD = 1.5$) did not differ significantly (t -test, $P = 0.29$ n.s.). Furthermore, the reported visual vividness in the people condition ($M = 4.2$, $SD = 2.5$) and in the food condition ($M = 3.8$, $SD = 2.2$) were not significantly different (t -test, $P = 0.31$, n.s.). Thus, the two conditions were equated for both difficulty and vividness.

The categorization experiment was successful in delineating the DM system, characterized by increased activation during the fixation baseline compared to the task periods. These regions (Fig. 2 A,B) include the regions of the bilateral posterior cingulate-precuneus (PCUN), bilateral superior frontal gyrus (SFG), inferior parietal lobule (IPL), dorsal-medial prefrontal cortex (DMPFC), ventral medial prefrontal cortex (VMPFC), and lateral temporal

cortex (LTL). These regions of the task negative system largely overlap with the DM network [Fox et al., 2005; Shulman et al., 1997]. Yet, the task negative system often includes regions that show negative responses due to task specific parameters, such as inhibition of peripheral visual regions in response to a central stimulus.

To map the DM as accurately as possible, we utilized the fact that the DM shows coherent fluctuations during rest [Fransson, 2005; Greicius et al., 2003]. This coherent pattern (also termed functional connectivity, FC) was used to delineate the network's boundaries. To verify the delineation of the DM we therefore examined the FC from a "seed" region within the system, which in this case was the left IPL (Fig. 2B). The connectivity map from the IPL seed region is depicted in Figure 2C. As can be seen, the resulting DM connectivity map was highly similar to that of the task negative system, but did not include the peripheral extrastriate visual regions which were included in the task negative system.

Although the DM typically responds by signal decrease to a large array of extrinsically oriented tasks, it can show positive activation on a subset of tasks that contain a strong self-referential component [Goldberg et al., 2006; Gusnard and Raichle, 2001; Preminger et al., 2010]. We therefore searched for cortical regions that presented positive (above resting baseline) activation to the task. Figure 3 depicts cortical regions which showed such positive activation in the people > rest contrast. As can be seen in Figure 3, this contrast activated dorsal medial prefrontal regions, premotor regions (including the inferior frontal gyrus, primarily in the left hemisphere), and part of the PCUN bilaterally. Notably, almost no deactivations were detected for this task, indicating that the task was associated with activity increases compared to resting baseline in both the intrinsic DM system as well as the extrinsic system.

In order to examine the BOLD time course of activation in these regions in an unbiased manner, we employed the "internal localizer" approach [Lerner et al., 2002; Nir et al., 2006]. In this procedure, a subset of the epochs served to localize regions of interest, while another subset, not used in the statistical localization tests, was used to evaluate the activation level. This approach is advantageous as the localization was done on epochs from the same scan in which the activation level was measured, hence minimizing inaccuracies due to head motion between scans. However, the measured activity is unbiased since the signal measurements are obtained from epochs that were not included in the statistical localizer mapping. This was done using a within subject ABABAB design (see Supporting Information Fig. S1), thus maintaining independence of ROI selection and statistical analysis. The average time courses obtained using this analysis are depicted in Figures 3 and 4.

Within the DM, only a subregion in the precuneus showed positive (above resting baseline) activity in the people condition (Fig. 3). As can be seen from the independently measured time courses of activation (Fig. 3, top

Figure 2.

Top: Intrinsic localizer - categorization>rest on unfolded brain. Middle: Intrinsic localizer - categorization>rest on flattened brain. Seed region for FC mapping of DM in Left IPL are marked. Bottom: The intrinsic system as derived from functional connectivity seed shown above during the rest run. All maps are

group level random effects ($N = 15$) corrected for multiple comparisons. CingS, cingulate sulcus; CS, central sulcus; PCUN, precuneus; IPL, inferior parietal lobe; MFG, middle frontal gyrus; SFG, superior frontal gyrus; STS, superior temporal sulcus.

Figure 3.

Flattened map of people>rest contrast with outlines of the Intrinsic system. Top graphs show activation time courses for regions selected independently (see Methods). Note above resting baseline activations in specific subregions of the DM, and the differential activation for the two tasks. Random effects corrected for multiple comparisons. CingS, cingulate sulcus; CS, central sulcus; PCUN, precuneus; IPL, inferior parietal lobe; MFG, middle frontal gyrus; SFG, superior frontal gyrus; STS, superior temporal sulcus.

panel), the activity increase was significant ($P < 0.01$) and selective for the people condition alone, with the food condition showing no response in this region ($P < 0.02$). The rest of the PCUN ROI showed no activation for this condition, suggesting functional subdivisions within this DM region. Another DM region, the DMPFC, also showed a positive activation to the people task but not to the food task ($P < 0.001$). Additionally, extrinsic regions of the precentral sulcus, expanding laterally to the inferior frontal gyrus and lateral sulcus, were robustly activated in the left hemisphere. These lateralized activations spatially correspond to regions typically associated with verbal activity.

A similar analysis was conducted with regard to the food category. The activity map resulting from half the events compared with rest epochs is presented in Figure 4. In the DM system, this contrast activated a region within the IIPL as well as prefrontal regions in the left hemisphere which resemble those found in the people>rest contrast. The activation in the IIPL region for the food condition was significantly above baseline ($P < 0.001$). However, the difference between the food and people specialization here was significant ($P < 0.007$), but only during the initial peak of activity (0–18 s after task onset). Within the IIPL node, only this specific region showed a strong response to the food condition, as the remaining expanses of the ROI showed little to no response to the self-referential conditions.

As previously noted, coherent “resting state” fluctuations can provide a useful indicator for the functional organization of cortical networks. We therefore examined the extent to which the putative subdivisions revealed by the different *self-referential* tasks were also reflected in the FC of these regions during *rest*. The results of this analysis for an example subject are shown in Figure 5, and for all subjects in Figure 6. As can be seen, the FC results also demonstrate clear subdivisions within the DM. Specifically, the FC analysis from the IIPL seed region, taken from the *food>rest* contrast in each subject (blue regions), revealed that the superior region of the IPL is strongly correlated with a network of regions that were largely confined to the DM. These include regions in the premotor cortex and middle frontal gyrus, primarily in the left hemisphere. A small cluster within the medial prefrontal gyrus was also correlated with the activity of this seed region. The PCUN seed region, based on the functional activation from the *people>rest* contrast (orange colored regions), again showed correlation largely confined to the DM. It correlated with a system of regions including the inferior part of the IPL, inferior temporal sulcus, anterior cingulate regions and medial prefrontal cortex. As can be seen in Figures 5 and 6, there was little overlap between the two DM networks, yet together they comprised most of the overall DM regions (outlined in red). Interestingly, it appears that the relative locations of the two networks

Figure 4.

Flattened map of food > rest with outlines of Intrinsic system. Note above resting baseline activations (top graphs) in specific subregions of the DM. Random effects corrected for multiple comparisons. CingS, cingulate sulcus; CS, central sulcus; PCUN, precuneus; IPL, inferior parietal lobe; MFG, middle frontal gyrus; SFG, superior frontal gyrus; STS, superior temporal sulcus.

Figure 5.

Two FC networks from the people seed in PCUN (yellow regions) and food seed in IPL (blue regions) from Subject BQ. Note little overlap between FC networks from two functional seeds, yet together they cover most of the DM regions. CingS, cingulate sulcus; CS, central sulcus; PCUN, precuneus; IPL, inferior parietal lobe; MFG, middle frontal gyrus; SFG, superior frontal gyrus; STS, superior temporal sulcus.

Figure 6.

Two FC networks from the people seed in PCUN (yellow) and food seed in IPL (blue) for all subjects. Note little overlap between FC networks from two functional seeds. Random effects corrected for multiple comparisons. CingS, cingulate sulcus; CS, central sulcus; PCUN, precuneus; IPL, inferior parietal lobe; MFG, middle frontal gyrus; SFG, superior frontal gyrus; STS, superior temporal sulcus.

undergo a reversal, moving from the PCUN to the IPL—so that in the PCUN the network revealed by the food seed is more anterior relative to people, while in the IPL this order is reversed.

To further test the reproducibility of our results, we defined the DM network regions using an additional seed chosen within the PCUN region (see methods). The DM network revealed using this second independently chosen

Figure 7.

A: Definition of the DM system using an anatomically defined seed in the PCUN. Black square denotes seed region in the PCUN region. Colored regions show the results of a random effects group FC analysis from the seed region, corrected for multiple comparisons. **B:** The two FC networks from the people seed in PCUN (yellow) and food seed in IPL (blue) for all subjects projected on a flattened brain. Note the red outline corre-

sponds to the mapping of the DM system using the PCUN seed region. As in Figure 6, the FC networks from the functionally defined seeds cover most of the DM regions. Random effects corrected for multiple comparisons. CingS, cingulate sulcus; CS, central sulcus; PCUN, precuneus; IPL, inferior parietal lobe; MFG, middle frontal gyrus; SFG, superior frontal gyrus; STS, superior temporal sulcus.

seed closely resembled the one observed using the IIPL seed, showing the robustness of the connectivity network of the DM during rest. We overlaid the FC networks from our functionally defined seeds (as seen in Figs. 5 and 6) with the network defined by the PCUN seed. The results, as can be seen in Figure 7, show that even when using an independent seed selection, the FC networks from the task-related seed regions extend over most of the DM network.

DISCUSSION

Our results demonstrate that under carefully chosen task conditions, the DM shows clear functional heterogeneity which appears both between different regions of the system, and locally within a single DM node (e.g. for IIPL Fig. 3, for PCUN Fig. 4). This is compatible with the hypothesis that as in the Extrinsic/sensory-motor system, the DM/Intrinsic system can be further subdivided into a mosaic of functionally differentiated brain regions.

Our work supports and expands the results of several previous studies that have highlighted heterogeneity in the properties of core regions of the DM. For example, the MPFC was reported to be involved in memory-of-self, emotional processing, self-related, and social cognition tasks [D'Argembeau et al., 2007; Gusnard et al., 2001b; Kelley et al., 2002; Macrae et al., 2004a], while the PCUN node of the DM has been shown to be preferentially involved in lapses of attention and daydreaming [Mason et al., 2007; Mckiernan et al., 2003], autobiographical memory [Sestieri et al., 2011; Spreng and Grady, 2010; Svoboda et al., 2006] and mental time travel [Schacter et al., 2007]. A differentiation between right and left IPL has been uncovered in voluntary decision tasks [Goldberg et al., 2008]. In addition, attempts have been made to define different subnetworks of the DM using anatomical-based coordinates or a variety of exploratory data analyses (e.g. ICA, k-mean clustering, task negative mapping). Although these analyses have revealed general subdivisions of the system [Andrews-Hanna et al., 2010; Harrison et al., 2008; Laird et al., 2009; Leech et al., 2011; Uddin et al., 2009b], they might have masked the functional specializations of specific regions. Here, we focused on identifying the specialization within different nodes of the DM based solely on their functionality.

Recently, a study has investigated functional subdivisions of the DM network using memory related tasks unconstrained by a priori definitions of the DM [Sestieri et al., 2011]. This study found functional dissociations between anterior and posterior nodes of the DM suggesting a task dependent fractionation of the DM system. Here we extend this observation by showing that functional subdivisions can be found within individual DM nodes. Furthermore, we demonstrate that these subdivisions are also reflected in the coherent FC patterns of this network. Our findings have revealed a novel subdivision within the

DM system, and also extended the specialization to distinct patterns within contiguous anatomical regions. Thus, our results demonstrate that different nodes of the DM – such as the IPL and PCUN, typically considered to be a cohesive functional unit – may actually be composed of several subregions with differing functional specializations. Interestingly, Seghier and colleagues, who utilized a similar functional analysis, used verbal and perceptual tasks to delineate several functional regions within the left inferior parietal cortex (BA 39), which corresponds to the subdivision found in our FC analysis of the IIPL [Seghier et al., 2010].

Importantly, the novel subdivisions found here are based on positive, rather than negative, activation of the “default system”. Typically, the DM is considered to be task-negative, i.e., a system showing reduced activation during task performance. However, as our present results reveal, such negative activation was task-dependent. As can be seen in Figures 3 and 4, we rarely found robust negative responses to either the people or food tasks, and instead found subdivisions with positive, albeit weak, activation in the DM proper. This provides further evidence against the notion that the DM is a universal task-negative or “default” system. Instead, it supports the proposition that the DM is a system that specializes in specific cognitive functions, such as intrinsically oriented processing, which are remote from sensory-motor tasks typically used in conventional brain imaging. This conclusion is compatible with a number of previous studies showing positive activation (compared to resting baseline) of the DM [Goldberg et al., 2006; Mitchell et al., 2005; Mitchell et al., 2006; Preminger et al., 2010], as well as numerous studies showing reduced negative responses in self-related conditions [D'Argembeau et al., 2005; Macrae et al., 2004b; Salomon et al., 2009].

In addition to the DM activation, our results showed a concurrent robust activity in premotor regions, both for the food and people tasks, that has been consistently linked to the task-positive, extrinsic system. These results illustrate that, as previous studies have also revealed, the DM/Intrinsic and the Extrinsic systems are not always in antagonistic relationship and, depending on the cognitive demands, can often coactivate [Sestieri et al., 2011]. The pre-motor activation was strongly left-lateralized, indicating that it was most likely associated with linguistic aspects of the two tasks.

It is important to emphasize that the aim of this study was to examine the hypothesis that the DM consists of distinct subdivisions both between different regions, and even within each DM node. It was not meant to precisely define the optimal response properties of these subdivisions, a task that will necessitate numerous experiments and is beyond the scope of this manuscript. Thus, our present results should not be taken as support for food-specialization or people-specialization in the activated regions. It is more likely that these preferential activations were related to a much more complex set of specialized

cognitive functions. This does not alter the fundamental finding of this study that a single task requiring specific self-related introspection, such as estimating the emotional distance to different people, differentially highlighted subdivisions within the DM network.

CONCLUSIONS

Our results support the notion that the default mode is not a unitary network, but rather a complex heterogeneous system, comprised of functionally specialized subregions even within classical DM nodes. Importantly, we extend previous research of this phenomenon to the level of subdivisions within individual nodes of the DM system. This indicates that the multilevel mosaic organization of the cerebral cortex is a common principle maintained across the entire human cortex, and specifically in the highly specialized DM network. Furthermore, this organization can be revealed by utilizing the different functional specializations of DM regions, as well as the coherent functional connectivity of the system during rest. It remains to be explored whether these findings can be extended to reveal other intriguing levels of organization in the DM system such as columnar or cellular specializations.

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