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

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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 multiple interacting regions, including the posterior cingulate cortex (PCC), temporal parietal junction (TPJ), and medial prefrontal cortex (MPFC). Yet, it remains unclear how regions within the DMN contribute to distinct cognitive processes and mental disorders. We applied a meta-analytic approach within the Neurosynth database to determine which cognitive processes and mental disorders were primarily associated with the activity of the DMN regions. To assess how DMN regions coactivate with the whole brain, we generated meta-analytic coactivation profiles by identifying voxels with a greater probability of coactivating with each region than with other DMN regions. Based on these profiles, we clustered voxels within each region into separable subregions. Results revealed that DMN regions were involved with overlapping as well as distinct functional networks with the rest of the brain. To map between functional states (cognitive processes and mental disorders) and DMN regions, we trained classifiers to predict which studies activated a given region. We found that all DMN regions support multiple cognitive functions such as social, decision making, memory and awareness. We also found that each region was differentially recruited by distinct cognitive processes and mental disorders. Furthermore, we observed more fine-grained functional specialization among subregions within each of the DMN regions. Taken together, our results support two broad conclusions regarding DMN. First, DMN is associated with multiple psychological functions and mental disorders. Second, although some functions are common to all DMN nodes, other functions are preferentially associated with specific DMN nodes.

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 activity 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 during DMN activity, 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 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 suggests there may be both 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 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 temporoparietal 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 (M E 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.

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 (Daniel P. Kennedy & Courchesne, 2008; Daniel P. 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 entirely 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 activity 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 activity 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 mental disorders; 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 no study has yet addressed this question.

To investigate how cognitive processes and mental disorders 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 that has 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). 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, which contains activation data from more than 12,000 fMRI studies (Yarkoni et al., 2011).

DMN mask

We first created a DMN mask defined by the intersections of functional activation and anatomical masks, in order to find regions that are functionally related but restricted to anatomical regions within DMN (Fig. 1A; Poldrack et al., 2017). Specifically, we performed

reverse-inference meta-analysis by searching 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 (Yarkoni et al., 2011). Thus, the resulting functional mask identified voxels in studies where term “DMN” was mentioned in their abstract given brain activation. 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).

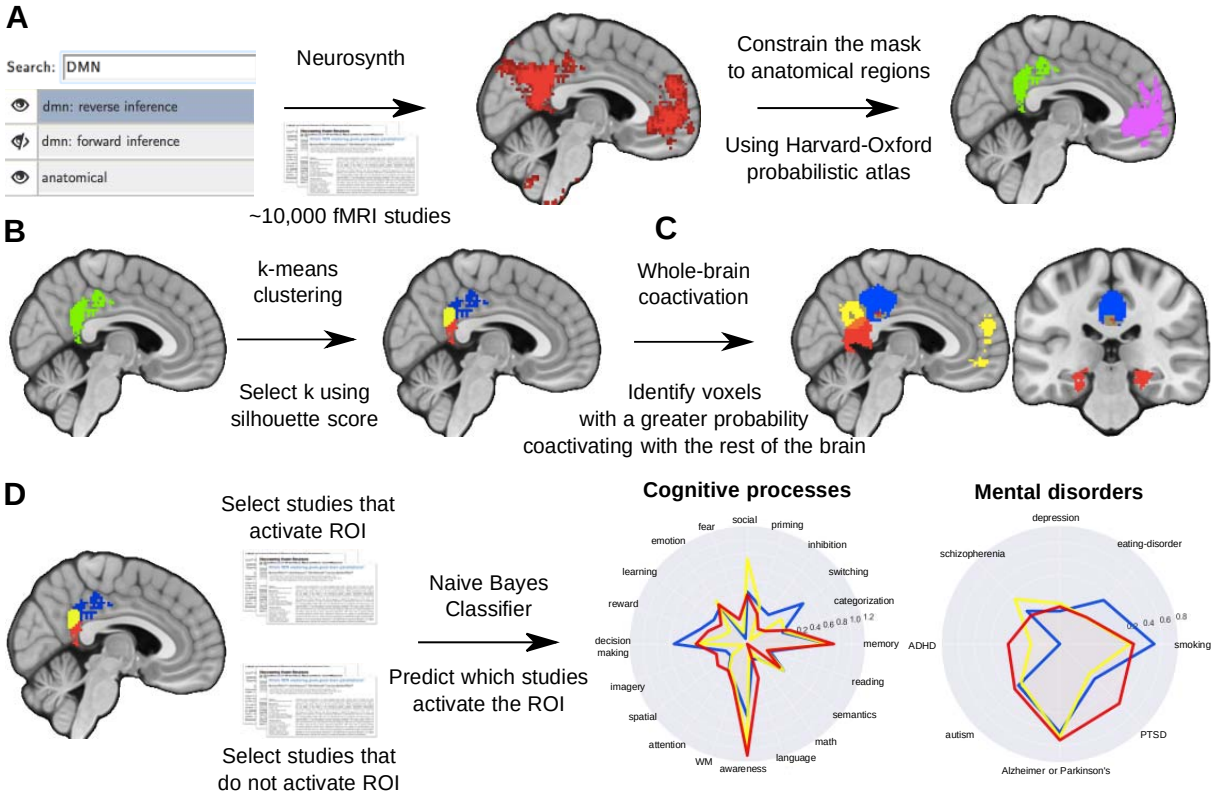

Fig 1. Overview of methods. *(A) We searched topic “DMN” in Neurosynth to create a*

functional mask, and then constrained the mask to 4 anatomical regions that belong to 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 mental disorders best predicted each region's (or subregion's) activity.

Coactivation-based clustering

To determine more fine-grained functional differences within four 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). For each region, we correlated activation pattern of each voxel with the rest of the brain across studies. The resulting coactivation matrix was then passed through principal component analysis, 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. 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). As pointed out by other researchers (Varoquaus & Thirion, 2014; Poldrack & Yarkoni, 2016), identifying the objectively correct number of clusters could become an intractable problem due to the fact that the goals and levels of analysis varied across investigators. Nevertheless, the silhouette score has

received success at assessing cluster solutions (Pauli et al., 2016; de la Vega et al., 2016, 2017)

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 to identify the voxels in the rest of the brain with a greater probability coactivating with ROI than other regions within DMN. 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.

Meta-analytic functional preference profiles

To map between functional states (e.g., cognitive processes, mental disorders) and regions of the DMN, we used a set of 60 topics identical to that used in previous studies (Poldrack et al., 2012a; de la Vega et al., 2016). These topics were derived from latent Dirichlet allocation topic modeling (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). 23 topics that were irrelevant to either cognitive processes or mental disorders were excluded from the generated topics, leaving 29 cognitive topics and 8 disorder-related topics.

We generated functional preference profiles by identifying which cognitive processes, or mental disorders 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. We then trained a naive Bayesian classifier (Yarkoni et al., 2011; 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., term "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 for 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.

Results

Coactivation and functional preference profiles for the DMN regions

We defined DMN mask on the basis of functional mapping that mapped topic “DMN” to brain regions, and constrained it to anatomical regions that belong to 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).

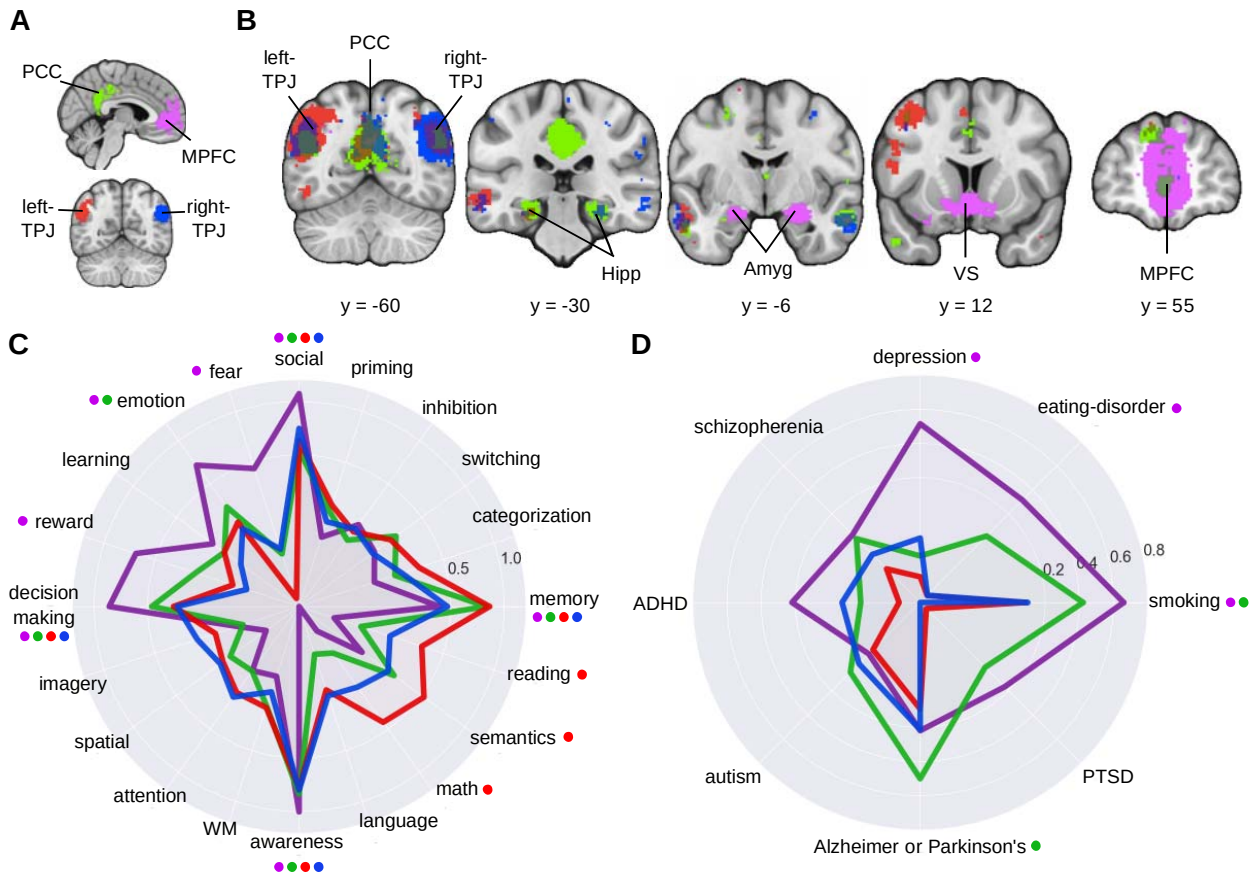

Fig 2. Meta-analytic coactivation and functional profiles for the DMN. *(A) Functionally and anatomically defined regions within DMN: medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), left and right temporal parietal junction (left- and right-TPJ). (B) Coactivation profiles for 4 regions. 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) based on permutation test. (D) DMN and mental disorders. Functional profiles related to mental disorders 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 certain regions are involved with distinct functional networks, particularly MPFC. MPFC 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, 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, and then those related to mental disorders. 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 was involved in social, decision-making, metallizing and memory processing. 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 mental disorders. 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 4 regions of DMN.

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, while 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).

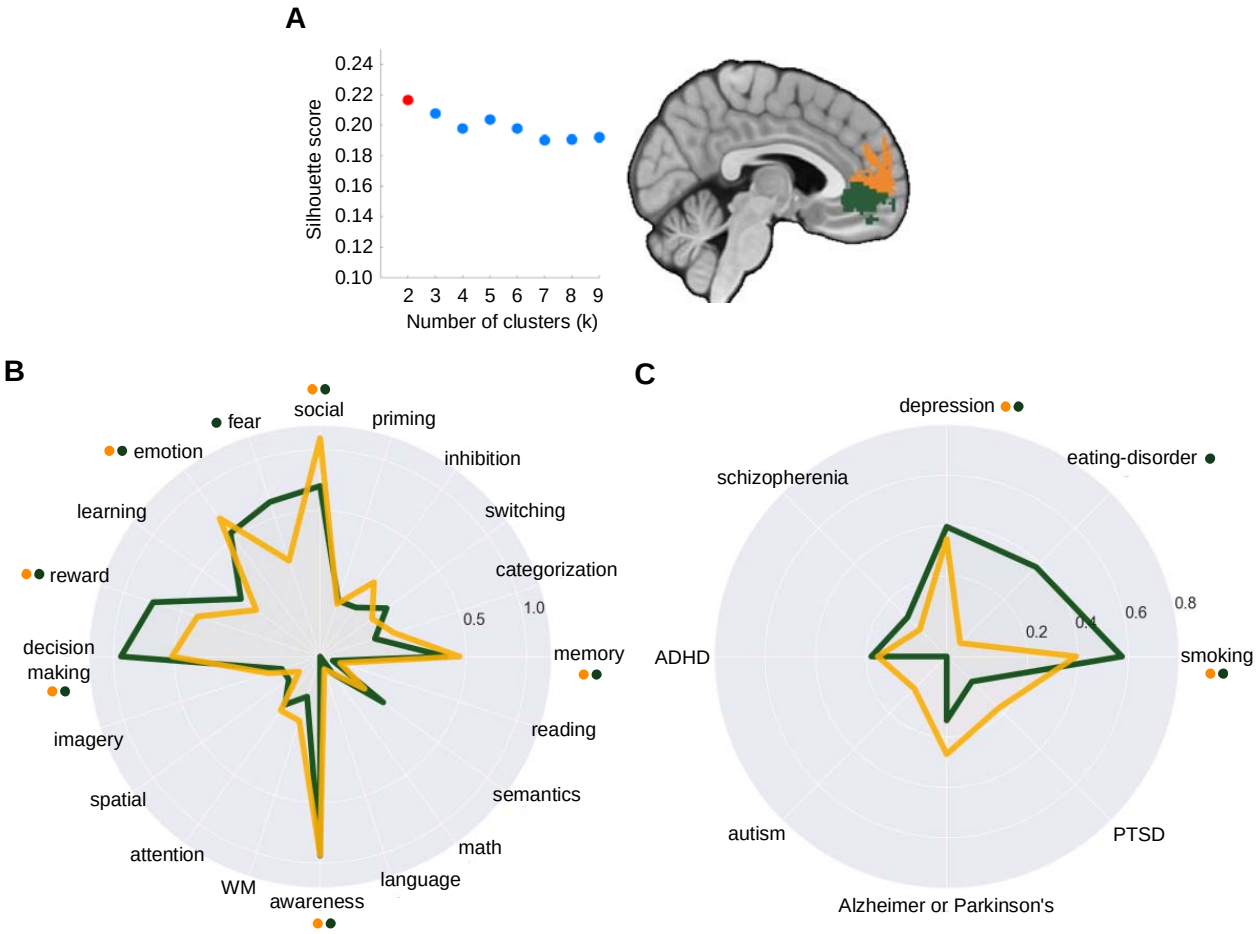

Fig 3. Coactivation-based clustering and functional preference profiles of MPFC. *(A) We*

identified two clusters within MPFC based on silhouette score: 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 mental disorders. Both clusters in MPFC were recruited by depression and smoking, but only the ventral one was associated with eating disorder.

Our silhouette score analysis (see Supplementary Table 1) revealed that a three-cluster solution was optimal for the right-TPJ (Fig 4A, left panel): a dorsal cluster (Fig 4A right panel, green), a ventral one (Fig 4A right panel, yellow) and a posterior cluster (Fig 4A right panel, purple). No cluster showed stronger coactivation with the rest of the brain. 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).

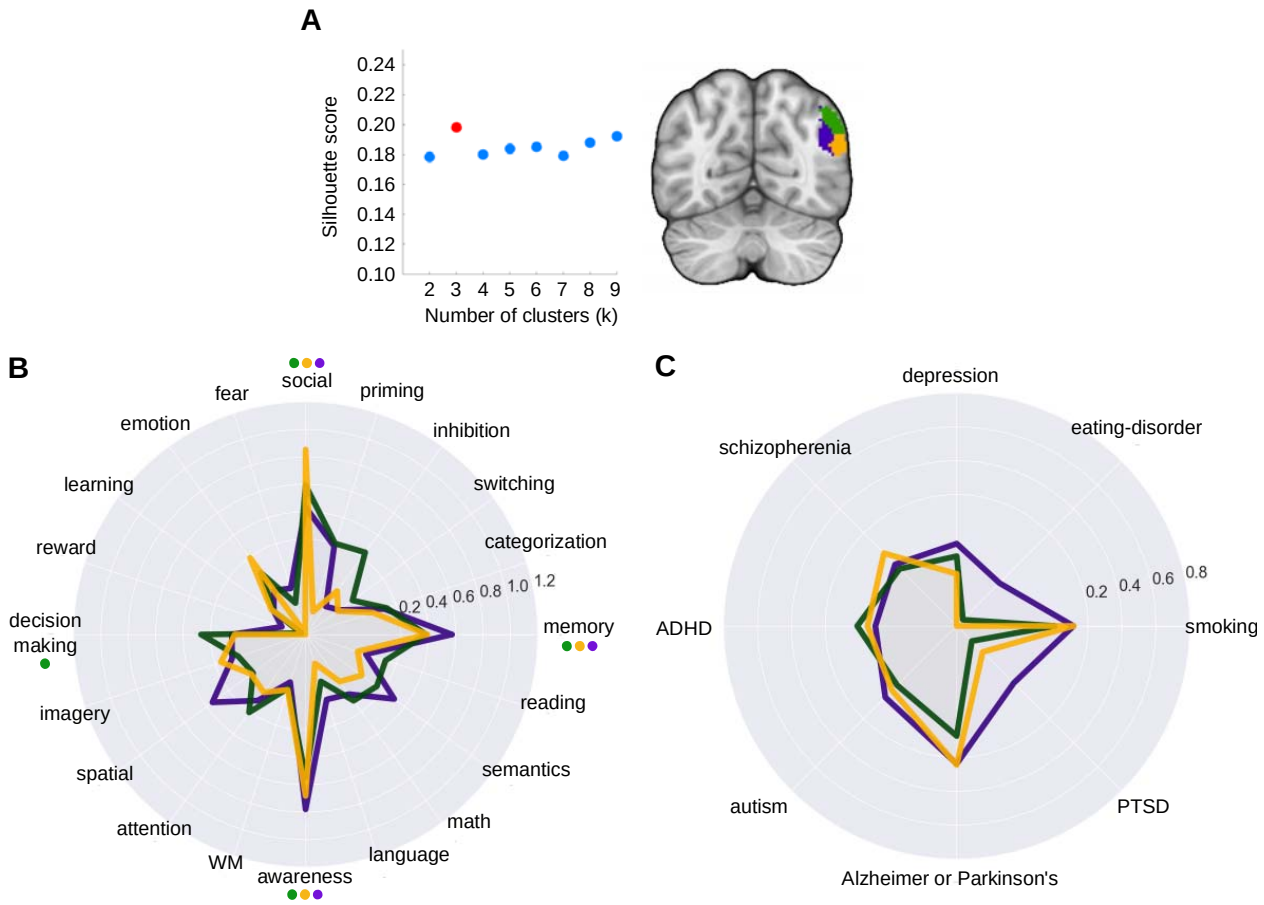

Fig 4. Coactivation-based clustering and functional preference profiles of right-TPJ. *(A) We identified two clusters within right-TPJ using silhouette score: a dorsal cluster (purple) and a ventral cluster (green). (B) Functional preference profiles of right-TPJ. Both clusters in right-TPJ were predicted by social, memory, and awareness, while only the dorsal cluster was predicted by decision making. (C) Right-TPJ and mental disorders. No subregions were significantly associated with disease-related topics.*

We identified three clusters within left-TPJ with silhouette score (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 coactivate with MPFC, posterior cluster showed strongly coactivation with ventral MPFC whereas ventral cluster coactivate 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, 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).

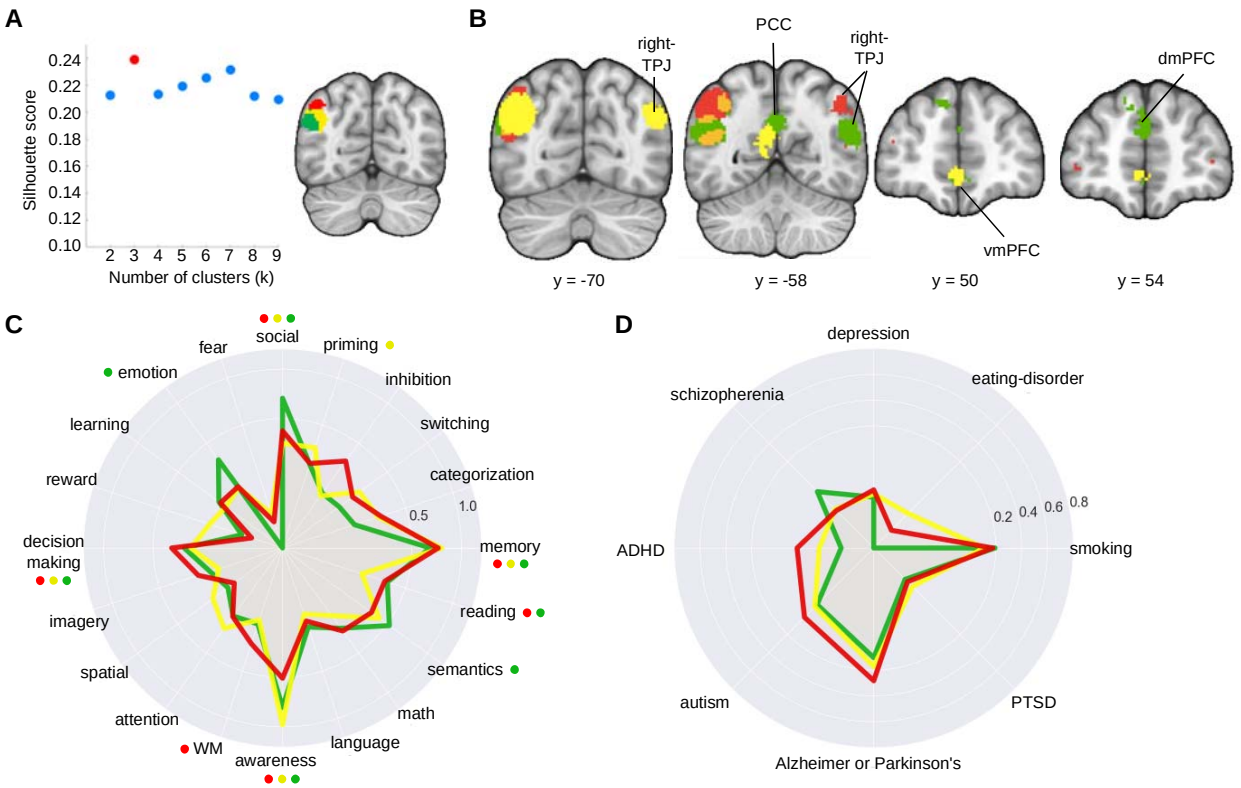

Fig 5. Coactivation-based clustering, meta-analytic coactivation contrasts and functional preference profiles of left-TPJ. *(A) We identified three clusters within the left-TPJ based on silhouette score: an anterior cluster (red), a posterior cluster (yellow) and a ventral cluster (green). (B) Coactivation contrasts of left-TPJ. All three regions strongly coactivate with left-TPJ. Posterior and ventral clusters showed stronger coactivation with left-TPJ. Posterior cluster showed more coactivation with ventral MPFC whereas ventral cluster more strongly coactivate with dorsal MPFC. (C) Functional preference profiles of left-TPJ. All clusters in left-TPJ were primarily predicted by social, decision-making, memory, and awareness. 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 mental disorders. No subregions were significantly associated with disease-related topics.*

We identified three clusters within PCC with silhouette score (Fig 6A, left panel): a dorsal cluster (Fig 6A right panel, blue), a medial cluster (Fig 6A right panel, yellow) and a ventral cluster (Fig 6A right panel, red). The medial cluster showed stronger coactivation with bilateral-TPJ and MPFC whereas the ventral cluster more strongly coactivate 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 6D). 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).

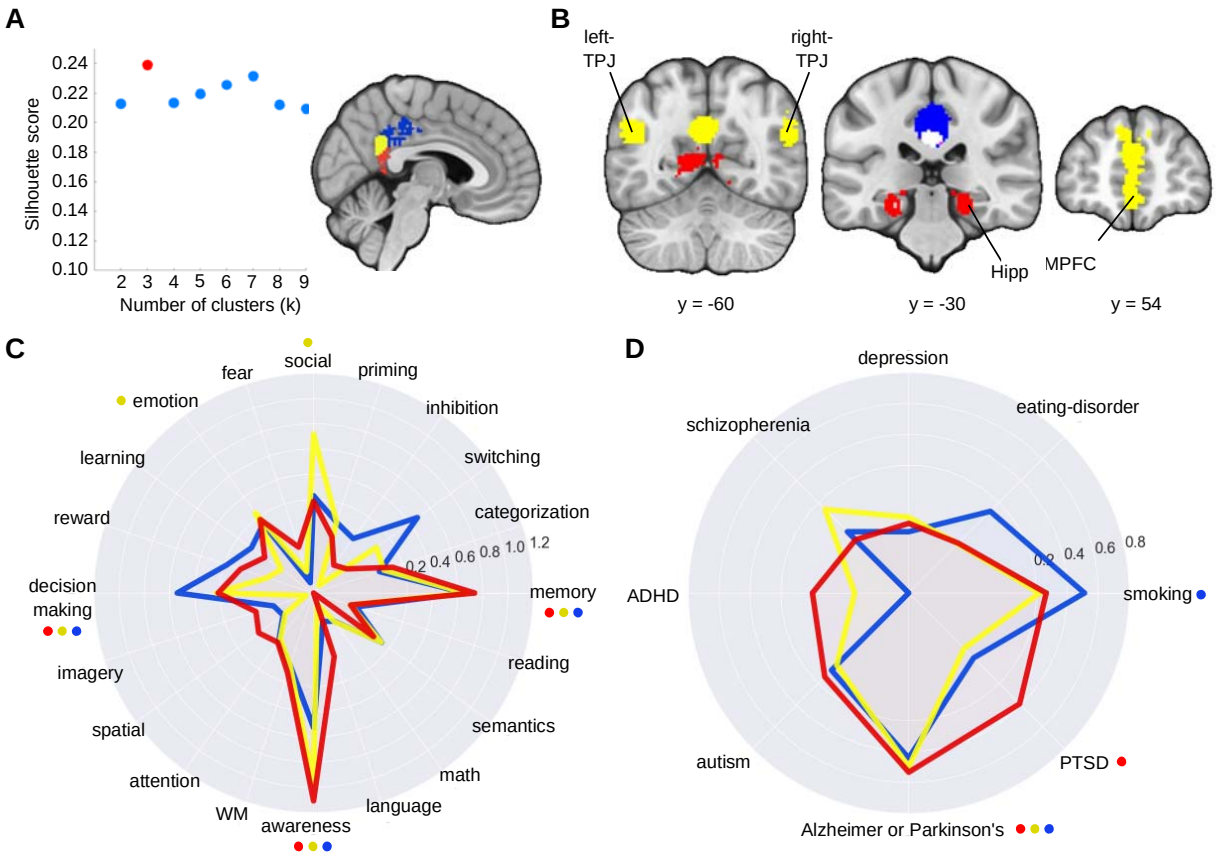

Fig 6. Coactivation-based clustering, meta-analytic coactivation contrasts and functional preference profiles of PCC. *(A) We identified three clusters within PCC on the basis of silhouette score: a dorsal cluster (blue), a medial cluster (yellow) and a ventral cluster (red). (B) Coactivation contrasts of PCC. The medial cluster showed stronger coactivation with bilateral-TPJ and MPFC whereas the ventral cluster more strongly coactivate with hippocampus. (C)Functional preference profiles of PCC. All clusters in PCC were predicted by memory, awareness and decision-making, while only the medial region was associated with social and emotion. (D) PCC and mental disorders. 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. Yet, we lack a comprehensive understanding of how function is associated with different nodes within the default mode network. To address this problem, the present study draws on high-powered meta-analysis of functional neuroimaging data to build upon previous work parcellating the MPFC and LFC by function (de la Vega et al., 2016, 2017). Our findings also help characterize 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, particularly smoking, eating disorders, and Alzheimer's & Parkinson's diseases. Further examination of these DMN ROIs revealed that they could be divided into subregions based on cognitive and disease-related functional subspecialization.

Our findings of strong associations between MPFC and memory, emotion, awareness, social, decision-making, and reward are consistent with previous studies of MPFC function (Etkin, Egner, & Kalisch, 2011a; Mars et al., 2012a). Within MPFC subdivisions, a ventral cluster was specifically associated with fear, consistent with prior work implicating vmPFC in extinction of conditioned fear (Milad et al., 2007; Maria A. Morgan & LeDoux, 1995). In addition to consolidating the vast literature on cognitive

functions associated with MPFC, 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., 2010a). 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, emotion, decision-making, and awareness. Among these heterogeneous functions, PCC has previously been shown to be a DMN node central for social cognition – specifically ascribing mental states to others (Robert Leech, Braga, & Sharp, 2012; Robert Leech, Kamourieh, Beckmann, & Sharp, 2011; Mars et al., 2012a) – and to have functional interactions at rest with inferior parietal and superior temporal regions, consistent with our observed pattern of coactivation with bilateral TPJ (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 et al., 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., 2011a; Chua, Liberzon, Welsh, & Strecher, 2009), and suppressing cue-induced craving (Brody et al., 2007a). 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 (Utevsky, Smith & Huettel, 2014; Acikalin, Gorgolewski & Poldrack, 2017).

We also report involvement with memory, awareness, social and decision-making 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 (Mars, 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, and showed strong coactivations with PCC (Mars et al., 2011). Our analyses similarly show strong TPJ-PCC coactivation and strong loading of the 'social' term across all PCC 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.

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) 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. We acknowledge that future studies should be conducted to address these limitations and provide a better understanding of the DMN functions. Meanwhile, it is important to note that our results mirrored findings from previous investigations using different datasets and analysis, thus strengthening our conclusions.

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 (i.e., PCC, TPJ, MPFC). 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 independent component analysis and have examined connectivity with those networks 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.

To conclude, we applied a meta-analytic approach in the present study to characterize functional mappings between cognitive processes, mental disorders 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 specialization 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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