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Subspecialization within default mode nodes characterized in 10,000 UK Biobank participants

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The human default mode network (DMN) is implicated in several unique mental capacities. In this study, we tested whether brain-wide interregional communication in the DMN can be derived from population variability in intrinsic activity fluctuations, gray-matter morphology, and fiber tract anatomy. In a sample of 10,000 UK Biobank participants, pattern-learning algorithms revealed functional coupling states in the DMN that are linked to connectivity profiles between other macroscopic brain networks. In addition, DMN gray-matter volume was co-varied with white-matter microstructure of the fornix. Collectively, functional and structural patterns unmasked a possible division of labor within major DMN nodes: Subregions most critical for cortical network interplay were adjacent to subregions most predictive of fornix fibers from the hippocampus that processes memories and places.

Significance

The default mode network (DMN) encompasses supramodal association areas involved in higher-order cognition. One speculation is that this neural system is important for brain-wide information flow. We tested this account by exploring whether DMN patterns are informative about functional coupling or structural associations in the rest of the brain. Our multimodal pattern analysis findings highlight how the DMN nodes are fractionated: In specific subregions, gray-matter morphology was linked to fiber tracts from the hippocampus in the medial temporal limbic system. In adjacent subnodes, fluctuations in neural activity were linked to between-network connectivity shifts. Such a mosaic architecture may be a prerequisite for many of the roles the DMN may play in advanced cognitive processes.

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from how information from other brain regions is expressed in different parts of the system.

Our population neuroscience study interrogated whether the role of the DMN in higher cognition may emerge from the ability to echo properties of remote large-scale brain networks (16). To this end, we capitalized on a recently available DMN atlas with subnode differentiation (13, 17–20). We reasoned that, if sub-specialized regions within the DMN nodes act as relays that promote information from different parts of the neural hierarchy, this would facilitate information exchange between unisensory networks and other subordinate brain systems (8, 16). Using a multimodal brain imaging approach combining functional and structural measures of brain organization, we identified functional relationships between different DMN subnodes and major brain networks as well as their underlying anatomical architecture. Uniformly collected data from a large human population were systematically explored by multivariate pattern learning algorithms guided by our recent topographical DMN atlas.

**Results**

In the structural domain, we tested whether patterns within combined measurements of DMN volume [structural MRI (sMRI)] and axonal fiber bundles [diffusion MRI (dMRI)] would allow the identification of the white matter tracts with the strongest structural association with the DMN. We quantified generalizable patterns in DMN gray matter that inform about microstructural differences of white matter tracts (Johns Hopkins University atlas) across individuals. Gray matter volume was extracted in 32 DMN subregions per participant (Fig. 1) and used for pattern recognition algorithms [maximum-margin support vector regression (SVR)]. This approach could nominate the anatomical fiber tracts that were most predictive of gray matter volume estimates from within the DMN. The target diffusion measures included fractional anisotropy (FA, directional coherence), magnitude of diffusion, axial diffusion, and radial diffusion, as well as NODDI parameters, including tract complexity (OD), neurite density (ICVF), and extracellular water diffusion (ISOVF). After accounting for confounds (age, age2, sex, their two-way interactions, head size, and body mass), pattern search models isolated structural associations between DMN and brain-wide anatomical tracts. Comparing 48 candidate tracts, microstructural differences of three fornix-related fiber tracts were highly predictable based on gray matter differences within the DMN (Fig. 2), explaining up to 24% of population variance in this major hippocampus output pathway of the limbic system. These associations persisted across different diffusion parameters (SI Appendix, Fig. S2). Gray matter volume differences in DMN subregions were predictive of microstructure in a specific subset of anatomical tracts. The prediction accuracy for the common FA measure of white matter integrity ranged from $R^2 = 0.00$ to 0.24 across all tracts, with mean performance of $0.04 \pm 0.04$ (±SD) in unsewn individuals (out-of-sample cross-validation). Across the atlas tracts, pattern detection performance was high for the fornix (Fig. 2 A and B) at an explained variance of 24% ($R^2 = 0.24 \pm 0.03$ SD across cross-validation splits), fornix fibers in the bilateral cres and stria terminalis (right: $R^2 = 0.09 \pm 0.01$; left: $R^2 = 0.08 \pm 0.02$), anterior corona radiata of the thalamus (left: $R^2 = 0.10 \pm 0.01$; right: $R^2 = 0.09 \pm 0.01$), posterior limb of the internal capsule (left: $R^2 = 0.08 \pm 0.03$; right: $R^2 = 0.06 \pm 0.02$), and superior frontal–occipital fasciculus (left: $R^2 = 0.12 \pm 0.02$; right: $R^2 = 0.05 \pm 0.02$).

We then examined which particular DMN subregions show strongest predictive associations with fornix microstructure differences (Fig. 2C). Robust contributions to this predictive relationship (bagging) were apparent in the right and left temporoparietal junctions (TPJ) ($weight_{TPJ-1} = -0.61 \pm 0.04$ (SD of bootstrap distributions), $weight_{TPJ-2} = 0.75 \pm 0.07$, $weight_{TPJ-3} = -0.25 \pm 0.06$, and $weight_{TPJ-4} = -0.18 \pm 0.07$), medial portions of left ventromedial prefrontal cortex (vmPFC; $weight_{vmPFC-1} = 0.17 \pm 0.03$, $weight_{vmPFC-2} = -0.64 \pm 0.07$), left middle temporal gyrus (MTG) ($weight_{MTG-1} = -0.32 \pm 0.05$, $weight_{MTG-2} = 0.31 \pm 0.04$), and in the dorsal posterior cingulate and retrosplenial cortex ($weight_{PCG-3} = -0.13 \pm 0.09$, $weight_{PMC-4} = 0.18 \pm 0.03$). We conclude that especially the right TPJ, its left counterpart, the left vmPFC, and posterior parts of the left MTG, as well as the posterior cingulate and retrosplenial midline were found most relevant among DMN gray matter patterns that predict fornix microstructure.

In the functional domain, we sought to identify connectivity patterns in the DMN that explain its correspondence with patterns of distributed neural activity. Topographical segregation of the DMN was obtained from the group-defined DMN atlas with 32 subregions (Fig. 1), while population-average definitions of 21 spatiotemporal networks were provided by UK Biobank. Canonical correlation analysis (CCA) was a natural choice of method to jointly decompose the functional relationships among DMN subregions and those between major networks across individuals. After confound removal (age, age2, sex, their two-way interactions, head motion, head size, and body mass), this doubly multivariate analysis extracted coherent patterns of connectivity modulation. These population “modes” provided a rich summary of how functional coupling changes in the segregated DMN covary with functional coupling changes of large-scale networks. To control the amount of detail in CCA modeling, we obtained family-wise error-corrected $P$ values for all modes by permutation testing analogous to previous research (21, 22). Among all estimated components, 19 modes of covariation were highly statistically significant at $P_{corr} < 0.001$ (Fig. 3B), in line with previous CCA analyses on UK Biobank participants (21). Each isolated DMN–networks mode captured a distinct source of covariation that together were mutually uncorrelated. Collectively, this analysis shows that neural
activity patterns within the DMN are related to distributed patterns of large-scale networks.

Next, we examined whether these modes of covariation were localized in particular DMN subregions. To aid interpretation, we visualized where average changes of coupling between DMN subregions were most related to between-network coupling changes. This summary highlights the DMN subregions most consistently associated with changes of global network connectivity across all significant modes (Fig. 3 A). Analogous to previous research (22), the cumulative increases and decreases of DMN subregion connectivity were examined separately.

Each major DMN node was found to have a subregion dedicated to overall network coupling. Specific subregions within a given DMN node tended to show mostly either increased or mostly decreased functional relationships that coherently cooccur with network coupling shifts. The lateral portion of the vmPFC (bilateral vmPFC-2) as well as the anterior TPJs (bilateral TPJ-1), anterior MTGs (bilateral MTG-1), and precuneus of the posterior medial cortex (PCM-1) increased in neural coupling, on average, in the context of global network communication. In contrast, mostly decreased coupling was observed in many adjacent subregions, including the left and right medial portions of the vmPFC (vmPFC-1/3), posterior TPJs (TPJ-2), posterior MTGs (MTG-3), and ventral posterior cingulate cortex (PCM-2/4). Conversely, we examined the overall connectivity changes of major brain networks (separately for positive and negative shifts) that most related to within-DMN connectivity changes across all modes (Fig. 3 C). In contrast to the DMN subregions, we found a high degree of spatial overlap between the brain networks that were subject to connectivity changes. The concurrent network coupling changes included the somatomotor cortex, thalamus, frontal eye field (FEF), dorsolateral prefrontal cortex (dlPFC), anterior insula (AI), intraparietal sulcus (IPS), anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC), as well as secondary associative visual (e.g., MT/VS) and auditory areas. These regions are often described as “task-positive” brain networks (23).

As a recurring theme across the 19 functional modes of population covariation, several coupling profiles showed one DMN subregion dominating intra-DMN connectivity in the context of broad network reconfiguration. The bilateral anterior TPJs (TPJ-1) were found to dominate in the DMN—networks correspondence (Fig. 4), as these two subregions showed prominent coupling increases in three modes. In the first mode of DMN—networks correspondence ($r = 0.83$), both anterior TPJs were increasingly coupled with most other DMN subregions, and the subregions of the left and right hippocampus increased their coupling among each other. Concurrently, at the global network level, the DMN was disengaged from the saliency network. Further, the somatomotor networks were more coupled among each other, increased in coupling with the medial temporal lobe and superior temporal gyrus, as well as decreased in coupling with the cerebellum and basal ganglia. In mode 5 ($r = 0.72$), the right anterior TPJ showed increased coupling with most DMN subregions, in particular with the postero medial cortex (PCM-1/2/3/4), midline parts of the ventromedial prefrontal cortex (vmPFC-1/3) and dorsomedial prefrontal cortex (dmPFC-1/2/3/4). Concurrently, the overall DMN had decreased coupling with the saliency network and with the left dorsal attention network in favor of the right dorsal attention network. Finally, in mode 8 ($r = 0.68$), the left anterior TPJ was up-regulated in coupling with many DMN subregions, in particular with the prefrontus (PCM-1), ventral and dorsal posterior cingulate cortex (PCM-2/3), and retrosplenial cortex (PCM-4). In this context, the entire DMN was decoupled from the right dorsal attention network, which, in
mind that this type of connectivity analysis is susceptible to noise and does not determine the underlying relationships between brain regions (49). It is, however, important to keep in mind that increased coupling of anterior TPJs with other DMN subregions was estimated to be dominantly involved in connectivity shifts of large-scale networks. Such partial-correlation analyses have become a standard to focus on immediate coupling patterns in the interactions between other brain networks.

We confirmed evidence from intrinsic coupling fluctuations by inducing “virtual DMN lesions” and computing a series of perturbed CCA models. This analysis tactic allowed the determination of sub-regions most critical across all 19 DMN—networks modes (SI Appendix, Figs. S7 and S8). Lower-correlation results indicate that removing that region leads to a quite different result, thus emphasizing the important influence of a “deleted” subregion in the original CCA decompositions. The obtained importance ranking substantiated the relevant connectivity links from particular DMN sub-regions: the anterior TPJs (right TPJ-1 $r = 0.15 \pm 0.16$ (SD of bootstrap distributions), left TPJ-1 $r = 0.46 \pm 0.17$), precuneus (PMC-1 $r = 0.109 \pm 0.12$), and lateral vmPFC (left vmPFC-2 $r = 0.26 \pm 0.18$, right vmPFC-2 $r = 0.44 \pm 0.17$). The analysis showed that neural signals in these subregions, rather than the DMN as a whole, were most important in the model’s ability to determine functionally related patterns in the interactions between other brain networks.

**Discussion**

Over the last 15 y, understanding the functional significance of the DMN has become an important topic in neuroscience. Although the DMN is often characterized as a cohesive brain system, increasing evidence has begun to challenge this view (8, 12, 14–16, 24, 25). A recent study has shown heterogeneity at the level of an individual (15), and we revisited this question from the perspective of a large-scale population study. Combining a high-throughput biomedical dataset with innovative data analytics, we used multimodal evidence to outline an organizational fragmentation of major DMN nodes. We characterized neighborhoods of structurally and functionally distinct yet complementary submodules within major nodes of the DMN, which interfaced with other brain regions in unique manners. We consider the relevance of these results for our understanding of the hypothesized role of the DMN in broader cortical dynamics.

In brain structure, we used pattern extraction algorithms to identify statistically rigorous links between DMN gray matter (sMRI) and white matter tract properties (dMRI)—two types of brain imaging usually studied separately. Our multimodal approach determined whether volume differences of DMN subregions are informative about microstructural features of axonal fiber bundles. Among 48 examined anatomical tracts, fornix fibers had the strongest association with DMN gray matter patterns, explaining up to 24% of this tract’s population variability. As with other small fiber tracts analyzed by diffusion imaging with tract-based spatial statistics (26), it is challenging to completely exclude the possibility that mild partial volume effects have influenced our fornix–DMN association results. Cerebrospinal fluid contamination may be alleviated by more sophisticated voxel-by-voxel correction techniques (27). Nevertheless, our predictive association of DMN gray matter with fornix fiber bundles was robust in 10,000 individuals and appears to fill an important gap in the neuroscience literature.

The fornix serves as backbone of the limbic system and main output tract of the hippocampus into the cortex. This tract guides axonal fibers from structures in the medial temporal space memory system to communicate with cortical association areas (28) by intermediates such as the anterior thalamic radiation.

![Brain network integration](image_url)

**Fig. 4.** Functional coupling shifts of the statistically strongest DMN—networks mode, depicting the single most important mode among 19 linked dimensions of within-DMN connectivity (Top) and between-network connectivity (Bottom). Increased coupling of anterior TPJs with other DMN subregions was estimated to be dominantly involved in connectivity shifts of large-scale networks. Such partial-correlation analyses have become a standard to focus on immediate coupling relationships between brain regions (49). It is, however, important to keep in mind that this type of connectivity analysis is susceptible to noise and does not permit statements about directional or causal functional influences (50).

precuneus showed increased coupling with most DMN subregions. Concurrently, at the network integration level, the DMN disengaged with the saliency network, analogous to mode 1, and showed decreased coupling with somatosensory cortices, dIPFC, dorsal attention networks, and lateral visual cortex. In mode 9 ($r = 0.66$), the lateral subregions of the right vmPFC similarly increased coupling with most DMN subregions. In this mode, the ventral attention network was disengaged with the dorsal attention network, posteroomedial cortices, and dIPFC, while the saliency network was decoupled from parietal cortices and was increased in coupling with dorsal attention network and dIPFC. We conclude that DMN subregions in the anterior TPJ, precuneus, and lateral vmPFC appear to play particularly important roles related to the functional interplay between large-scale networks.
Consistent with our demonstrated population association between the fornix and the vmPFC, probabilistic diffusion tractography in humans and monkeys showed that fornix-carried fiber bundles play a prominent role in connections of the hippocampus with the vmPFC (29). Moreover, hippocampal lesions in six neurological patients led to significant FA reductions in the fornix but no other white matter tracts, functional connectivity alterations in the DMN, and episodic memory impairments (30). Similarly, in patients with posttraumatic amnesia, functional connectivity between the medial temporal lobe and the posteromedial DMN correlated with associative memory performance and information processing speed (31). Building on these studies, our work leverages large-scale population data to highlight the relevance of the hippocampal–neocortical pathways in the functioning of the DMN and suggests that subregions, such as vmPFC and TPJ, which are most selective structural predictors of fornix anatomy, may be particularly important in this process.

In animals, single-cell recordings in the hippocampus have confirmed the existence of neuron assemblies involved in retrospective and prospective processing of spatial contexts, experienced events, and their complicated interaction (32). In fact, the limbic medial temporal lobe, including the hippocampus, is believed to be particularly prominent in the modulation by theta-band oscillations (32). Accumulating evidence from animal experiments suggests oscillatory synchrony in the theta regime to subserve neuronal coding in the hippocampus, including previously experienced, ongoing, and upcoming events, and its partners in the limbic system, as well as hippocampal long-distance communication with neocortical partners (32). Indeed, specific electrophysiological signals recorded in the monkey hippocampus were recently reported to trigger distributed neural activity changes in the DMN, but not other common cortical networks (33).

In humans, hippocampal–prefrontal oscillations in the theta band have also been linked to memory processes (34), and coordination between the prefrontal and temporoparietal DMN was shown to largely underlie theta-mediated oscillatory coupling (35). Congruently, seeding spontaneous fMRI activity fluctuations in the human hippocampus revealed signal reverberations in the major DMN nodes, which suggests an “ongoing functional relationship” (36). Further, quantitative metaanalyses of human neuroimaging tasks have established extensive spatial overlap in the DMN for natural stimuli, perhaps suggesting preparatory states and their accompanying functional connectivity patterns (37). Accumulating evidence fromanimal experiments suggests that hippocampal theta-band oscillations (see SI Appendix, Figs. S9–S11) are in line with a whole-brain graph analysis (41) that reported individuals with higher IQ to have shorter path length in nodes of the DMN, which the authors interpreted as improved global efficiency ofinformation transfer across networks. Hubs underlying general network control have been mainly identified in the DMN (38). Our analysis suggests that these hubs may make different contributions to cortical functioning.

There are a number of caveats that should be borne in mind while considering our results obtained at the population level. First, since we chose a DMN subregion atlas, our study aimed at insight into how segregation and integration unfold within this brain phenomenon. However, we do not provide insight into how these observations fit into views of other networks or neural systems. It will be important to examine how network fragmentation approaches may play out in other cortical networks, such as the frontoparietal network. Second, we explored how the group-defined DMN links to primary sensory cortices, but further research is required for understanding the nodes of this system through their variation across 10,000 individuals. While our analysis highlights the topographic location in which signals within the group-defined DMN possibly carry information about neural processing distributed across the cortex, there is likely to be important information that can be gained by exploring this problem at a more fine-grained level. Recent evidence suggests the existence of parallel interdigitated networks that together make up what is commonly labeled as DMN after averaging across individuals (15). Despite the considerable methodological differences between this previous participant level and our population level results, there are nonetheless certain similarities. In particular, the DMN subtype A proposed by Braga and Buckner (15) appears to extend toward more posterior regions of the TPJ (similar to TPJ-2 in our study), more ventromedial prefrontal cortex (vmPFC-1/3 here), and ventral/retrosplenial PCC (PMC-2/4). In contrast, the DMN subtype B appears localized to the anterior TPJ (TPJ-1 here), more dorsomedial prefrontal cortex (dmPFC-1/2/3/4 here), and dorsal PCC (PMC-3 here). These similarities are noteworthy given the diverging methodology in the two studies. It is the objective of a population neuroscience study to target major principles of brain organization. We highlight those regions of the DMN that are most robustly involved in patterns of within- and between-network interactions. However, both the hard boundaries of our DMN definition and their deviations through the registration process (cf. refs. 42–44) may obscure certain aspects of the underlying function (15, 42, 45). In

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particular, it is unclear in our current analyses whether DMN subregions highlight areas with homogeneous patterns of neural activity with a unified functional purpose, or whether they describe areas where the interfacing of different neural function occurs, which may represent “a generalized anatomic mechanism for processing information from two or more cortical sources in the central nervous system” (ref. 46, p. 792).

In conclusion, our results suggest spatial proximity between subregions in major DMN nodes that offer complementary structural and functional properties. Such topographic organization could provide a scaffold for communication between subregions that track unique aspects of whole-brain functional modes. We identified cortical subregions of the DMN that were closely allied to fornix microarchitecture, which, we speculate, may perhaps be related to processing information from the hippocampus in the medial temporal lobe as well as other DMN subregions that were important in explaining functional coupling shifts between major cortical networks. This mosaic biological design, we further speculate, may contribute to resolving competing requirements of modular functional specialization with between-network interplay via long-distance connections. While the DMN has repeatedly been shown to be located at the heart of the brain network hierarchy (3, 7, 38), the DMN is itself composed of distributed modules, each of which embodies distinct submodules (8, 16, 24).

Materials and Methods

The 500,000 UK Biobank participants were recruited from across Great Britain. All participants provided informed consent. The project number was UK Biobank application number 25163. Further information on the consent procedure can be found here (biobank.ctsu.ox.ac.uk/rystaff/field.cgi?id=200). Our study involved brain imaging from 10,129 individuals, 47.6% males and 52.4% females, aged 40 to 69 y, to detail the neurobiological properties of the DMN by means of T1-weighted MRI [245/1.23, TR/TE=600/155–156, and resting-state functional MRI (r-fMRI)].

Jointly analyzing gray matter volume (dMRI) and white matter microstructure (dMRI) allowed testing whether individual differences in DMN volume are linked to variability in fiber bundle microstructure. The DMN subregion volumes of each subject provided the input data for pattern learning analyses based on maximum–margin linear SVR to assess predictability of water diffusion characteristics of 48 white matter tracts. Functional connectivity measures among DMN subregions were derived by computing the partial correlations between their neural activity fluctuations (fMRI), guided by the DMN atlas. Topographical definitions of 21 common large-scale networks were used with the network analysis tool from FSL (FSLNet) to compute partial correlations between every pair of networks.

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