Functional Parcellation of the Default Mode Network: A Large-Scale Meta-Analysis

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Acknowledgments:
We thank Alejandro de la Vega for sharing his analysis code and answering technical questions. We also thank Victoria Kelly and Christine Reice for their comments on an earlier draft of the manuscript. This work was supported in part by NIH grant R21-MH113917 (DVS).

Data and code availability:
All data are publicly available on Neurosynth database (http://neurosynth.org). In addition, all analysis code can be found on our lab GitHub (https://github.com/DVS-Lab/dmn-parcellation).

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Abstract

The default mode network (DMN) consists of several regions that selectively interact to support distinct domains of cognition. Of the various sites that partake in DMN function, the posterior cingulate cortex (PCC), temporal parietal junction (TPJ), and medial prefrontal cortex (MPFC) are frequently identified as key contributors. Yet, despite the accumulating knowledge surrounding the DMN's involvement across numerous cognitive measures, it remains unclear whether these subcomponents of the DMN make unique contributions to specific cognitive processes and health conditions. Here, we address this gap at two different levels of analysis. First, using the Neurosynth database and a Gaussian Naïve Bayes classifier, we quantified the association between PCC, TPJ, and MPFC activation and specific topics related to cognition and health (e.g., decision making and smoking). This analysis replicated prior observations that the PCC, TPJ, and mPFC collectively support multiple cognitive functions such as social, decision making, memory, and awareness. Second, to gain insight into the functional organization of each site, we parceled each region based on their coactivation patterns with the rest of the brain. This analysis indicated that each region could be further subdivided into discrete subregions, with some exhibiting functionally distinct involvement in certain topics. For example, the ventral part of left-TPJ was associated with emotion, whereas the posterior part was associated with priming. Taken together, our results help further break down regional DMN activity and how each subcomponent contributes to a wide range of cognitive processes and health conditions.

Introduction

The default mode network (DMN) has garnered increasing interest as recent brain imaging studies implicate it in a wide range of cognitive functions and disease processes (Shulman et al., 1997; Raichle et al., 2001; Garrity et al., 2007). The DMN consists of the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and left and right temporal-parietal junction (left- and right-TPJ) (Leech et al., 2011; Braga et al., 2013). These regions have been shown to preferentially activate when the brain is at rest, and decrease in activity when engaged in a goal-directed task (Raichle, 2015). Yet, it remains unclear how individual regions of DMN may differentially contribute to the various cognitive processes associated with DMN function.

DMN responses is primarily implicated in spontaneous thought processes that occur when humans are not actively engaged in a directed task, and is thus thought to be responsible for self-referential processing (Davey, Pujol, & Harrison, 2016) and mind-wandering (Brewer et al., 2011). However, task-based patterns of activation are also seen across DMN regions during autobiographical memory retrieval (Spreng & Grady, 2010), self-judgements (Buckner, Andrews-Hanna, & Schacter, 2008; Gusnard, Akbudak, Shulman, & Raichle, 2001), prospective thinking (Spreng & Grady, 2010), decision-making (Greene, Sommerville, Nystrom, Darley, & Cohen, 2001; Harrison et al., 2008), and social cognition (Mars et al., 2012a), indicating a possible indirect role of the same networked areas in these psychological processes (Harrison et al., 2008). In particular, MPFC has been implicated in self-referential processing with functional specialization observed within MPFC: ventral MPFC deactivates more when making self-referential judgments while dorsal MPFC activity increases (Gusnard et al., 2001). Moreover, there seems to be

ventral-dorsal subspecialization in MPFC, with ventral MPFC responsible for emotional processing and dorsal for cognitive function (Gusnard et al., 2001). Recent meta-analysis attempted to further delineate regional differences in MPFC's function, identifying anterior, middle, and posterior zones, responsible for episodic memory and social processing, cognitive control, and motor function, respectively (de la Vega, Chang, Banich, Wager, & Yarkoni, 2016). Importantly, these works also suggest there may be overlap in function and sub-specialization within MPFC regions (de la Vega et al., 2016), leaving room for further research into the more fine-grained aspects of MPFC's function.

Although these previous lines of investigation into DMN functional specialization have largely focused on MPFC, two other DMN regions – posterior cingulate cortex (PCC) and bilateral temporo-parietal junction (TPJ) – may also serve a wide range of functions. For example, the PCC is thought to play a key role in focused attention during task-based activities (Small et al., 2003; Castellanos et al., 2008) and continuous monitoring of internal and external stimuli at rest (Raichle et al., 2001). It has also been implicated in retrieval of episodic memory (Cabeza, Dolcos, Graham, & Nyberg, 2002; Greicius, Krasnow, Reiss, & Menon, 2003), emotional processing (Maddock, 1999), and self-referential processing (Northoff et al., 2006). Similarly, TPJ has been shown to play a role in self-referential processing (Davey et al., 2016); and is important for social cognition in conjunction with other DMN regions (PCC and MPFC; Laird et al., 2011; Mars et al., 2012a). Although less is known about potential functional subspecialization within the PCC and TPJ, these DMN regions may also show regional differences in cognitive processing similar to MPFC (Bzdok et al., 2013, 2015).

In addition to studies linking DMN to various cognitive processes, recent efforts have explored the role of DMN in studies of a range of health problems, including psychopathology and neurological diseases. A growing body of literature suggests that DMN dysfunction may underlie disease states including Alzheimer's disease, schizophrenia, ADHD, Parkinson's disease, depression and anxiety (Broyd et al., 2009). Decreased activity of DMN at rest and decreased task-induced deactivation of DMN has been observed in individuals with autism (Assaf et al., 2010; Padmanabhan et al., 2017), particularly in the MPFC (Kennedy & Courchesne, 2008; Kennedy, Redcay, & Courchesne, 2006). Patients with anxiety disorders show reduced deactivation of MPFC and increased deactivation of PCC (Broyd et al., 2009), while the component regions of DMN appear to change during major depressive episodes, with activity of thalamus and subgenual cingulate increasingly seen at rest (Greicius et al., 2007). Alzheimer's patients not only show altered DMN responses at rest, but different task-induced deactivation patterns during a working memory task (Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005) and regional activation differences within PCC (He et al., 2007). In schizophrenia, both resting state and task-based DMN response changes have been associated with positive disease symptoms (Bluhm et al., 2007; Broyd et al., 2009; Garrity et al., 2007). Of note, while the aforementioned disease states share the commonality of generally altered DMN function, specific findings from these studies also suggest that altered activity in different DMN nodes may be specific to different health conditions; for instance, with PCC specifically implicated in Alzheimer's and ADHD, and MPFC in schizophrenia and anxiety (Broyd et al., 2009). As specific nodes of the DMN appear to be responsible for specific

cognitive processes, it is plausible that specific nodes may also be associated with different disease states, although few studies have addressed this question.

To investigate how cognitive processes and health conditions are linked to activation within distinct subunits of the DMN, we utilized the Neurosynth database and identified core DMN regions based on prior work and anatomical landmarks. We also used tools and methods developed in prior work (Eickhoff et al., 2011; Ray et al., 2015), that have successfully characterized the functional substructure of the medial prefrontal cortex (de la Vega et al., 2016) and the lateral prefrontal cortex (de la Vega et al., 2017). Our application of these analytical methods to the DMN is important because it allows us to quantify how those DMN regions are functionally associated with cognitive processes and disease states—thus extending and complementing prior efforts to fractionate the DMN (Laird et al., 2009; Andrews-Hanna et al., 2010; Bzdok et al., 2013, 2015, 2016; Eickhoff, Laird, Fox, Bzdok, & Hensel, 2016; Margulies et al., 2009; Ray et al., 2015). Our primary analyses focus on two key questions. First, are different psychological functions and disease states preferentially associated with distinct nodes of the DMN? Second, are there functionally distinct subregions within individual DMN nodes?

Methods

Our analysis was based on version 0.6 of the Neurosynth dataset (i.e., articles up to July 2015), which contains activation data from more than 12,000 fMRI studies (Yarkoni et al., 2011).

DMN mask

First, to find regions that are functionally related but restricted to anatomical regions within the DMN, we created a DMN mask defined by the intersections of functional activation and anatomical masks (Fig. 1A; Poldrack et al., 2017). Specifically, we performed reverse-inference meta-analysis by searching the topic “DMN" in Neurosynth with false discovery rate at 0.01 to create a functional mask that specifically mapped term “DMN” to brain regions. We chose reverse inference because it can help estimate the relative specificity between brain activity and the DMN (Poldrack, 2006; Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). The resulting mask included 9,650 activations from 366 studies. Thus, the resulting functional mask identified voxels in studies where the term “DMN” was mentioned in their abstract given brain activation (seeded with a 6mm sphere). We next constrained the mask to anatomical regions that belong to DMN by using the Harvard-Oxford probabilistic atlas at $P > 0.25$ (Desikan et al., 2006), including medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), and left and right temporal parietal junction (left- and right-TPJ).

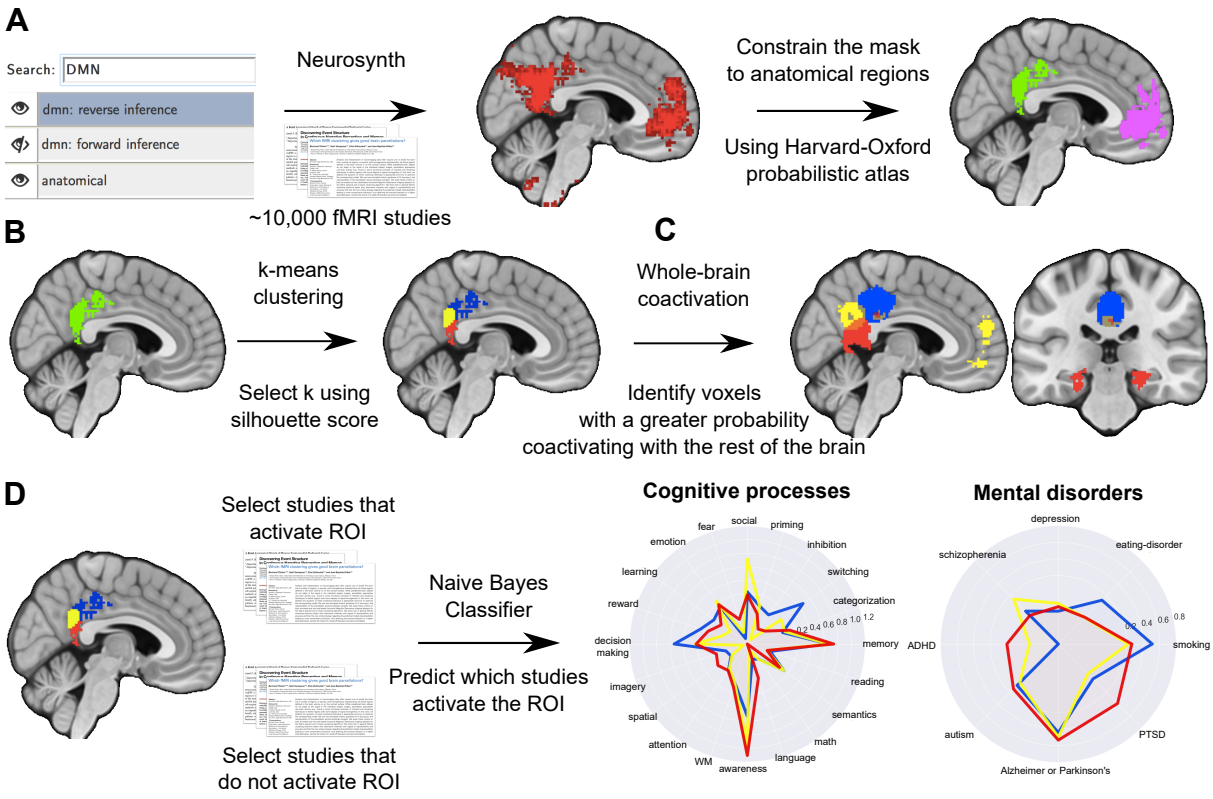

Fig 1. Overview of methods. *(A) We searched for the topic "DMN" in Neurosynth to create a functional mask, and then constrained the mask to 4 anatomical regions that belong to the DMN by using Harvard-Oxford probabilistic atlas. (B) We applied k-means clustering to determine functionally different subregions within each of the 4 regions. (C) We generated whole-brain coactivation profiles to reveal functional networks for different regions. (D) Functional profiles were generated to identify which cognitive processes or health conditions best predicted each region's (or subregion's) activity.*

Coactivation-based clustering

To determine more fine-grained functional differences within the four primary DMN regions, we applied a clustering method used by previous work (de la Vega et al., 2016) to cluster individual voxels inside each of the four regions based on their meta-analytic coactivation with voxels in the rest of the brain (Fig. 1B; Eickhoff et al., 2011). For each

region, we correlated the activation pattern of each voxel with the rest of the brain across studies. The resulting coactivation matrix was then passed through principal component analysis (PCA), where the dimensionality of the matrix was reduced to 100 components. Subsequently, we calculated Pearson correlation distance between every voxel with each whole-brain PCA component in each of the four DMN regions. We note that inclusion of a PCA preprocessing step helps to reduce the computational cost that would have been induced with whole-brain correlation matrix (de la Vega et al., 2016; de la Vega, Yarkoni, Wager, & Banich, 2017). Based on correlation coefficients, k-means clustering algorithm was used to group voxels into 2-9 clusters for each region separately (Thirion et al., 2014). To select the number of clusters, we computed silhouette coefficients to select the number of clusters for each region (Rousseeuw, 1987). Previous reports caution that issues may arise when identifying the appropriate number of clusters due to variations in goals and levels of analysis used across investigations (Poldrack & Yarkoni, 2016; Varoquaux & Thirion, 2014). Nevertheless, recent work has confirmed that the silhouette score can successfully assess cluster solutions (Pauli et al., 2016; de la Vega et al., 2016, 2017; Eickhoff, Thirion, Varoquaux, & Bzdok, 2015).

Coactivation profiles

We next analyzed the differences in whole-brain coactivation patterns between regions to reveal their functional networks (Fig. 1C, de la Vega et al., 2016). We contrasted the coactivation pattern of each region (e.g., MPFC) with the other three (e.g., PCC, left and right TPJ) to show differences between regions. Specifically, we performed a meta-analytic contrast to the studies that activated the region of interest (ROI) and studies that activated control regions (e.g., other regions within DMN), to identify the voxels in the rest

of the brain with a greater probability coactivating with ROI than other regions within DMN. For instance, purple voxels in Figure 2B indicate voxels that are active more frequently in studies in which MPFC is active than in studies in which other DMN regions are active. We then conducted a two-way chi-square test between two sets of studies and calculated *p* values to threshold the coactivation images using False Discovery Rate ($q<0.01$). The resulting images were binarized and visualized using the NiLearn Library in Python (Abraham et al., 2014).

Meta-analytic functional preference profiles

To map between functional states (e.g., cognitive processes, health conditions) and regions of the DMN, we used a set of 60 topics. These topics were generated from words that co-occur among fMRI study abstracts in the database (Poldrack et al., 2012a; de la Vega et al., 2016). Topics were derived from from Dirichlet allocation topic modeling (e.g., Blei, Ng & Jordan, 2003), which helped reduce the level of redundancy and ambiguity in term-based meta-analysis maps in Neurosynth (de la Vega et al., 2016). Topics that were irrelevant to either cognitive processes or health conditions were excluded from the generated topics (N=23), leaving 29 cognitive topics and 8 disorder-related topics.

We generated functional preference profiles by identifying which cognitive processes or health conditions best predicted each region's (or cluster's) activity across studies (Fig. 1D). We adopted the same procedure used in a previous study to select studies in Neurosynth that activated a given region (or cluster) and studies that did not (de la Vega et al., 2016). A study was defined as activating a given region if at least 5% of voxels in the region was activated in that study. Following the lead of Yarkoni et al (2011), we then trained a naive Bayesian classifier (de la Vega et al., 2016) to discriminate

between two sets of studies based on cognitive and disease-related topics for each region. Due to the redundancy and ambiguity in term-based meta-analytic maps (e.g., “memory” could refer to working memory or episodic memory), we trained models to predict whether studies activated the region, given the semantic representation of the latent conceptual structure underlying descriptive terms (de la Vega et al., 2016, 2017). These predictions could then be used to characterize the extent to which a study activated a region, given that the topics were mentioned in that study.

We next extracted the log-odds ratio (LOR) of a topic, defined as the log of the ratio between the probability of a given topic in active studies and the probability of the topic in inactive studies, for each region (or cluster) separately. A positive LOR value indicates that a topic is predictive of activation in a given region (or cluster). Based on LOR values, we identified 20 cognitive topics that loaded most strongly to whole DMN mask for further analysis. We applied a procedure used in previous study to determine the statistical significance of these associations (de la Vega et al., 2016). To do so, we performed a permutation test for each region-topic log odds ratio 1000 times. This resulted in a null distribution of LOR for each topic and each region. We calculated *p* values for each pairwise relationship between topics and regions and then adjusted the *p*-values using a False Discovery Rate at 0.01 to account for multiple comparisons within 20 selected cognitive topics and 8 disease-related topics, separately. We reported associations significant at the corrected $p < 0.05$ threshold. Finally, to determine whether certain topics showed greater preference for one region versus another, we conducted exploratory, post hoc comparisons by determining whether the 99.9% confidence intervals (CI) of the LOR of a specific topic for one region overlapped with the 99.9% CI of the same

topic for another region. We applied a similar procedure reported in previous studies (de la Vega et al., 2016), generated CIs using bootstrapping, sampling with replacement, and recalculating log-odds ratios for each cluster 1000 times.

Results

Coactivation and functional preference profiles for the DMN regions

We defined the DMN mask on the basis of functional mapping that mapped topic "DMN" to brain regions and constrained it to anatomical regions that belong to the DMN (Fig. 2A). The resulting anatomical mask contains 4 spatially dissociable regions: medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), left and right temporal parietal junction (left-TPJ and right-TPJ). Note that our TPJ region corresponded to what was labeled as "posterior-TPJ" in a previous study (Mars, et al., 2012a).

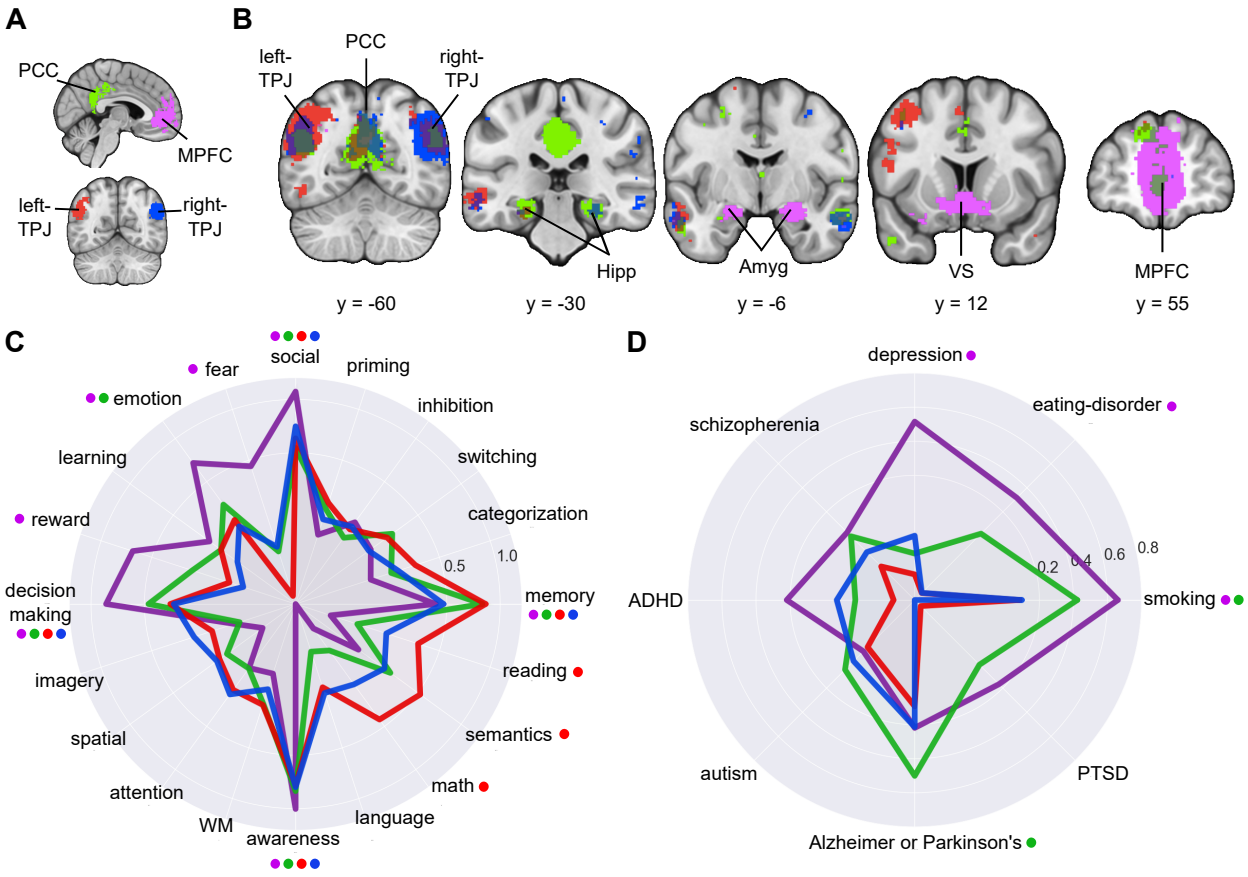

Fig 2. Meta-analytic coactivation and functional profiles for the DMN. *(A) Functionally defined regions within DMN: medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), left and right temporal parietal junction (left- and right-TPJ). (B) Coactivation profiles for 4 regions. Colored voxels indicate significantly greater coactivation with the region of same color (Fig. 2A) than control regions. Some regions were involved in overlapping functional networks whereas some were involved with distinct functional networks. Related subcortical structures are labeled as: Hipp, hippocampus; Amyg, amygdala; VS, ventral striatum. (C) Functional preference profiles of DMN. Functional profiles were generated by determining which cognitive topics best predicted each region's activity within DMN. All regions within DMN were primarily involved with social, decision-making, awareness, and memory. Distinct functions were also observed across MPFC, PCC and left-TPJ. LOR is used to measure strength of association, and color-coded dots corresponding to each region are used to indicate significance ($p < 0.05$, corrected) based on permutation test. (D) DMN and health conditions. Functional profiles related to health conditions were generated to determine whether regions within DMN were differentially recruited by psychological diseases.*

We next sought to characterize functional similarities and differences across regions of DMN. To do so, we adopted an approach used by previous work (de la Vega et al., 2016, 2017). To determine how regions of DMN coactivate with voxels across the brain, we identified voxels with a greater probability of coactivating with each region of interest (ROI) than with other regions within DMN. We found that regions within DMN interactively coactivated with each other. Specifically, PCC and MPFC strongly coactivates with each other, and both regions showed greater coactivation with bilateral-TPJ (Fig. 2B). This pattern suggests that DMN as a whole operates to support multiple cognitive functions. Additionally, we found that different regions were involved with overlapping functional networks. For example, PCC and bilateral-TPJ showed stronger coactivation with hippocampus, an important region for memory, suggesting that there are functional similarities between regions of DMN. Finally, we also found that some regions are involved with distinct functional networks. For instance, MPFC was more strongly coactivated with amygdala and ventral striatum, regions known for emotion processing and decision-making (Fig. 2B). Taken together, these coactivation patterns demonstrate that there are both functional similarities and differences within the DMN.

To further explore functional properties among DMN regions, a meta-analysis was used to select studies that activated a given ROI, and a naive Bayesian classifier was trained to predict which studies activated the region (de la Vega et al., 2016). We first describe functional preference profiles based on cognitive processes, followed by those related to health conditions. Cognitive predictors were limited to 20 psychological topics previously shown to be relevant to DMN function. We found that all regions of DMN were

primarily predicted by the topics “social”, “decision making”, “awareness”, and “memory” (Fig. 2C), consistent with previous evidence suggesting DMN involvement across these domains. Functional distinctions were also observed among DMN regions: activity in MPFC was predicted by fear, emotion, and reward; activity in PCC was predicted by emotion; and activity in left TPJ was predicted by math, semantics, and reading. Next, we entered 8 disorder-related topics as predictors to examine whether regions within DMN were differentially recruited by health conditions. We found that distinct disorders were predicted by MPFC or PCC: activity in MPFC was associated with smoking, eating disorder and depression, whereas activity in PCC was associated with smoking and Alzheimer’s/Parkinson’s disease (Fig. 2D). These results are consistent with observed coactivation patterns among regions of DMN, supporting the notion that there are functional similarities as well as differences among these four regions of the DMN. Our post hoc analysis suggested that none of the topics showed greater preference for one region over another within DMN (or any of the subregions in the results that follow). Note that we caution interpretation of these results because these comparisons were post hoc and exploratory (de la Vega et al., 2016).

Functional Distinctions Within DMN Subregions

We clustered individual voxels inside MPFC, bilateral-TPJ and PCC based on their meta-analytic coactivation with voxels in the rest of the brain to distinguish more fine-grained functional differences among subregions (Smith et al., 2009; Chang et al., 2013; de la Vega et al., 2016). We used the silhouette score to select optimal solutions for each region, and generated coactivation and functional preferences profiles for each subregion. We describe the results for four regions separately.

Within the MPFC, we identified two clusters based on silhouette score (Fig. 3A, left panel): a dorsal cluster (Fig. 3A right panel, orange) and a ventral cluster (Fig. 3A right panel, green). Our analysis did not reveal any cluster that coactivated more strongly with the rest of the brain. Both clusters in MPFC were associated with social, emotion, reward, decision-making, awareness, and memory; whereas only the ventral cluster was associated with fear (Fig. 3B). Additionally, both clusters in MPFC were associated with depression and smoking, but only the ventral cluster was associated with eating-disorders (Fig. 3C).

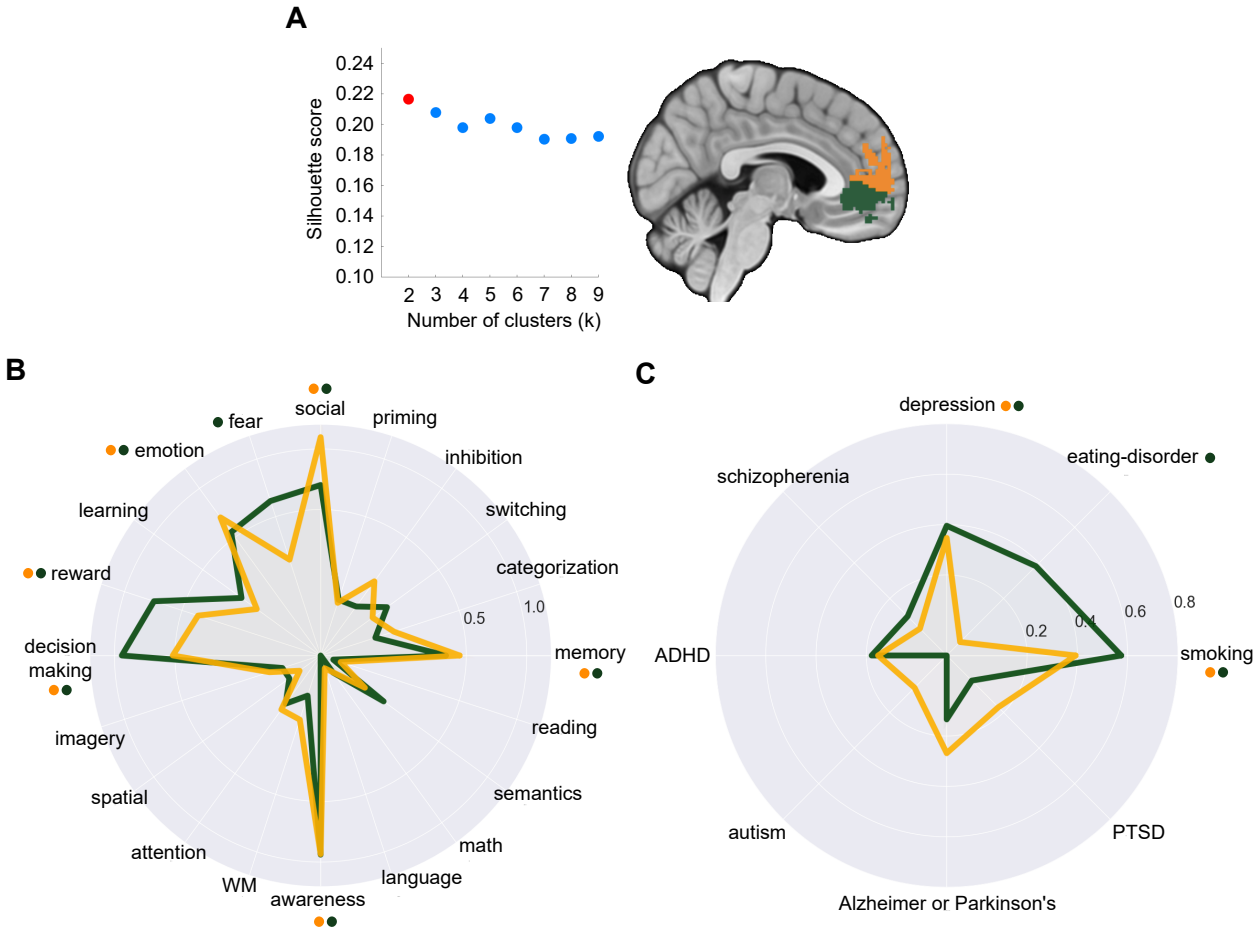

Fig 3. Coactivation-based clustering and functional preference profiles of MPFC. *(A) We identified two clusters within MPFC based on silhouette scoring: a dorsal cluster (orange) and a ventral cluster (green). (B) Functional preference profiles of MPFC. Both clusters in MPFC were predicted by social, emotion, reward, decision-making, awareness and memory, whereas the ventral cluster was predicted by fear. (C) MPFC and health conditions. Both clusters in MPFC were recruited by depression and smoking, but only the ventral cluster was associated with eating disorders.*

Our silhouette score analysis revealed that a three-cluster solution was optimal for the right-TPJ (Fig. 4A, left panel): a dorsal cluster (Fig. 4A, green), a ventral one (Fig. 4A, yellow) and a posterior cluster (Fig. 4A, purple). All three clusters were strongly coactivated with left-TPJ. The ventral cluster showed more coactivation with PCC. All clusters were predicted by social, memory, and awareness, while only the dorsal cluster was predicted by decision making (Fig. 4B). No subregions were more significantly associated with disorder-related topics (Fig. 4C).

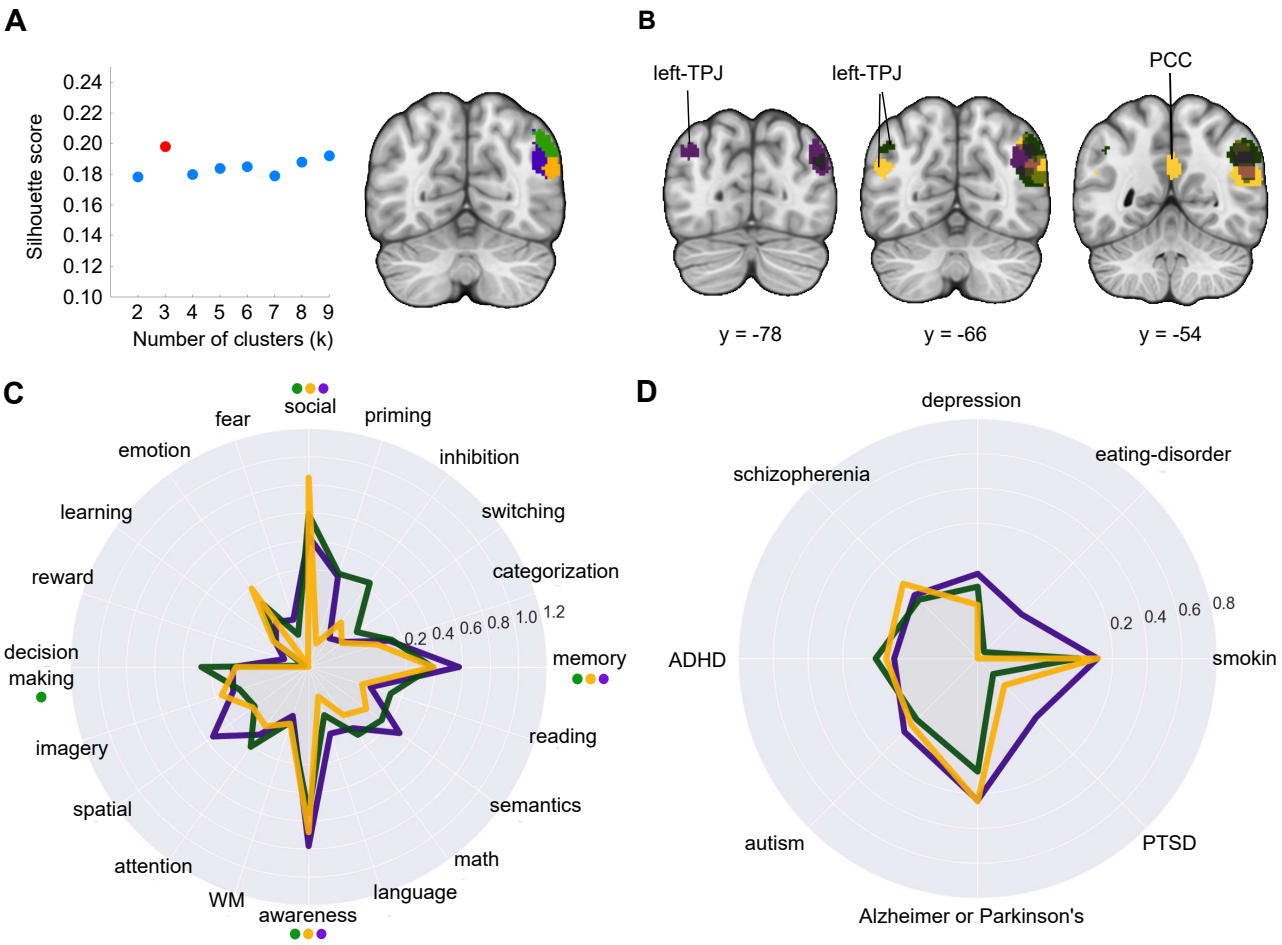

Fig 4. Coactivation-based clustering and functional preference profiles of right-TPJ. *(A) We identified three clusters within right-TPJ using silhouette scoring: a dorsal cluster (green), a ventral cluster (yellow) and a posterior cluster (purple). (B) Coactivation contrasts for right-TPJ. All clusters strongly coactivated with left-TPJ. The ventral cluster showed more coactivation with PCC. (C) Functional preference profiles of right-TPJ. All clusters in right-TPJ were predicted by social, memory, and awareness, while only the dorsal cluster was predicted by decision making. (D) Right-TPJ and health conditions. No subregions were significantly associated with disease-related topics.*

We identified three clusters within left-TPJ with silhouette scoring (Fig. 5A, left panel): an anterior cluster (Fig. 5A right panel, red), a posterior cluster (Fig 5A right panel, yellow) and a ventral cluster (Fig. 5A right panel, green). We directly contrasted the

coactivation patterns of each subregion. We found all three regions strongly coactivate with right-TPJ. In addition, the posterior and ventral clusters showed stronger coactivation with PCC (Fig. 5B). While both clusters also strongly coactivated with MPFC, the posterior cluster showed strong coactivation with ventral MPFC, whereas the ventral cluster coactivated with dorsal MPFC more (Fig 5B). Consistent with functional patterns in DMN, all clusters in left-TPJ were primarily predicted by social, decision-making, memory, and awareness (Fig 5C). However, the ventral cluster was more strongly associated with reading, semantics and emotion whereas the anterior cluster showed stronger association with reading and working memory (Fig. 5C). In contrast, the posterior cluster was more strongly predicted by priming. No subregions were more significantly associated with disorder-related topics (Fig. 5D). Note that the parcellations within left- and right- TPJ partially mirror each other (Table 1), which increases confidence in the clustering of coactivation patterns (de la Vega et al., 2016, 2017).

Table 1. Percent overlapping voxels within subregions of left- and right- TPJ.

% overlap	Left-TPJ		
Right-TPJ	anterior	ventral	posterior
dorsal	0.50	0.28	0.01
ventral	0.01	0.63	0.00
posterior	0.04	0.33	0.51

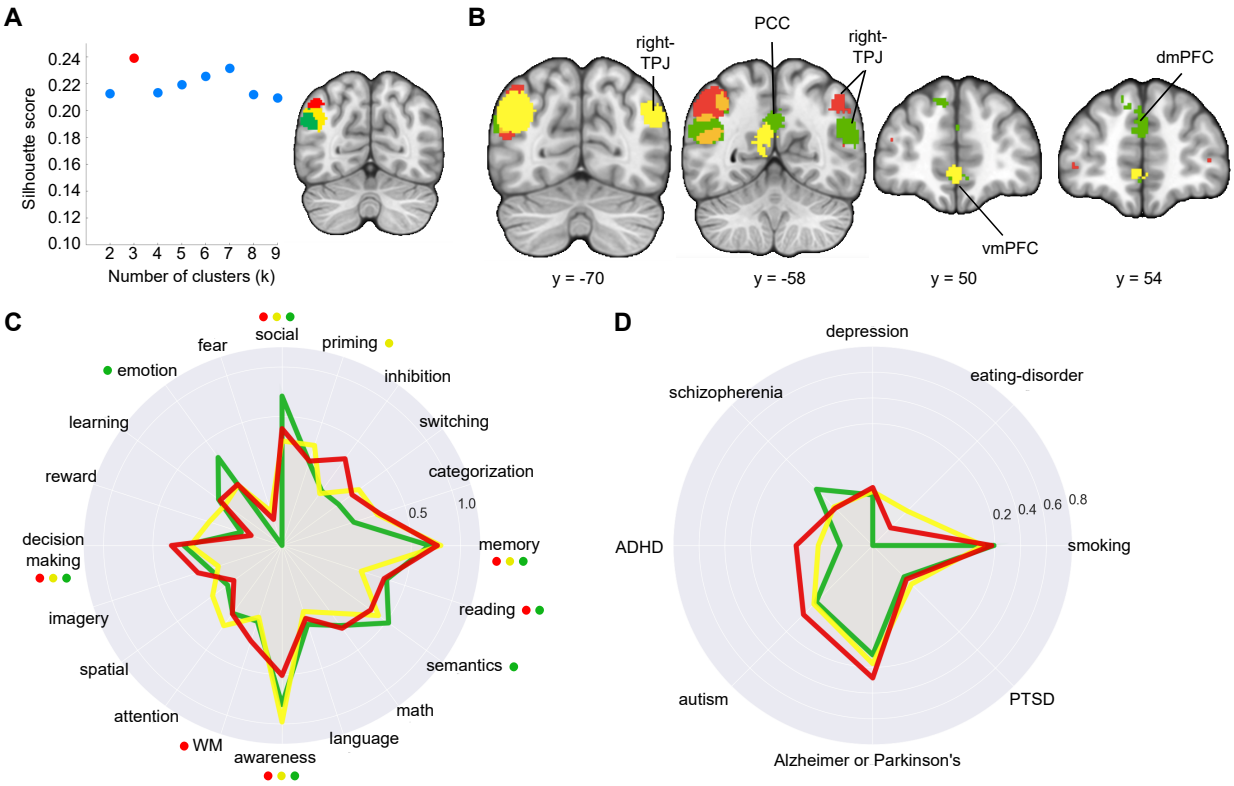

Fig 5. Coactivation-based clustering, meta-analytic coactivation contrasts and functional preference profiles of left-TPJ. *(A) We identified three clusters within the left-TPJ based on silhouette scoring: an anterior cluster (red), a posterior cluster (yellow) and a ventral cluster (green). (B) Coactivation contrasts of left-TPJ. All three regions strongly coactivate with right-TPJ. The osterior and ventral clusters showed stronger coactivation with the right-TPJ. The posterior cluster showed more coactivation with the ventral MPFC whereas the ventral cluster more strongly coactivated with dorsal MPFC. (C) Functional preference profiles of left-TPJ. All clusters in the left-TPJ were primarily predicted by social, decision-making, memory, and awareness. The ventral cluster was more strongly associated with reading, semantics and emotion whereas the anterior cluster showed stronger association with reading and working memory. The posterior cluster was more strongly predicted by priming. (D) Left-TPJ and health conditions. No subregions were significantly associated with disease-related topics.*

We identified three clusters within PCC with silhouette scoring (Fig. 6A, left panel): a dorsal cluster (Fig. 6A right panel, blue), a medial cluster (Fig. 6A right panel, yellow) and

a ventral cluster (Fi.g 6A right panel, red). The medial cluster showed stronger coactivation with bilateral-TPJ and MPFC, whereas the ventral cluster more strongly coactivated with hippocampus (Fig. 6B). Similar to this coactivation pattern, all clusters in PCC were predicted by memory, awareness, and decision-making, while only the medial region was associated with social and emotion (Fig. 6C). Additionally, all PCC clusters were associated with Alzheimer's/Parkinson's disease. However, the dorsal cluster was more strongly associated with smoking whereas the ventral cluster was more associated with PTSD (Fig. 6D).

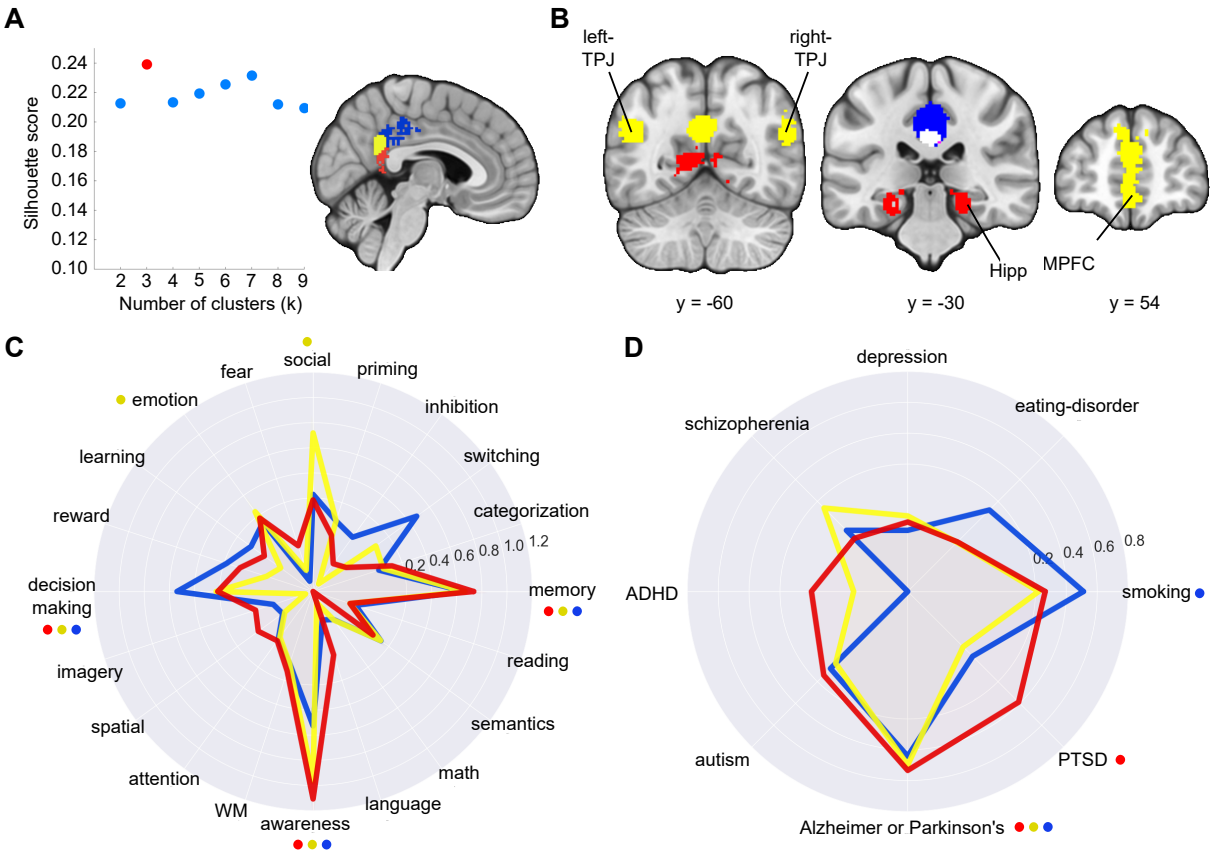

Fig 6. Coactivation-based clustering, meta-analytic coactivation contrasts and functional preference profiles of PCC. *(A) We identified three clusters within the PCC on the basis of*

silhouette scoring: a dorsal cluster (blue), a medial cluster (yellow) and a ventral cluster (red). (B) Coactivation contrasts of PCC. The medial cluster showed stronger coactivation with the bilateral-TPJ and MPFC whereas the ventral cluster more strongly coactivated with hippocampus. (C) Functional preference profiles of PCC. All clusters in the PCC were predicted by memory, awareness and decision-making, while only the medial region was associated with social and emotion. (D) PCC and health conditions. All PCC clusters were associated with Alzheimer's/Parkinson's disease. The dorsal cluster was more strongly associated with smoking whereas the ventral cluster was more associated with PTSD.

Discussion

The default mode network has been linked to a wide range of cognitive functions and disease states. Numerous studies have elucidated the functional architecture of the network through coactivation- or connectivity-based analysis (Amft et al., 2015; Bzdok et al., 2013, 2015, Eickhoff et al., 2011, 2016; A. R. Laird et al., 2009, 2011; Ray et al., 2015). Yet, we lack a comprehensive understanding of the mappings between psychological functions and different nodes within the default mode network. To address this question, the present study builds upon previous work that draws on high-powered meta-analysis of functional neuroimaging data to parcellate the MPFC and LFC by topic modeling of psychological functions (de la Vega et al., 2016, 2017). Our findings also help characterize the functional specialization and subspecialization in two other key DMN regions, PCC and TPJ. Here, we report coactivation among DMN regions and between DMN and hippocampus, amygdala, and striatum. Overlap in function among DMN regions was observed with all ROIs sharing social, decision-making, awareness, and memory; DMN regions were also differentiated by function, with MPFC associated with emotion, reward,

and fear; PCC associated with emotion; and left-TPJ associated with math, semantics, working memory, and reading. Moreover, DMN regions were uniquely associated with psychopathology and neurological diseases: PCC was associated with Alzheimer's & Parkinson's diseases and smoking while MPFC was associated with smoking, eating disorder and depression. Further examination of these DMN ROIs revealed that they could be divided into subregions based on cognitive and disease-related functional subspecialization.

Regional Account of the Default Mode Network.

Across all DMN nodes, we observe consistent patterns of involvement with social, memory, decision making and awareness. Our analysis also show strong coactivations patterns between PCC and TPJ, suggesting their interactive roles in support of functions, such as social cognition and memory processes (Bzdok et al., 2013, 2015; R. B. Mars et al., 2011). These findings recapitulate the notion that nodes within DMN jointly contribute to multiple psychological processes (Buckner et al., 2008; A. R. Laird et al., 2009; Marcus E. Raichle, 2015). In addition, our result also reveal that MPFC, as compared to other nodes, has more heterogeneous functional characteristics. We show that MPFC coactivates with many subcortical regions, such as amygdala and ventral striatum. Consistent with this pattern, our analysis further shows that MPFC is strongly associated with fear, emotion and reward, consolidating the vast literature on MPFC's interactions with regions related to affect and reward learning (Etkin et al., 2011; Mars, et al., 2012).

Unifying Observations Across DMN Regions

Within MPFC, our finding of strong association between a ventral cluster and fear is consistent with prior work implicating vmPFC in extinction of conditioned fear (Milad et al., 2007; Morgan & LeDoux, 1995). Our analyses further delineate psychological disorders associated with MPFC. In particular, depression, which has been previously associated with altered DMN patterns (Belzung, Willner, & Philippot, 2015), loaded most strongly onto MPFC. In patients with major depressive disorder, increased functional connectivity of MPFC has been observed (Zhu et al., 2012), as well as increased MPFC activation during self-referential processing (Lemogne et al., 2010). The fact that both dorsal and ventral MPFC clusters were associated with depression lends further support to previous work suggesting involvement of both MPFC subregions in major depressive disorder, with dorsal MPFC activation during depressive self-comparisons and ventral MPFC activation during the attentional component of depressive self-focus (Lemogne, Delaveau, Freton, Guionnet, & Fossati, 2012).

Consistent with previous literature on PCC, the present study shows associations between PCC and social cognition. It has been shown that PCC is a central node of DMN for social cognition – specifically ascribing mental states to others (Leech, Braga, & Sharp, 2012; Leech, Kamourieh, Beckmann, & Sharp, 2011; Mars et al., 2012a) – and to have functional interactions at rest with inferior parietal and superior temporal regions (Mars, et al., 2012a). While previously the role of PCC in social cognition has not been well-delineated, our results suggest that a medial cluster of PCC may be most strongly associated with social cognition (Alcalá-López et al., 2017). The same medial PCC cluster was shown to be specific to emotion; while there is relatively less evidence for the role of PCC in emotion, previous work has shown that PCC activates in response to emotional

words and may mediate interactions between emotional and memory processes (Maddock, 1999), consistent with our parallel finding of an association between PCC and memory (Vatansever, Manktelow, Sahakian, Menon, & Stamatakis, 2017). In addition to a primary association with memory, all PCC clusters loaded on Alzheimer's/Parkinson's disease, consistent with previous reports of PCC-DMN functional connectivity in patients with Alzheimer's disease and mild cognitive impairment (Hafkemeijer, van der Grond, & Rombouts, 2012). This association may also be linked to our finding of coactivation between PCC and hippocampus, as previous research has suggested disrupted resting state functional connectivity between PCC and hippocampus as a mechanism underling Alzheimer's disease (Hafkemeijer et al., 2012).

Our analyses also highlight the association of both dorsal and ventral PCC with smoking. Although most prior neuroimaging studies of smoking behavior focus on anterior cingulate and subcortical circuitry, nicotine has also been shown to consistently enhance functional connectivity between PCC and medial frontal/anterior cingulate cortex, as well as local connectivity between dorsal and ventral PCC (Hong et al., 2009). Additionally, PCC activity has been associated with craving (Garavan et al., 2000), viewing smoking cessation messages (Chua et al., 2011; Chua, Liberzon, Welsh, & Strecher, 2009), and suppressing cue-induced craving (Brody et al., 2007). Taken together, these functional distinctions indicate that subregions within PCC were differentially recruited by different cognitive processes, a pattern consistent with previous literature suggesting the multifaceted role of PCC in cognition (Acikalin, Gorgolewski, & Poldrack, 2017; Margulies et al., 2009; Utevsky, Smith, & Huettel, 2014).

We also report involvement with social throughout TPJ, with left TPJ specific to math, semantics, reading, emotion, and working memory. Within the domain of social cognition, previous research has established TPJ as most associated with mentalizing and theory of mind (Saxe, 2006). In addition, previous work has suggested functional heterogeneity within TPJ on the basis of its functional and structural connectivity (Bzdok et al., 2016; Mars, et al., 2012; Schilbach et al., 2012). One study in particular attempted to map social cognition in the human brain, including parcellating TPJ using diffusion-weighted imaging with comparison to non-human primates (Mars et al., 2011). This work suggested that posterior TPJ was most strongly associated with social cognition. Our analysis similarly show strong loading of the 'social' term across all TPJ clusters; the previously reported social association with posterior and not anterior TPJ may be a result of TPJ mask definition, as Mars et al. (2011) include a broader anterior area of TPJ that overlaps further with the inferior parietal lobe.

Limitations

Although our study provides a comprehensive characterization of the functional roles of the DMN, we note that our findings accompanied by three caveats. First, the classifier used in our analysis did not distinguish activations from deactivations. However, it is well known that the DMN might be activated for some processes (e.g., social cognition; Schilbach et al., 2008; Mars et al., 2012; Amft et al., 2015) and deactivated for others (e.g., executive control; Anticevic et al., 2010; Binder, 2012; Koshino et al., 2014). Thus, it is conceivable that a dataset capable of detecting deactivations would potentially extend our current findings and provide a full account of the functional architecture of the DMN. Second, the coactivation maps may not be directly related to connectivity between brain

regions because they are based on correlations. Indeed, correlations between brain regions can be driven by a number of factors that are not related to connectivity or coupling, including changes in signal-to-noise ratio in either region or a change in another brain region (Gerstein & Perkel, 1969; Friston 2011). A thorough examination of connectivity would necessitate integrating behavioral tasks with effective connectivity measures, such as psychophysiological interactions analysis (PPI; Friston et al., 1997, 2011; O'Reilly et al., 2012; Smith et al., 2016; Smith & Delgado, 2017). This alternative approach would provide insight into how specific tasks and processes drive connectivity with the DMN. Finally, the nature of the topic modeling oversimplified the mapping between psychological ontology to complex, dynamic brain activity (Poldrack & Yarkoni, 2016; de la Vega et al., 2017). For example, each topic used in our analysis represents a combination of many cognitive processes operating at different levels. As a result, mappings between specific psychological concepts and brain activity require identification of more fine-grained definition of cognitive processes.

In addition to these limitations, we also note that our approach for defining and fractionating the DMN merits additional consideration. For example, we defined the DMN based on a combination of anatomy and function and then parceled individual nodes of DMN. Although an analogous approach has been used in prior studies (e.g., Leech et al., 2011), we note that other studies have parceled networks using responses from all nodes (Alcalá-López et al., 2017). Both approaches assume a given network is composed of distinct nodes, which depends critically on the definition of those nodes (Cole, Smith & Beckman, 2010; Smith et al., 2011). To address this issue, some papers have defined networks using continuous maps (e.g., those derived from independent component

analysis) and have examined connectivity with those maps using dual-regression analysis (Filippini et al., 2009; Smith et al., 2014; Yu et al., 2017). We believe that integrating this approach with our current analytical framework (de la Vega, 2016, 2017) and unthresholded whole-brain maps (Gorgolewski et al., 2015) will help future studies refine functional parcellations of the DMN.

Conclusions

To conclude, we applied a meta-analytic approach in the present study to characterize functional mappings between cognitive processes, health conditions and the DMN. Although the DMN as a whole contributes to multiple cognitive processes, we found distinct functional properties for each region. We also identified functional parcellation for each subregion. These results help clarify the functional roles of the DMN across a large corpus of neuroimaging studies. We believe our results also help complement other studies focused on refining the theoretical and computational framework associated with the DMN (Dohmatob, Dumas & Bzdok, 2017).

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