The default network and processing of personally relevant information: Converging evidence from task-related modulations and functional connectivity

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Abstract

Despite a growing interest in the default network (DN), its composition and function are not fully known. Here we examined whether the DN, as a whole, is specifically active during a task involving judgments about the self, or whether this engagement extends to judgments about a close other. We also aimed to provide converging evidence of DN involvement from across-task functional connectivity, and resting-state functional connectivity analyses, to provide a more comprehensive delineation of this network. Using functional MRI we measured brain activity in young adults during tasks and rest, and utilized a multivariate method to assess task-related changes as well as functional connectivity. An overlapping set of regions showed increased activity for judgments about the self, and about a close other, and strong functional connectivity with the posterior cingulate, a critical node of the DN. These areas included ventromedial prefrontal cortex, posterior parietal cortex, and medial temporal regions, all thought to be part of the DN. Several additional regions, such as the left inferior frontal gyrus and bilateral caudate, also showed the same pattern of activity and connectivity. These results provide evidence that the default network, as an integrated whole, supports internally oriented cognition involving information that is personally relevant, but not limited specifically to the self. They also suggest that the DN may be somewhat more extensive than currently thought.

Keywords

functional MRI; brain; resting state networks; posterior cingulate cortex; self reference

1. Introduction

The default network (DN) is a topic of much research in recent years (Buckner, Andrews-Hanna, & Schacter, 2008; Greicius, Krasnow, Reiss, & Menon, 2003; Gusnard, Akbudak, Shulman, & Raichle, 2001; Raichle et al., 2001; Shulman et al., 1997). This network of brain areas is active when one is engaged in internally-driven thought and decreases when

there is a switch into a condition in which an external task-based focus is required (Gusnard et al., 2001; Raichle et al., 2001; Shulman et al., 1997). Despite growing literature, the composition of the network (which brain areas participate in it) and its functional connectivity (how these areas interact) are still not fully known. Currently, a set of regions has been reported in several studies (Buckner et al., 2008; Fox et al., 2005; Toro, Fox, & Paus, 2008) that is generally considered to represent the nodes of the DN: these are the superior frontal cortex, medial prefrontal cortex (including ventromedial prefrontal cortex (VMPFC) and more dorsal regions), inferior temporal cortex, lateral parietal cortex, posterior cingulate/retrosplenial cortex, and the hippocampal formation. Some studies (e.g., Fransson & Marrelec, 2008; Grady et al., 2010; Greicius et al., 2003; Greicius, Supekar, Menon, & Dougherty, 2009) have shown evidence of functional connectivity (FC) among these putative DN regions, mostly concentrating on major nodes, such as the posterior cingulate cortex (PCC). The DN may reflect a fundamental organizational property of the brain, as it develops early in childhood (Fair et al., 2008; Fransson et al., 2007), is preserved during sleep and anesthesia (Boly et al., 2008), and can be identified in chimpanzees (Rilling et al., 2007). In addition, some progress has been made in outlining DN structure through white matter tractography (Greicius et al., 2009), and default mode activity has been successfully simulated using information on structural connections from the non-human primate literature (Ghosh, Rho, McIntosh, Kotter, & Jirsa, 2008). Thus, despite some discrepancy in the reported nodes of the network, there is growing evidence that the DN consists of a group of anatomically and functionally connected regions that together may subserve a fundamental cognitive state.

Exactly what this cognitive state might be is still unclear. However, current evidence (Buckner et al., 2008; Buckner & Carroll, 2007; Gusnard et al., 2001; Johnson et al., 2002; Mason et al., 2007; Uddin, Iacoboni, Lange, & Keenan, 2007; Weissman, Roberts, Visscher, & Woldorff, 2006) indicates a role for self-referential processing, which can be engaged during a variety of cognitive tasks, including autobiographical memory retrieval, thinking about the future, and judgments about how well descriptions, such as “honest”, apply to one’s self. Studies exploring the neuronal correlates of the self (Fossati et al., 2003; Gusnard et al., 2001; Johnson et al., 2002; Kelley et al., 2002; Northoff & Bermpohl, 2004; Uddin et al., 2007) indicate that at least some areas currently believed to be part of the DN, primarily medial prefrontal cortex, exhibit increased activity during tasks requiring self-referential processing. These studies suggest that the DN supports internally generated processes that depend on, or are related to, representations of the self. However there are no studies to date showing that the DN, as an integrated whole, supports self-referential processing specifically.

The goal of our study was to address this question of whether the DN is involved in self referential processing, and to do this by both activating and deactivating the network during tasks, and by assessing its functional connectivity during these tasks and during rest. Most studies have attempted to derive the DN either through analyses of the resting state or task-related modulations (Buckner et al., 2008; Damoiseaux et al., 2006; Fox et al., 2005; Greicius et al., 2003; Mason et al., 2007; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Raichle et al., 2001; Shulman et al., 1997; Toro et al., 2008), but not both. We aimed to provide a more comprehensive assessment of the role of the DN in self related

processing and also of the composition of the DN by combining, within one study, activating and deactivating conditions, in addition to rest. One previous study (Harrison et al., 2008) used a similar approach, but utilized quite different and complex tasks for activating and deactivating the DN. We sought to constrain the processing engaged by our participants by requiring them to carry out a relatively simple self-reference task, i.e., judging whether trait descriptors characterized themselves. In addition, some have suggested that making decisions about a close other is thought to involve self-related cognitive processing (Ames, Jenkins, Banaji, & Mitchell, 2008; Buckner & Carroll, 2007; Kelley et al., 2002) and is reported by some to activate the same brain regions that are active for self-reference, including some DN regions (Ames et al., 2008; Ochsner et al., 2005). However, making judgments about another person, even if someone close to you, undoubtedly involves other processes in addition to any thoughts about the self that might occur. So examining the utilization of the DN in both self and other judgments could be a way of determining if this network supports self-reference specifically, or a wider range of personally relevant information. Therefore, we also included a task involving judgments about a close other, to assess whether the DN is engaged to a greater degree in processing information about the self, which would suggest a role in self reference per se, or equally engaged for self and close other, which would indicate a broader role.

For comparison to the internal tasks, we used two externally-driven tasks that would be expected to reduce activity in the DN (a sensorimotor control task and a vowel detection task). For these tasks we also used trait descriptors to ensure similar input and output characteristics, varying only the specific task demands. Our analysis also differed in an important way from previous studies because we opted not to specify *a priori* the brain areas that make up the DN, as other studies have done (e.g., Harrison et al., 2008). Rather than restricting the analysis to only a pre-selected set of regions, we used an approach that examined activity across the entire brain, so that a common set of regions across task and rest conditions could be identified, in an attempt to be inclusive rather than exclusive. We were then able to compare this set of regions to those of the putative DN in the literature. Data from a separate resting-state run also were obtained. The analysis consisted of contrasting task to baseline, as well as FC analyses of both task and resting state runs, to provide converging evidence regarding the areas involved in the DN. Moreover, we used a multivariate analysis combined with resampling statistics, an approach more sensitive and statistically powerful than the conventional univariate GLM approach to identifying task-related activations or deactivations (Fletcher et al., 1996; Lukic, Wernick, & Strother, 2002; McIntosh & Lobaugh, 2004; Nichols & Holmes, 2002). We expected to find a set of brain regions, consistent with the putative DN, to exhibit the highest level of activity during the self-relevant condition, less activity during the other condition and resting baseline, and the lowest activity during the external conditions. In addition, using a commonly accepted node of the DN, the posterior cingulate as a seed, we expected to find strong functional connectivity among DN regions across the task conditions, as well as during the resting-state run. This would provide converging evidence that the set of brain regions active when individuals perform relatively simple tasks that require them to process information relevant to themselves is the same set of regions that are functionally inter-connected and known as the DN. In addition, the overlap of regions with task modulations, functional connectivity

during the tasks and functional connectivity at rest would contribute to our knowledge of the composition of the DN.

2. Methods

2.1. Participants

Twenty healthy right-handed subjects (age $M=23.7$ years, $SD=3$; 10 males) participated in this study after providing informed consent. The ethics committee of Baycrest Centre approved this experiment.

2.2. Tasks

The eight task-runs were composed of 17 blocks of 20 seconds each, alternating between task and a resting baseline. Each task block contained five trials of the same task type. Trials included a fixation screen shown for one second, followed by a task screen shown for three seconds. The task screen included a personality-trait word, a cue word (representing the task) and two response options. In the pre-scan briefing, we instructed subjects that rapid responses are not required, but to respond within the three-second time frame. We selected 320 personality-trait words from a widely-used source (Anderson, 1968). Word order within the session was randomized, and no word was repeated.

We used four task types: self-reference, other-reference, vowel identification, and motor. In the Self task (cue: “You?”) subjects needed to decide whether the word represents them or not, in the Other task (“Other?”) subjects needed to decide whether the word represents a person they know well, and in the Vowel task (“Vowel?”) subjects needed to identify whether the third letter from the end of the word was a vowel. The possible answers for these three tasks were “yes” or “no”. In the Motor task (“Button:”) subjects needed to press button 1 or 2, depending on a number shown on the screen. The responses, and the timing, were recorded.

2.3. Image acquisition and Preprocessing

We used a Siemens Trio 3T scanner. Anatomical scans were acquired with a 3D MP-RAGE sequence ($TR=2$ sec, $TE=2.63$ msec, $FOV=25.6$ cm², 256×256 matrix, 160 slices of 1 mm thickness). Functional runs were acquired with an EPI sequence (170 volumes, $TR=2$ sec, $TE=30$ msec, flip angle = 70° , $FOV=20$ cm², 64×64 matrix, 30 slices of 5 mm thickness, no gap). Pulse and respiration were measured during scanning.

The scanning session included a high-resolution structural scan, followed by 10 functional runs, each lasting 5:40 minutes. The first and last runs were resting-state runs, where subjects were instructed to lie still with their eyes closed, relax, and clear their minds, but to not avoid any thoughts that may spontaneously arise. Following scanning, subjects were asked if they fell asleep during the resting runs.

Preprocessing was performed with AFNI (Cox, 1996) and consisted of physiological motion correction (Glover, Li, & Ress, 2000), slice-timing correction for the resting run, rigid-body motion correction, concatenation of the 8 task runs, spatial normalization to the MNI

template (TT_avg152T1, resampling our data to $2 \times 2 \times 2$ mm), and smoothing (full-width half-maximum, 6 mm).

2.4. Data analysis

Image analysis was performed with partial least squares, or PLS (McIntosh, Bookstein, Haxby, & Grady, 1996; McIntosh & Lobaugh, 2004), a multivariate analysis approach that robustly identifies spatiotemporal patterns related to varying tasks (task-PLS) or correlated to neuronal activity (seed-PLS). Because the decomposition of the data matrix is done in a single analytic step, no correction for multiple comparisons is required for this approach. PLS performs block-based signal normalization and then uses singular value decomposition to extract patterns of activity that characterize the covariance between activity in all voxels and the experimental conditions or seed activity. In task-PLS each spatial pattern, or latent variable (LV), contains a spatial activity pattern depicting the brain regions that, as a whole, show the strongest relation to (e.g. are covariant with) the task contrast identified by the LV. In seed-PLS the signal in a reference region is correlated with activity in all other brain voxels to assess the seed's functional connectivity (McIntosh, 1999). In a seed analysis the LVs indicate the patterns of correlation, or connectivity, that characterize each condition.

In a PLS analysis, each brain voxel has a weight, known as a salience, which is proportional to the covariance of activity with the task contrast on each LV. The significance for each LV as a whole was determined by using a permutation test (McIntosh et al., 1996), using 750–1000 permutations. In addition to the permutation test, a second and independent step was to determine the reliability of the saliences for the brain voxels characterizing each pattern identified by the LVs. To do this, all saliences were submitted to a bootstrap estimation (500 bootstraps) of the standard errors (SE, Efron, 1981). Reliability for each voxel was determined from the ratio of salience value to the SE for that voxel (bootstrap ratio, or BSR), and clusters of activity were identified using a BSR of ≥ 3.3 ($p < 0.001$), a cluster size of 80 voxels (0.64 ml), and a minimum distance between peaks of 1 cm. The local maximum for each cluster was defined as the voxel with a salience/SE ratio higher than any other voxel in a 2-cm cube centered on that voxel. Locations of these maxima are reported as coordinates in MNI space. Anatomical labels were assigned using the Eickhoff Anatomy Toolbox (Eickhoff et al., 2005) and an anatomy atlas (Mai, Paxinos, & Voss, 2007). Finally, to obtain summary measures of each participant's expression of each LV pattern, we calculated 'brain scores' by multiplying each voxel's salience by the BOLD signal in the voxel, and summing over all brain voxels for each participant. These brain scores were then mean-centered and confidence intervals (95%) for the mean brain scores in each condition were calculated from the bootstrap. Differences in activity between conditions were determined via a lack of overlap in these confidence intervals.

The task analysis was followed by two seed-PLS analyses to investigate whole-brain functional connectivity of the DN. We used seed-PLS (McIntosh, 1999) to calculate correlations of activity with each brain voxel and a PCC seed ($-2, -50, 28$, a peak coordinate identified in the contrast task-PLS). The seed analysis of the task data involved extracting the mean signal from the seed voxel across task conditions and baseline, and correlating this with the signal in all other brain voxels, across participants. The seed analysis of the resting

data (only the first resting run was used here) involved a similar extraction after a temporal resampling of the time series by averaging each consecutive 5 volumes, to produce 30 volumes of TR="10" sec each. This averaging produced an effective low-pass filter of 0.1 Hz and reduced temporal noise. Since PLS calculates covariance across subjects and does not perform time course correlations, there was no need to apply a band pass filter to reduce the bias that is introduced by respiratory and cardiac fluctuations into this type of calculation. Nevertheless, we did apply physiological motion correction and the abovementioned temporal resampling. Due to extensive head motion, we did not use resting data from two individuals. To provide a measure of how strongly seed activity covaried with the pattern of activity seen on each LV, correlations between brain scores and seed activity were computed for each group. Reliability of these correlations (confidence intervals of 95%) was calculated from the bootstrap procedure.

To determine the brain areas showing functional connectivity during both the task conditions and rest, we created a conjunction map by multiplying the voxel BSR maps of the two connectivity analyses. In addition, a second conjunction map comparing regions with common functional connectivity and task-related activity changes was calculated (i.e., the overlap between the task-PLS and the seed-PLS analyses). Finally, we determined if the regions comprising the DN reported in two previous papers (Fox et al., 2005; Toro et al., 2008) were included within our clusters.

3. Results

3.1. Behavioral measures

The response times of the participants on the four tasks are shown in Figure 1. A repeated measures ANOVA revealed a main effect of task, $F(3,54) = 113.5$, $p < 0.001$. Pairwise post-hoc comparisons found significant differences in response times across all tasks ($p < 0.05$, Bonferroni corrected for multiple comparisons). Although participants were instructed to avoid rapid responses, the response time differences indicate differences in the amount of time needed to complete the tasks in the various conditions.

3.2. Task-Related Brain Activity

To explore activity changes across the tasks, we first used PLS in the typical manner, which is to carry out a data driven analysis across the four task conditions and baseline without pre-specified contrasts so that the result reflects the patterns of activity that account for the most covariance in the data. This analysis resulted in a significant LV that distinguished the internal from the external tasks ($p = 0.001$, explaining 23% of the covariance, Figure 2a). Using this approach, we did not find that activity was higher for the Self task relative to the Other task; indeed, activity in these two tasks did not differ, but both of them were reliably different from the Vowel and Motor tasks (as indicated by the non-overlapping confidence intervals seen in Figure 2a), with activity for the resting baseline condition falling in between. To confirm this pattern, we used a variant of PLS, called non-rotated PLS (McIntosh & Lobaugh, 2004), which allowed us to enter a pre-specified contrast (Figure 2b) that directly tested for greater activity in both the Self and Other conditions, intermediate activity for resting baseline (i.e., activity equivalent to the mean over all conditions), and

lowest activity in the Motor and Vowel tasks. This analysis identified essentially the same set of brain regions ($p=0.001$) that was revealed by the data-driven analysis. We report here the results from the analysis using the contrast seen in Figure 2b.

Increased activity in the Self and Other tasks, relative to the Motor and Vowel tasks, was found in regions thought to be part of the DN, such as VMPFC, posterior cingulate cortex, anterior cingulate cortex, medial cerebellum, and the left angular gyrus (Figure 2c). Increased activity also was seen in other areas, including a large cluster in the left hemisphere that extended into the inferior frontal and precentral gyri, caudate, and hippocampus. The opposite activity pattern (i.e. more activity in the Motor and Vowel tasks) was found in areas such as bilateral superior frontal gyri, middle occipital gyrus and parietal regions bilaterally. The full list of regions is reported in Table 1.

A potential confound that might influence the pattern of brain activity related to the tasks is the fact that the response times differed across the conditions. It is unlikely that the pattern of brain activity that distinguished the Self and Other tasks from the Motor and Vowel tasks was due entirely to differences in response time given that brain scores in the Vowel condition were maximally distinguished from those in Self and Other (unconstrained analysis, Figure 2a), and the fastest RTs were in the Motor condition (Figure 1). However, to rule out the possibility of an influence of RT on the pattern of task activity seen in Figure 2c, correlations between RTs in each task condition and brain activity were examined with PLS (using the same approach as for seed-PLS described in Methods). A single significant pattern of brain-behavior correlations was found ($p < 0.05$, explaining 43% of the covariance see Supplementary Figure 1) which characterized all task conditions equally. In addition, the regions associated with faster or slower RTs were much less extensive and largely different from those seen in Figure 2. Therefore, the pattern of activity that differentiated the Self and Other tasks from the Motor and Vowel conditions reflected differences in task demands and not differences in response times.

3.3. Functional connectivity (FC) analyses

The activation analysis identified a set of regions consistent with the DN, as well as additional areas. Some of these areas may have been recruited due to the task demands, in addition to the DN regions, and may or may not be functionally connected to the DN as a whole. To explore how these task-related regions corresponded to the DN, as defined by functional connectivity, we carried out two whole-brain FC analyses for a seed located in the PCC (a prominent node in the DN), using the PCC peak identified in the task analysis (see Table 1). One analysis was performed on the resting-state data, to identify the network in rest, and one on the task data, to identify the network as it coherently modulates its activity across different cognitive states.

The connectivity analysis of the resting state data revealed a significant pattern of regions functionally connected with the PCC seed ($p<0.001$, 56.9% of the covariance). The areas that were found to be functionally connected to the PCC (Figure 3a) included all putative DN regions, including VMPFC, inferior temporal regions, the angular gyri, superior frontal cortex, medial cerebellum, and medial temporal cortex. In addition, other areas, not commonly identified as DN nodes, showed functional connectivity with the PCC, such as

bilateral inferior frontal gyrus and precentral gyrus, insula, thalamus, and caudate/putamen. The full list can be found in Supplementary Table 1.

A similar set of regions was found to be functionally connected with the PCC seed in the connectivity analysis of the tasks ($p < 0.001$, 68.6% of covariance). Again, many of these regions are part of the current conception of the DN, such as VMPFC, angular gyrus, right superior frontal gyrus, and left hippocampus (Figure 3b). Additional areas also were functionally connected to the PCC during the tasks, such as bilateral middle frontal areas, inferior frontal gyrus, caudate/putamen, and sensorimotor regions. The full list of regions is provided in Supplementary table 2.

3.4. Conjunction between resting state and task FC patterns

The two functional connectivity analyses appeared to be quite similar, with many regions showing connectivity with the PCC during the tasks as well as during the resting run. To highlight the commonalities across the two FC analyses, we created a conjunction map of the spatial overlap between these two analyses (Figure 3c). This conjunction map highlighted regions exhibiting highly reliable positive correlations in both resting-state and across-task connectivity analyses ($p < 10^{-8}$). Most of the regions corresponding to the DN were seen in the conjunction map, i.e., bilateral superior frontal gyrus, angular gyrus, ventromedial prefrontal cortex, hippocampus and other areas of medial temporal cortex, and medial cerebellum. In addition, the large cluster containing the PCC seed region extended down into the retrosplenial area and up into the precuneus, a region that is sometimes considered to be part of the DN (Buckner et al., 2008; Spreng, Mar, & Kim, 2009). The conjunction map also showed other areas, not commonly identified as part of the DN, including bilateral sensorimotor regions, lateral cerebellum, middle frontal gyrus, and putamen (see Table 2 for a full list of regions). Some peaks that were not found to be common across the two analyses were areas in right inferior frontal gyrus and left precentral gyrus (seen in the across-task FC analysis) and an area of left inferior frontal gyrus (seen in the resting-state FC analysis).

We compared the regions from the conjunction map to the peak coordinates reported in two earlier papers (Fox et al., 2005; Toro et al., 2008) to determine if these previously reported areas were located within our clusters. All of the “task-negative” loci reported by Fox et al were in close proximity ($< 2\text{cm}$) to our peaks. Eight out of the 12 “cingulo-parietal network” loci from Toro et al were in close proximity to peaks in the conjunction analysis (the exceptions were left and right parahippocampus, nucleus accumbens, and right inferior temporal cortex). In short, the majority of DN regions, as identified by these two papers, were also found to belong to the DN as we identified it in our functional connectivity analyses.

Lastly, we compared the activation analysis results (the task-PLS results seen in Figure 2c) to the results of the FC analyses (conjunction map, Figure 3c), to assess how closely these different approaches to identifying the DN coincide. We created a new overlap map using the positive BSR values of the task-PLS map (i.e., only those voxels with more activity for the Self and Other relative to the external tasks) and the conjunction map of the two connectivity analyses (Figure 4). This map coded each voxel according to which analysis

identified it (only task activation, only FC, both approaches). In general, there was considerable overlap between the results of the task and FC analyses, and the regions identified by all three are summarized in Table 3. Both task and FC analyses identified the majority of regions currently thought to comprise the DN, as well as a number of regions currently not included in the DN, such as the caudate nuclei and putamen, lateral cerebellum and left inferior frontal areas. In addition, the task analysis identified more extensive regions in left prefrontal cortex and basal ganglia bilaterally, whereas the connectivity analyses revealed more extensive medial and lateral parietal areas.

4. Discussion

In the current study we investigated whether self reference would activate the DN as a whole, and if these regions would overlap with the DN as defined using functional connectivity measures in both the resting-state and the task conditions. We found a highly overlapping set of regions with more activity during the Self task relative to two externally-driven tasks and strong functional connectivity with the PCC that were very similar to models of the DN reported by others. We also identified some additional areas not typically considered to be part of this network, which may have been identified due to the comprehensive multivariate approach that we took to characterizing the DN across multiple analyses. However, this same pattern of activation and functional connectivity also was seen during the Other task. Therefore, there are three main findings from this study: 1) increased activity in the DN supports self reference, but is not specific just to judgments about the self, suggesting a broader role in processing multiple types of information that might form a social context of which the self is a part; 2) these activated regions are functionally interconnected, suggesting that the DN as a whole, integrated network supports thought about ourselves and others that are close to us; and 3) the DN may encompass more regions than are currently thought to be part of this network. In particular, those regions that were identified in both the task and connectivity analyses (see Table 3) may need to be considered for inclusion in the DN.

We based our experimental approach on the idea that if the DN, as an integrated whole, supports a particular cognitive process, then the best way to assess its function is to combine task-related DN deactivation, task-related DN activation, and functional connectivity, all of which have been used in isolation in previous studies. Our results supported the use of this approach, since our across-tasks activation analysis identified areas thought to be part of the DN, and that were functionally connected to the PCC. We found equivalent increases of DN activity for both the Self and Other conditions, and strong functional connectivity among DN regions in both conditions, consistent with other reports of similar activation for judgments of self and close others (Ames et al., 2008; Ochsner et al., 2005). This result indicates that engagement of the DN is not limited to self reference *per se*, but plays a broader role. We have reported that the DN was engaged during theory of mind, as well as memory and self-relevant future thought (Spreng & Grady, 2010), although the past and future self conditions also activated some DN regions more than did theory of mind. The results of this previous study, taken together with the current results, suggest that this network is involved in processing self-relevant information, but does not appear to be exclusive to it. Thus, although the results of this study are consistent with the idea that the

DN facilitates the projection of the self across time and space (Buckner & Carroll, 2007), our work would suggest that the DN also participates in processing information that may be relevant to the self but extends beyond the self to encompass information about other people. It is probably safe to say that the precise role of the DN remains elusive, although our results can perhaps rule out a narrow interpretation of its function. One reason that it has proven difficult to precisely define the cognitive function of the DN is that it is primarily active during internally-oriented cognition, which, because it is less constrained, can encompass numerous domains (Northoff & Bermpohl, 2004) and by its very nature is likely to be fluid. A strength of our approach is that each analysis drew upon a different aspect of our data (activation, connectivity, task, rest), yet all our analyses identified similar brain regions. This converging approach provided evidence in line with previous studies showing that self reference is associated with activity in nodes of the DN, such as medial PFC and posterior cingulate (Fossati et al., 2003; Gusnard et al., 2001; Johnson et al., 2002; Kelley et al., 2002; Northoff & Bermpohl, 2004; Uddin et al., 2007), but went a step beyond these earlier data to show that the regions involved in processing personally relevant information are consistent with a functionally connected network, that network being the DN. In addition, we were able to show that increased activity in DN regions during the Self and Other tasks was not related to the slower response times in these tasks, but to the type of processing engaged during the tasks.

Despite the high degree of overlap between the areas that were active during the Self and Other tasks and the connectivity of the PCC, there were differences between the analyses. These differences could be due to several factors. For example, the DN is likely not a spatially rigid system, but may be modulated with brain state. That is, internally-driven task demands may call upon the DN in general, but may influence activity in some DN regions either upward or downward as the task is being performed (see also, Spreng & Grady, 2010). This could explain why the right angular gyrus was functionally connected to the PCC, as part of the DN, but not activated for the Self and Other tasks. The tasks also may require the recruitment of additional processes, not mediated by the DN. The more extensive recruitment of left inferior prefrontal cortex seen during the Self and Other tasks, but not in the FC analyses (see Figure 4, green areas), may be related to the engagement of cognitive control (Dove, Brett, Cusack, & Owen, 2006; Seeley et al., 2007) or autobiographical memory processes (Addis, McIntosh, Moscovitch, Crawley, & McAndrews, 2004; Burianova & Grady, 2007; Maguire & Frith, 2003) during these tasks. This would be consistent with reports of predominantly left hemisphere activation during autobiographical memory tasks. In addition, the few differences noted between the two FC analyses may be due to fluctuations in network connectivity resulting from carrying out a task of any kind, vs. a less constrained cognitive state. Critically, the similarities across the three different analyses were more striking than the differences.

One strength of our study is that we used relatively simple tasks and tightly controlled the stimuli used in the tasks in an attempt to limit differences across conditions to task demands. We also used a sensitive multivariate analysis approach that allowed us to assess patterns of covariance across the task conditions as well as those related to activity in a specific brain region, resulting in a set of regions with a common covariance pattern regardless of the particular analysis used. With this converging approach we identified the regions currently

thought to comprise the DN, as well as a few more. A number of these additional regions were found to be common across all three analyses, suggesting that the appearance of these areas was not due to a specific type of analysis. The regions found across all three analyses were several left hemisphere frontal regions (in the inferior, middle and superior frontal gyri), right thalamus, and caudate/putamen, lateral cerebellum, and anterior middle temporal gyrus bilaterally. Some of these regions have been reported in prior DN studies (e.g., Fransson, 2006; Zuo et al., 2010) but are typically not included as important nodes of the DN. We found all of them to be related to task as well as functionally connected during both tasks and rest, so the entire set of regions seen here may represent an upper bound of areas that potentially form the network. However, it is likely that the components of the DN that will be identified in any particular study depend to some extent on the method used to identify them, including the algorithm used (e.g., ICA or PLS), whether or not one uses a template, whether the experiment assesses task deactivation or connectivity, and choice of region to use as the seed. Thus, it still is not clear if the DN is composed of a core element that is always functionally connected and more variable subcomponents whose involvement in the network is transient and task-dependent, as suggested by some (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Buckner et al., 2008), or if the DN itself is more extensive than previously thought. Regardless, until more knowledge of the DN and its function accumulate, it may be useful to consider the network more inclusively. Applying a mask, using a template, or otherwise restricting assessment of the DN to an *a priori* set of regions assumes that the structure of the network is completely known, and leaves no room for further exploration. Our results suggest that there is a need to cast a wider net when attempting to characterize and understand brain networks.

In conclusion, our study has provided evidence that the DN as an integrated network subserves internally-oriented cognition that includes, but is not strictly limited to, self reference. Our results also suggest that understanding the composition of the DN and its function will be well served by considering it more broadly and using a variety of analytic approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Mean response times for the four tasks. The bars are standard deviation measures for each task.

Figure 2.

Task-related changes in brain activity. a) Whole-brain activity pattern found in the unconstrained, data-driven analysis. Plotted are the mean-centered brain scores for each condition, so that 0 represents the overall mean (error bars are the 95% confidence intervals). b) The contrast used for the second analysis directly testing for Self/Other > baseline > Motor/Vowel. c) The brain pattern differentiating the internal and external tasks (bootstrap ratios or BSRs), resulting from the contrast analysis shown in b. Red BSRs = increased activity during Self and Other tasks; Blue BSRs = increased activity during Motor and Vowel tasks. Axial level relative to the AC-PC line is shown for each image. The color bar shows the range of BSR values (BSR > 3.3, equivalent to $p < 0.001$).

Figure 3.

PCC seed FC analyses, and the conjunction analysis, showing commonalities between them.

a) The resting-state FC analysis, aimed at identifying brain regions that modulate together with the PCC at rest (BSR threshold >6 , equivalent to $p < 0.0001$). b) The across-tasks FC

analysis, aimed at identifying brain regions that modulate together with the PCC during the tasks (BSR threshold >4 , equivalent to $p < 0.0001$; individual condition correlations between brain scores and PCC activity: baseline=0.75, Self=0.62, Other=0.6, Motor=0.52, Vowel=0.63). c) The conjunction map, showing common regions shared by both connectivity analyses ($p < 10^{-8}$).

Figure 4. Overlap of task-related activation and FC maps. Green= activation (from the task-PLS), Blue= FC (from both seed-PLS analyses), Red= areas identified in all three analyses.

Table 1

Brain areas showing task-related activity changes

Region	Hem	X(mm)	Y(mm)	Z(mm)	BSR
Self/Other > Motor/Vowel					
Superior frontal gyrus	L	-26	58	6	8.04
Ventromedial prefrontal cortex	L	-6	48	32	10.12
Anterior cingulate cortex	midline	-2	34	22	10.51
Inferior frontal gyrus (p. orbitalis)	R	42	28	-6	6.38
Inferior frontal gyrus (p. triangularis)	L	-48	20	18	9.29
Insula	L	-32	20	-12	11.11
Superior temporal gyrus	R	40	20	-26	5.82
Supplementary motor area	midline	2	12	56	9.23
Caudate nucleus	R	16	12	4	6.95
Middle temporal gyrus	R	60	8	-26	6.29
Precentral gyrus	L	-42	6	44	7.50
Caudate nucleus	L	-14	4	12	13.79
Middle temporal gyrus	L	-50	-12	-10	6.64
Middle temporal gyrus	L	-50	-40	2	7.38
Posterior cingulate cortex	midline	-2	-50	28	5.23
Cerebellum	R	4	-58	-46	7.96
Angular gyrus	L	-50	-62	30	4.19
Cerebellum	R	26	-72	-30	11.60
Cerebellum	L	-26	-78	-32	6.59
Calcarine gyrus	L	-16	-96	-4	5.78
Motor/Vowel > Self/Other					
Superior orbital gyrus	R	20	24	-14	-5.54
Superior frontal gyrus	L	-18	8	48	-5.46
Superior frontal gyrus	R	30	4	44	-4.79
Inferior frontal gyrus (p. opercularis)	R	48	0	18	-5.72
Middle cingulate cortex	R	8	-40	40	-8.46
Supramarginal gyrus	R	48	-40	38	-7.50

Region	Hem	X(mm)	Y(mm)	Z(mm)	BSR
Inferior parietal lobule	L	-32	-44	46	-6.42
Cerebellum	L	-12	-52	-52	-5.92
Inferior temporal gyrus	R	54	-56	-10	-7.48
Middle occipital gyrus	L	-22	-58	40	-7.23
Inferior temporal gyrus	L	-50	-60	-8	-5.83
Precuneus	R	16	-62	40	-8.77
Middle occipital gyrus	R	40	-72	22	-7.86
Superior occipital gyrus	R	32	-72	42	-9.07
Superior occipital gyrus	L	-22	-80	34	-8.71

MNI coordinates of cluster maxima showing the pattern of activity depicted in Figure 2b, clusters shown in Figure 2c. Positive BSRs (bootstrap ratios) = more activity for Self and Other. Negative BSRs = more activity for Motor and Vowel. BSR >3.3 is equivalent to $p < 0.001$. Hem = hemisphere; R = right; L = left.

Table 2

Brain areas identified by the conjunction analysis of the two functional connectivity analyses (rest and task).

Region	Hemisphere	X(mm)	Y(mm)	Z(mm)
DN regions				
Medial prefrontal cortex	R	12	55	31
VMPFC/ACC	R	7	53	3
Superior frontal gyrus	L	-18	47	35
Superior frontal gyrus	R	21	43	41
Hippocampus	R	37	-19	-16
Hippocampus	L	-27	-23	-13
Inferior temporal gyrus	R	63	-29	-16
Middle temporal gyrus	L	-61	-29	-1
PCC/retrosplenial/precuneus cluster ^I	midline	-2	-50	28
Angular gyrus	R	61	-57	33
Angular gyrus	L	-45	-62	35
Medial cerebellum	midline	1	-62	-46
Other areas				
Superior frontal gyrus	L	-16	64	9
Middle frontal gyrus	R	35	61	-7
Rectal gyrus	midline	1	51	-17
Inferior frontal gyrus (p. orbitalis)	L	-44	34	-18
Middle frontal gyrus	L	-29	23	34
Putamen	L	-27	6	2
Putamen	R	31	2	2
Middle temporal gyrus (anterior)	R	65	-8	-18
Middle temporal gyrus (anterior)	L	-55	-9	-18
Precentral gyrus - BA6	R	29	-15	66
Postcentral gyrus	R	46	-17	30
Middle cingulate cortex	midline	-3	-19	35
Postcentral gyrus	L	-43	-21	38
Paracentral lobule	L	-9	-31	70
Superior temporal gyrus	R	59	-39	21
Lateral cerebellum	R	42	-54	-29
Lateral cerebellum	L	-37	-63	-27
Superior parietal lobe	R	42	-67	48
Lateral cerebellum	R	27	-84	-29

ACC = anterior cingulate cortex; VMPFC = ventromedial prefrontal cortex.

DN regions are those generally accepted to be part of the network.

^IThis is the seed coordinate – The cluster around it covers a large area, including the PCC, retrosplenial, and precuneus, all considered DN regions.

Table 3

Brain areas identified by the conjunction of the two functional connectivity analyses and the task activation analysis

Region	Hemisphere
DN regions	
Angular gyrus	L
Hippocampus	L
Inferior temporal gyrus	L
Medial prefrontal cortex	midline
Medial cerebellum	midline
Posterior cingulate cortex	midline
Retrosplenial	midline
Superior frontal gyrus	R+L
Ventromedial prefrontal cortex/Other areas	midline
Caudate and putamen	R+L
Inferior frontal gyrus	L
Lateral cerebellum	R+L
Middle frontal gyrus	L
Middle temporal gyrus (anterior)	R+L
Superior frontal gyrus (frontal)	L
Thalamus	R

DN regions are those generally accepted to be part of the network.