

Modularity maps reveal community structure in the resting human brain

Paul J. Laurienti¹, Christina E. Hugenschmidt¹, and Satoru Hayasaka^{1,2}

Departments of Radiology¹ and Biostatistical Sciences²
Wake Forest University School of Medicine

The brain is a complex network of interconnecting neurons that combines regional specificity with distributed processing. Recent advances in the field of network theory^{1, 2} have facilitated ground-breaking analyses demonstrating that brain connectivity exhibits small-world properties³⁻⁹ similar to other self-organized networks such as the internet, the genome, or even social organizations. Brain connectivity supports local and global processing through high clustering and short connectivity paths, respectively. While these comprehensive network indices highlight the global organization of the network, the regional specificity is related to the interconnectivity of local neighborhoods within the global system. The work presented here evaluated the community structure^{10, 11} of resting human brain networks to identify the local neighborhoods and map those interconnected areas back to the brain. The study identified predictable clustering in unisensory cortices. However, the unexpected community structure in the default-mode network (DMN^{12, 13}) revealed three separate modules and included the lateral frontal cortices in addition to traditional DMN regions. These results are the first to map modularity across the entire brain without restricting analyses to predefined anatomical structures^{8, 14-16}. Such analyses provide an unbiased view of network communities and promise to provide new insights into organization of the brain. Evaluation of modular brain structure across states, during demanding tasks, or in disease populations will reveal dynamic connectivity changes in whole-brain networks.

From our social interactions to our economic transactions to our biological reactions, complex networks govern the processes that rule our lives. The theory of complex networks is a new and evolving field born from mathematics and statistical physics. The discovery of small-world networks by Watts and Strogatz¹ and the nearly simultaneous finding of scale-free networks by Barabasi and Albert² launched a field that is now being used in virtually every scientific discipline. Small-world networks have the unique property that all elements (vertices or nodes) in the network are within a few links (connections or edges) of each other but maintain high clustering between neighboring elements¹. Scale-free networks have a very small number of nodes that have an extraordinarily high number of connections (hubs) and a distribution of connections that follows a power law². The brain is a structure that exhibits regional specificity and distributed processing, and network science is ideal for analyzing a system with such an organizational structure. In the past several years investigators have begun to evaluate the structural and functional connectivity of the brain using network analysis tools^{3, 6, 8, 16-18} and have repeatedly demonstrated that the brain is a small-world network with specific regions serving as the network hubs^{6, 8, 15, 19}. Most analyses have focused on global network properties by averaging metrics across the entire network. However, the combination of regional specificity and distributed processing that occurs in the brain necessitates the evaluation of local neighborhoods, or community structure for understanding normal and abnormal function.

Community structure is particularly interesting in the brain because neighborhoods represent highly interconnected brain regions that process similar information. In this case, local community does not necessarily reflect adjacency in space, but rather refers to a high level of interconnectivity. Thus, a neighborhood could consist of 2 or more heavily connected regions that could reside in adjacent or distant locations in the brain. The community organization, or modularity, could change dynamically based on the current cognitive state of the individual. Recent studies have evaluated the modular structure of the human brain based on both functional²⁰ and structural^{8, 19} data. This work, primarily based on human brain imaging, has demonstrated that the modular organization of the network recapitulates known organizational brain properties and has identified local communities that correspond to previously described structure-function relationships within the cortex. For example, sub-divisions of visual cortex known as “what and where” pathways can be identified using modularity analyses.

However, most studies have divided the brain into 90 structural areas prior to performing the analyses. This introduces a strong bias that parceling the brain into anatomical areas assumes that the entirety of each anatomical region belongs to the same module. This need not be the case as one gyrus can have many functional subdivisions. By averaging the signal across the anatomical region, a small portion of the area that exhibits unique but important information could be averaged out. Evaluations of the brain community structure have likely not been performed using high-resolution data because computational demand grows rapidly with network size. However, higher resolution data is more likely to reveal the true community structure of the brain. The work presented here is the first demonstration of the community structure of the human brain using whole-brain analyses of human functional imaging data. Modularity maps were generated for each individual subject using single imaging voxels as nodes rather than averaging over pre-defined anatomical areas.

Identifying community structure in a network relies on finding the best partitions that break a minimal number of connections while preserving maximal connectivity within the clusters. Identification of network communities is an NP-hard problem. Fortunately, Girvan and Newman proposed the concept of modularity to optimize the community structure problem²¹. Modularity (Q) is a metric that identifies the degree to which a network division results in interconnected communities compared to the same division of a network but with random connectivity (see supplemental methods). Several algorithms that maximize modularity and balance the trade-off between computation time and accuracy²² have been developed to identify the community structure of networks. In the current work the QCut method was used¹⁰. This is a 2-step method that first minimizes the ratio of the number of broken network edges to the total number of edges in the smallest partition using a spectral partitioning method. Then the process is refined by moving individual nodes and merging clusters attempting to maximize Q.

The results presented here are from networks generated from resting functional magnetic resonance (fMRI) in six normal young adults (See supplementary methods for details). Briefly, cross-correlations analyses were performed on fMRI time-series data from each subject on a voxel-wise level with approximately 20,000 nodes. The resulting correlation matrix was then thresholded by choosing a correlation coefficient that yielded a network with an average degree of ~30. The resulting adjacency matrix was processed using the QCut method (Figure S1). The primary modules were identified manually by spatial location in the brain and were overlapped across subjects. The number of modules identified in each subject varied from 9 to 30. However, in each of the subjects there were six modules that were consistently localized to specific brain regions. Figure 1 shows the six primary modules each in a distinct color in the group modularity map and in a representative subject. In the group map, only voxels that were present in at least 3 out of the 6 six subjects for each module are shown. Note that the modules are spatially constrained as opposed to being sparsely distributed across the brain. Three of the modules replicated known structure/function findings of previous studies and were located in primary sensory cortices (see also Figure S2). Not only were the modules for each sensory modality restricted to the known cortical areas, but the community structure across subjects was highly reproducible. Thus, the module located in early visual cortex was similar across the subject population and had few nodes located outside of this cortical region.

It was not surprising that the DMN exhibited a modular structure, as the current study evaluated resting brain data. However, the DMN was split between the 3 remaining primary modules that were readily identifiable in the study population (Figure 2). One of the modules was localized to the medial frontal cortex with little extension outside of this region. Another module included the inferior, posterior aspect of the parietal lobe extending into the parahippocampal gyrus. The final module included the more superior, anterior portion of the

cuneus gyrus, bilateral inferior parietal cortex, and the bilateral middle frontal gyrus. Combined together, these 3 modules cover all areas typically included in the DMN but, also include the lateral frontal cortices, areas not typically included in this resting brain network.

The results from this study have implications that go well beyond the functional organization of the resting brain. This is the first study to our knowledge that has performed a whole brain analysis to identify community structure without biasing the results toward predefined anatomical partitions. The use of a voxel-wise analysis allows anatomical regions to be subdivided across modules and does not require that the time-series signals be averaged over large brain areas. In fact, prior modularity analyses based on anatomical parcellations did not reveal that the resting brain network is actually composed of 3 distinct modules^{8, 17, 20, 21}. This has considerable significance as there is a growing interest in alteration in the resting brain network in many neurological disorders and conditions¹², including normal aging, Alzheimer's disease, attention deficit hyperactivity disorder, and schizophrenia. For example, it has been clearly demonstrated that the DMN is altered in normal aging and that failure to suppress this network during the performance of externally mediated tasks is associated with age-related declines in performance. It has very recently been shown that community structure in the aging brain is different from that observed in young brains²³. In particular, older adults exhibit dissociation between medial frontal and parietal cortices. The findings of this study demonstrate that when the spatial resolution of the data is sufficient, community structure in young adults actually divides the DMN into multiple modules. Thus, future studies may not be focused on determining if the DMN is altered in a particular condition, but rather, which module of the DMN is altered.

The current work set the foundation for a broad range of studies ranging from cognitive and clinical neuroscience to methodological development in functional brain imaging. This initial evaluation of the community structure of the resting brain using functional MRI is intriguing in its own right, but will be much more useful when compared to maps of community structure for various cognitive tasks or states. Furthermore, the modularity observed in cognitively normal adults can serve as the reference for evaluations of modularity in individuals with neurological or psychiatric disorders. The consistency of the modular structure across subjects was evident in the data presented here. The benefit of using the network analyses presented here for performing the functional mapping is that the entire brain is considered all at once rather than focusing on a single brain region. Clearly, if one brain region is altered, it will have down-stream effects resulting potential global network changes that can only be evaluated in a multivariate framework. Regrettably the analysis tools available for performing network studies remain fairly limited, especially for community structure assessment in the brain. New mathematical frameworks are needed to identify comparable modules across subjects or populations that can account for deleted modules, merged or divided modules, or even new and unique modules. This exciting and new field of network science is ideal for application to the brain, and future use of these and yet undiscovered methodologies will help reveal the functional organization of the brain in a way that reductionistic techniques are unable to achieve.

Methods Summary

Data from 6 normal subjects were included in this analysis (1 female, average age 28.5 years old [4.5 SD]). Functional magnetic resonance imaging (fMRI) time-series were collected over 7 minutes while subjects viewed a gray fixation point on a black background. Data were preprocessed using standard algorithms in SPM5 as described in the supplemental methods. Functional connectivity analyses were performed on these denoised motion-corrected time series by calculating Pearson correlation coefficients between each voxel and all the voxels in the entire 3D brain time series resulting in a 6D correlation matrix containing approximately 480 million data points. The 6D correlation images were thresholded and converted to a binary adjacency matrix by choosing a correlation threshold for each subject which produced a network with an average node degree $K \approx 30$. This procedure yielded an undirected, unweighted graph for each subject.

The adjacency matrix for each subject was analyzed using the community detection algorithm developed by Ruan and Zhang¹⁰. The method (Qcut) identifies the optimal split of the adjacency matrix using a spectral partitioning method. Each split attempts to identify the division that minimizes the ratio of the number of broken edges to the total degree of the smallest partition. At each step the modularity (Q) is calculated and the split with the highest Q is chosen. Then vertices are moved between modules and modules are merged to determine if Q can be improved. The spectral partition step is then repeated on each subdivision to see if division of the new structure improves Q. The individual modules are then mapped back into brain space with each module being a distinct color for visualization purposes (see Supplemental Figure 1).

Acknowledgements:

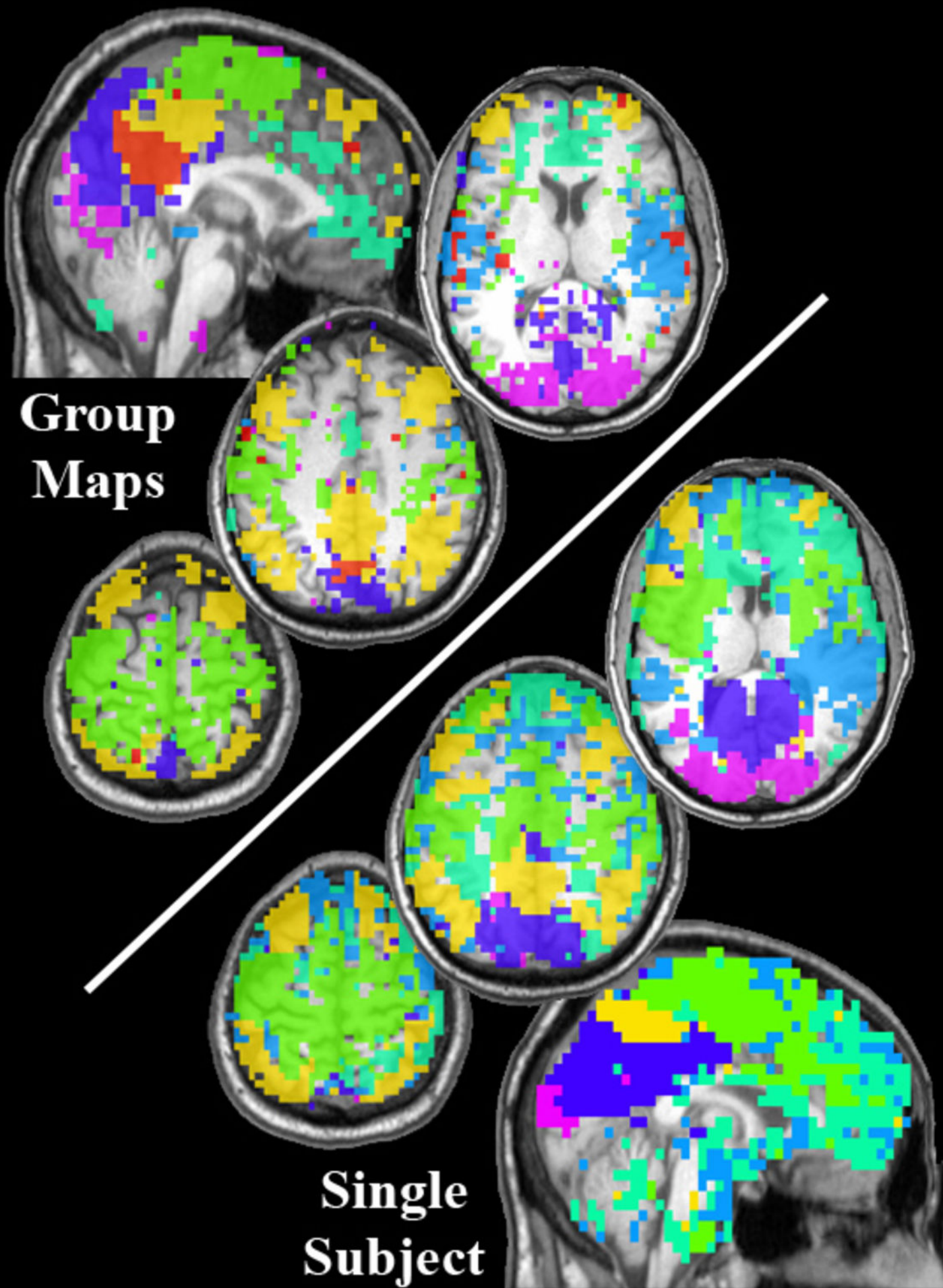
This work was funded by NIH grants NS042568 and RR07122. Additional funding was provided by the Kulynych Center for Memory and Cognition Research and the Translational Science Institute, both at Wake Forest University.

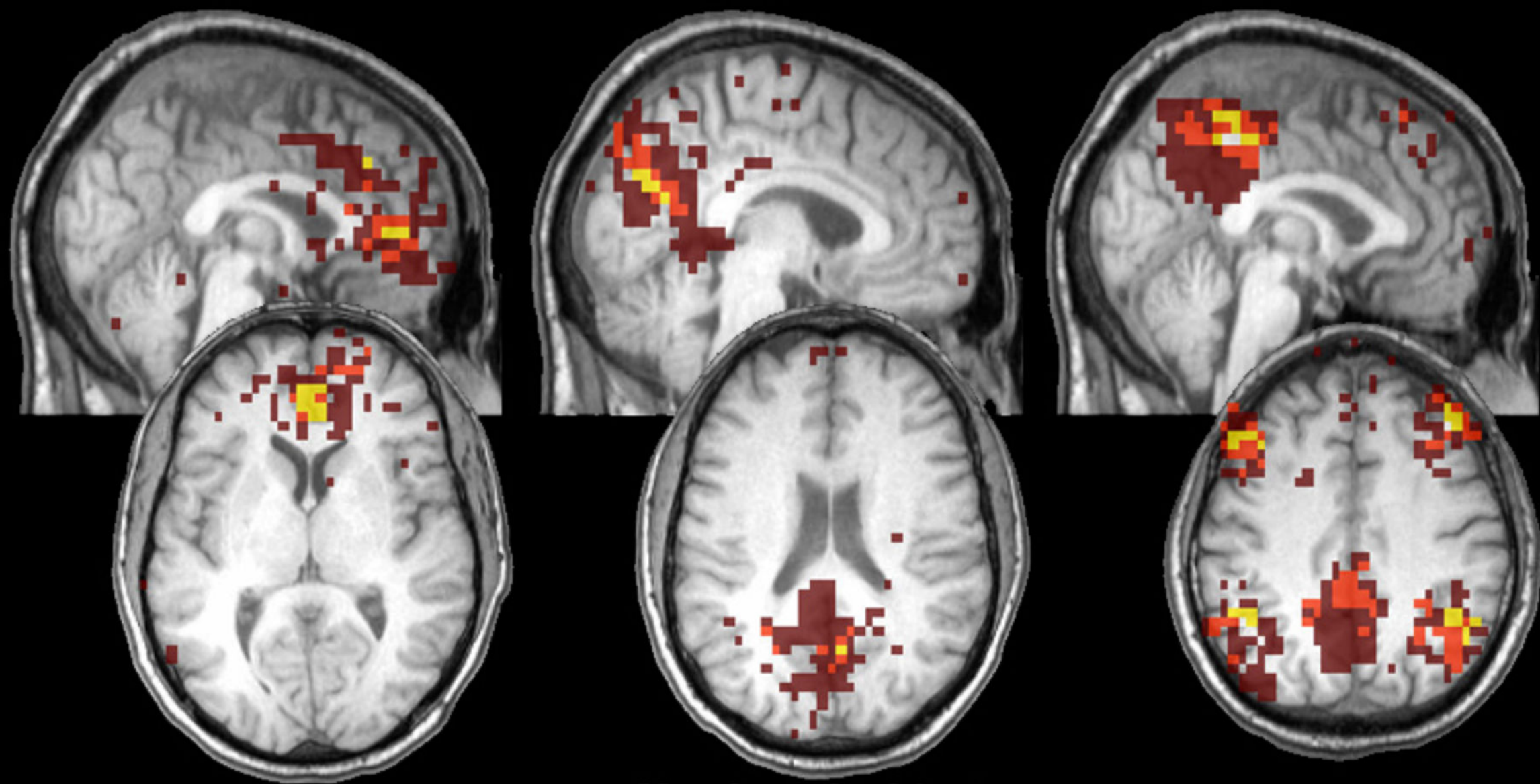
REFERENCE LIST

1. Watts, D. J. & Strogatz, S. H. Collective dynamics of 'small-world' networks. *Nature* 393, 440-2 (1998).
2. Barabasi, A. L. & Albert, R. Emergence of scaling in random networks. *Science* 286, 509-12 (1999).
3. Eguiluz, V. M., Chialvo, D. R., Cecchi, G. A., Baliki, M. & Apkarian, A. V. Scale-free brain functional networks. *Phys Rev Lett* 94, 018102 (2005).
4. Chialvo, D. R. Critical brain networks. *Physica A* 340, 756-765 (2004).
5. Hilgetag, C. C., Burns, G. A., O'Neill, M. A., Scannell, J. W. & Young, M. P. Anatomical connectivity defines the organization of clusters of cortical areas in the macaque monkey and the cat. *Philos Trans R Soc Lond B Biol Sci* 355, 91-110 (2000).
6. Achard, S., Salvador, R., Whitcher, B., Suckling, J. & Bullmore, E. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. *J Neurosci* 26, 63-72 (2006).
7. Stam, C. J. & Reijneveld, J. C. Graph theoretical analysis of complex networks in the brain. *Nonlinear Biomed Phys* 1, 3 (2007).
8. Hagmann, P. et al. Mapping the Structural Core of Human Cerebral Cortex. *PLoS Biol* 6, e159 (2008).
9. Sporns, O. & Zwi, J. D. The small world of the cerebral cortex. *Neuroinformatics* 2, 145-62 (2004).
10. Ruan, J. & Zhang, W. Identifying network communities with a high resolution. *Phys Rev E Stat Nonlin Soft Matter Phys* 77, 016104 (2008).
11. Newman, M. E. Mixing patterns in networks. *Phys Rev E Stat Nonlin Soft Matter Phys* 67, 026126 (2003).
12. Buckner, R. L., Andrews-Hanna, J. R. & Schacter, D. L. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 1124, 1-38 (2008).
13. Raichle, M. E. et al. A default mode of brain function. *Proc Natl Acad Sci U S A* 98, 676-82 (2001).
14. Ferrarini, L. et al. Hierarchical functional modularity in the resting-state human brain. *Hum Brain Mapp* (2008).
15. Sporns, O., Honey, C. J. & Kotter, R. Identification and classification of hubs in brain networks. *PLoS ONE* 2, e1049 (2007).
16. He, Y., Chen, Z. J. & Evans, A. C. Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. *Cereb Cortex* 17, 2407-19 (2007).
17. Bullmore, E. & Sporns, O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci* 10, 186-98 (2009).
18. Stam, C. J. Functional connectivity patterns of human magnetoencephalographic recordings: a 'small-world' network? *Neurosci Lett* 355, 25-8 (2004).
19. Gong, G. et al. Mapping Anatomical Connectivity Patterns of Human Cerebral Cortex Using In Vivo Diffusion Tensor Imaging Tractography. *Cereb Cortex* (2008).
20. Salvador, R. et al. Neurophysiological architecture of functional magnetic resonance images of human brain. *Cereb Cortex* 15, 1332-42 (2005).
21. Girvan, M. & Newman, M. E. Community structure in social and biological networks. *Proc Natl Acad Sci U S A* 99, 7821-6 (2002).
22. Danon, L., Diaz-Guilera, A., Duch, J. & Arenas, A. in *J Stat Mech: Theory and Experiment* (2005).
23. Meunier, D., Achard, S., Morcom, A. & Bullmore, E. Age-related changes in modular organization of human brain functional networks. *Neuroimage* 44, 715-23 (2009).

Figure 1. Modularity maps for the group (top) and a representative subject (bottom). The maps show the 6 primary modules consistently identified across the population of subjects. The group map includes voxels where the modules were present in at least 3 of the 6 subjects. The modules were located in visual cortex (light purple), bilateral auditory cortex (light blue) medial and lateral sensorimotor cortex (green), medial prefrontal cortex (turquoise), precuneus, lateral frontal and parietal (yellow), and posterior cingulate/ parahippocampal (dark blue). The red area is overlap between multiple modules. The striking finding is a clear spatial segregation of the modules that is consistent with known structure/function relationships. The individual subject map has the same color-coding as the group map.

Figure 2. DMN modules. Modularity analyses demonstrated that the DMN is comprised of 3 distinct modules. The maps show the location and spatial extent of each of the 3 modules. Each voxel is color-coded based on the number of subjects that had the particular voxel in that module. One of the modules occupies the medial prefrontal cortex (left) with minor foci outside of this region. Another module occupied the posterior portion of the medial parietal cortex/posterior cingulate extending into the parahippocampal gyrus (middle). The final module contained the precuneus and lateral parietal (right) portions of the DMN. This module also contained the lateral frontal cortices.





Number of subjects

2

6