Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Behavioral Sciences

# Precision functional mapping of human memory systems

Adrian W Gilmore[1], Steven M Nelson[2,3,4] and Kathleen B McDermott[5,6]

Precision functional MRI has enabled identification of individual-specific network configurations. A comparison of these individual-specific maps with group-average maps has yielded novel insights into network organization of memory-related brain systems. For example, the default mode network was previously thought to be comprised of three subsystems, but precision fMRI has demonstrated that one of those three subsystems may have arisen as an artifact of group averaging. Further, understanding of a second network—the parietal memory network—has been enhanced through precision fMRI. Specifically, one of the three canonical regions of this network—the posterior inferior parietal lobule—is identifiable within only about half of participants using current methods. In addition, 'network variants' have been identified, which are the existence of islands of network membership outside the typical configuration or regions that do not fall within the typical network assignment. The behavioral significance of such variants remains a topic for future consideration.

**Addresses**
[1] Laboratory of Brain and Cognition, National Institute of Mental Health, United States
[2] VISN 17 Center of Excellence for Research on Returning War Veterans, United States
[3] University of Texas at Dallas Center for Vital Longevity, United States
[4] Baylor University, Department of Psychology and Neuroscience, United States
[5] Washington University, Department of Psychological and Brain Sciences, St Louis, MO 63130, United States
[6] Department of Radiology, United States

Corresponding authors:
Gilmore, Adrian W (adrian.gilmore@nih.gov), McDermott, Kathleen B (kathleen.mcdermott@wustl.edu)

**Current Opinion in Behavioral Sciences** 2021, **40**:52–57

This review comes from a themed issue on **Deep imaging - personalized neuroscience**

Edited by **Caterina Gratton** and **Rodrigo Martin Braga**

https://doi.org/10.1016/j.cobeha.2020.12.013



## Introduction

The advent of neuroimaging enabled researchers to study brain-behavior relationships *in vivo*. With the development of fMRI, researchers gained access to improved spatial and temporal resolution over position emission tomography and could study cognitive neuroscientific questions with greater specificity. In a typical experiment, fMRI researchers collect relatively small quantities of data across a moderate number of participants; the participants are assumed to be a homogenous group, and data are analyzed via averaging across participants. This approach has proven remarkably successful, and researchers have made great strides in understanding how the functional networks of a typical brain support a multitude of cognitive processes. At the same time, group averaging prohibits meaningful explorations of individual participants' functional neuroanatomy. Hence, a limitation in the clinical and theoretical utility of much fMRI research is its inability to explore individual variability across people.

In contrast to this standard approach, there is an emerging trend to obtain large quantities of data on a small number of individual people with the goal of better capturing and characterizing individual variability. This approach has come to be known as precision fMRI (or precision functional mapping). The first such attempt was performed by Russ Poldrack, who obtained fMRI data on himself once per week for over a year [the MyConnectome project; 1,2•]. More recently, research groups at Washington University [3; https://openneuro.org/datasets/ds000224] and Harvard University [4•,5,6•] have separately obtained many hours of both task and rest fMRI data per participant to better understand the functional organization of single individuals. Analyses resulting from these datasets have already documented potential clinical implications [e.g., 7•,8–10, also discussed by Buckner and DiNicola 11] in addition to informing basic science.

The current review covers what we have learned from precision fMRI with respect to neural systems thought to support human memory. By necessity, it also focuses on the neocortex; the hippocampus is currently a glaring omission from the emerging precision functional mapping literature, despite the structure's central role in memory. Although much of the brain may very well contribute to human memory function, there are two memory-related systems that have been particularly well informed by the shift to precision fMRI: the 'default mode network' ['DMN', 12,13], which is strongly associated with vivid recall and 'mentalizing' (social cognition and theory of mind) among other processes; and the smaller and adjacent 'parietal memory network' ['PMN', 14,15], which appears important for orienting toward and recognizing

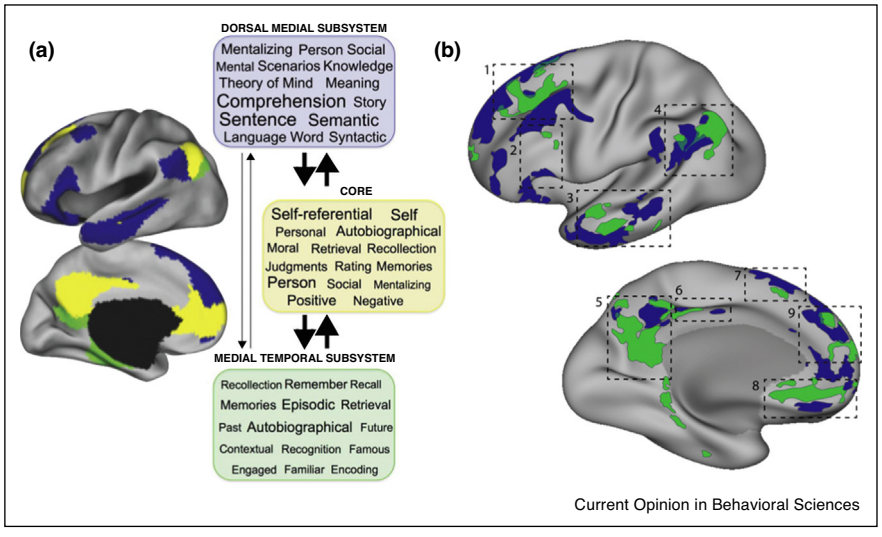
recently encountered or familiar stimuli. For both networks, precision fMRI has provided not just complementary, but also unexpected, findings based on what was known from the extant literature that is built on group-averaged data.

## Group averaging may have fundamentally mischaracterized the organization of the default mode network

The DMN was first characterized as a large and largely singular processing entity, notable because regions within it tend to deactivate (relative to resting baseline) across a range of tasks that require externally directing one's attention [e.g., 16,17]. However, researchers soon recognized functional heterogeneity within the network, and a number of fMRI studies have, since the DMN was first described, suggested it to be composed of three distinct subsystems, each consisting of multiple, distributed regions [18–21]. The two cognitive domains generally associated with the default mode network are associated with two of its putative subsystems: episodic recall is thought to be supported by the 'medial temporal lobe subsystem', which consists primarily of the parahippocampal cortex, ventral medial parietal/parietal occipital sulcus, and posterior angular gyrus (Figure 1a, green). Rather than being restricted to episodic recall, this system (which is also described separately from the default mode network using terms such as 'scene construction' [22] or 'contextual association' [23]) appears critical for any task that requires one to mentally construct a rich spatial context [for related ideas and discussion, see Ref. 24]. Mentalizing, in contrast, is associated with a 'dorsal medial' subsystem that consists of lateral and anterior temporal cortex, aspects of the posterior cingulate cortex, lateral and anterior frontal cortex, and other regions (Figure 1a, blue). These regions have been described by some as forming the 'social brain' [e.g., 25,26] and seem to provide broad access to socially relevant memory and knowledge. The 'core' subsystem (Figure 1a, yellow), anatomically interposed between the two, has been theorized to support self-referential processing as well as mediating information exchange between the two subnetworks [18].

The multifaceted nature of DMN organization and the diversity of the functions with which it has been associated might lead one to consider it a prime target for precision fMRI research. This expectation has been borne out, albeit not for a reason many would have considered likely: rather than identifying and offering novel insights into the three DMN subsystems, precision fMRI has instead led to the observation that the 'core' network is not readily identified at the individual level. In contrast, networks corresponding to the other two subsystems have been readily identified [3,4•,5,6•,28•]; these same experiments

**Figure 1**



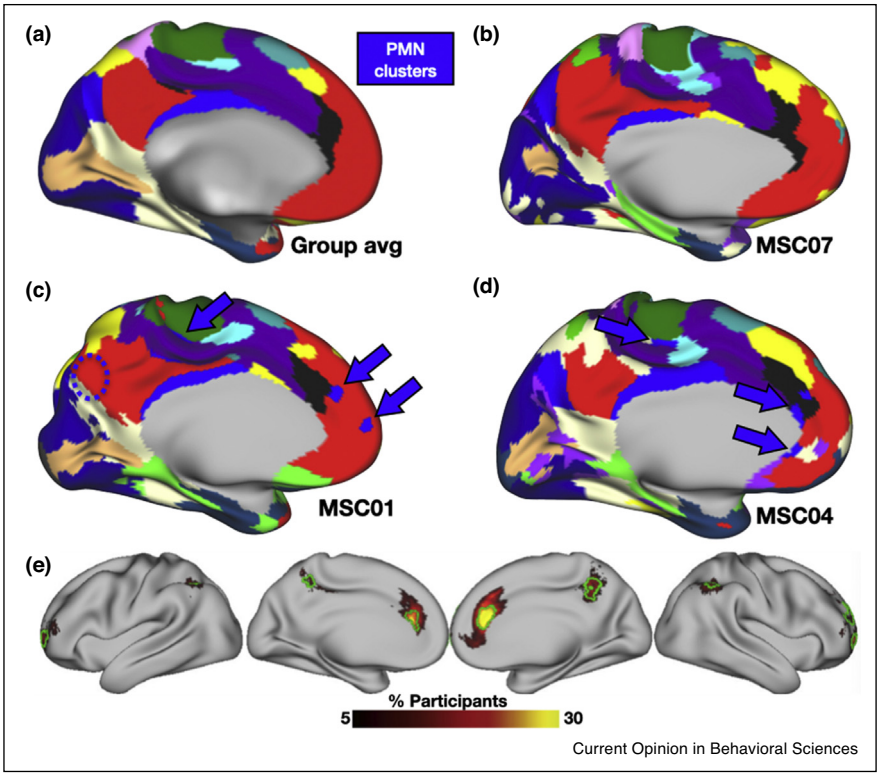

Precision functional mapping has led to a revised understanding of the organization of the DMN. **(a)** Evidence from group-based connectivity studies suggested a '3-subsystem' model of DMN organization [18,20], with the broader network comprised of a dorsal medial subsystem, a medial temporal subsystem (which sometimes described as a 'scene construction' [22] or 'contextual association' [27] network), and a 'core' subsystem acting as a central hub that also supports self-referential processing. Word clouds represent terms and concepts commonly associated with each subsystem. Figure panel adapted from Andrews-Hanna *et al.* [20]. **(b)** Studies of highly sampled individuals do not similarly observe a large, anatomically interposed 'core' [4•,5]. Rather, these studies suggest the 'core' is an artifact of averaging and across-subject variability, arising from juxtaposition and interdigitation of the other two subsystems. Numbered boxes represent regions of particularly close proximity between the two networks. Figure panel adapted from Braga and Buckner [4•].

indicated that the two observable systems were parallel, interdigitated, and variable in location across individuals (Figure 1b). Furthermore, analysis of BOLD responses during theory of mind or episodic projection/scene construction tasks revealed a within-subject functional double-dissociation [6•], as would be expected from prior characterizations of the dorsal medial and medial temporal subsystems. Recent work based on intracranial recordings has reached substantially similar conclusions [29].

Where, then, is the 'core'? It appears that, when averaging highly and idiosyncratically interdigitated networks across individuals, the resulting blurring produces a 'phantom' third network. The same blurring that gave rise to the apparent network could also produce activity profiles that could easily be interpreted as coordinating activity between the two remaining networks.

Precision fMRI has suggested that key hypotheses guiding our understanding of the organizational hierarchy of the DMN should be revised. While there will doubtless be many downstream ripples of such revision, fundamental questions may become more directly addressable, if only due to improvements in functional-anatomic mapping. One such question concerns the relation of episodic and semantic memory [30], which has re-emerged as a topic of interest [e.g., 31,32]. To what degree are these hypothetically distinct (yet related) systems truly separable? One recent source of concern has been the widespread anatomical overlap between regions associated with episodic and semantic retrieval, which appear to overlap strongly with default network regions [recently discussed by Renoult and Rugg 33]. Is such overlap also present within single individuals? By understanding the similarities and differences in their neural correlates, we can leverage knowledge about the brain to inform understanding of how episodic and semantic memory may relate to one another.

**Figure 2**




Precision functional mapping has identified network variants that are not present in group network analyses or are present in the group but not in individuals. **(a)** An average network community map generated from the Midnight Scan Club dataset. Each color represents a distinct functional network, and regions of the parietal memory network (PMN) represented in blue (color highlighted in inset box). **(b)** In some individuals, no clear PMN network variants emerge (i.e., the network structure looks much like the group average). **(c)** In other individuals, canonical network regions such as the precuneus may be missing or shifted far outside their expected locations (dotted circle). This participant also possesses variants along the paracentral lobule, dorsal anterior cingulate, and anterior medial prefrontal cortex (blue arrows). **(d)** A different individual possesses both typical midline PMN regions as well as variant locations. **(e)** An analysis of connectivity patterns in Human Connectome Project (HCP) data revealed anatomically consistent variant PMN locations in frontal, parietal, and cingulate cortex usually assigned to other networks. Heat maps represent the percentage of HCP participants with a PMN network variant in a specific location on the cortical surface, and green outlines represent centers of mass for variant clusters. Figure panels adapted from [34].

## Individuals possess network variants that involve additional, missing, and/or shifted functional regions commonly associated with memory-related networks

Precision fMRI [2•] experiments have frequently emphasized that a single individual may possesses 'islands' of a given network in locations that that do not exist at the group level [Figure 2; see also 34], echoing observations in earlier studies that focused on individual-specific functional localization [35–37]. By the same token, it has since become clear that specific regions that are present in the group (Figure 2c) may be absent within individual participants (or at least, may not observed using current approaches). Such additions and deletions have come to be known as 'network variants' [7•]; these variants are stable within individuals, and precision fMRI has revealed striking variant patterns in the PMN.

For example, it appears that only about 50% of participants possess identifiable PMN regions in the pIPL/dAG [38], which group studies have suggested as one of three primary regions that compose the network [14,39,40]. Similar results were obtained in analyses of human connectome project data [34] in a study that also identified variant locations in the dorsal anterior cingulate cortex/medial prefrontal cortex (≥30% of participants), frontopolar cortex (≥20% of participants), and adjacent to the paracentral lobule (≥15% of participants) (Figure 2e).

What is to be made of these observations? It seems reasonable to hypothesize (if one assumes that absent regions are missing, and not simply undetectable given current acquisition and analysis limitations) that information processing should be impacted in cases where participants have more or fewer regions within a network than is typical. Intriguing work in line with this possibility was recently reported by Seitzman *et al.* [7•], who examined broader behavioral associates with network variants. Using a combination of MSC and HCP data, the authors were able to cluster participants according to patterns of variation and identify small, but appreciable, links between clustered subgroups and standard measures of life-experience positivity or drug use history. A similar analysis, conducted with a more targeted focus on memory abilities, may provide insight into how the presence or absence of regions within a given network can influence an individual's encoding or retrieval abilities.

In the case of the PMN, activity in the network appears to reflect a combination of the perceived familiarity of a given stimulus (i.e., the degree to which one is aware of prior experience(s) with a person, object, etc.), as well as the salience of the familiarity signal (e.g., the degree to which it is task relevant or otherwise captures one's attention) [14,41]. Repeated presentations of a stimulus produce repetition enhancement in the PMN (in the case of the precuneus, such increases can be observed across 60 stimulus presentations under certain conditions [42]), and network activity is further amplified when one engages in explicit (as compared to incidental) item recognition [43] or when one is repeatedly tested on a particular set of stimuli [39]. One might thus imagine that individuals with variant PMN locations that fall in dorsal anterior cingulate cortex—a region commonly associated with cognitive control and attention—may show differential sensitivity relative to those without a variant in this location to manipulations involving the salience of a stimulus. On the other hand, participants who lack a PMN region in canonical locations such as the precuneus may demonstrate relatively less sensitivity to manipulations of stimulus familiarity. These possibilities, while speculative, can motivate future work that seeks to better understand both the processes behind basic memory phenomena, and the large-scale neural systems with which memory has become associated.

## Conclusion

Multiple functional networks exist that seem to be important in supporting memory function, including the DMN (which may more accurately be considered two distinct networks) and PMN. At this point, we have a broad understanding of what differentiates these networks and have data to support their role in self-referential components of remembering: mentalizing (dorsal medial system), memory strength that can be bolstered by attention mechanisms (PMN), and processing of scenes or spatial context that accompany memories from our past (medial temporal system/scene construction/contextual association network). Precision fMRI affords the opportunity to more accurately localize these networks and their subcomponents, which in the end will yield a richer understanding of the processes occurring within each region of each network and to identify these locations appropriately in each participant. Failure to do so will inevitably lead to functional accounts of these networks that miss the mark or invite additional networks to be explored that only exist in the average brain.

## Conflict of interest statement

Nothing declared.

## Acknowledgements

A. Gilmore is supported by the Intramural Research Program, National Institute of Mental Health (ZIAMH002920). K. McDermott received support from the McDonnell Center for Systems Neuroscience at Washington University in St. Louis.

## References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest

1. Poldrack RA, Laumann TO, Koyejo O, Gregory B, Hover A, Chen M-Y, Gorgolewski KJ, Luci J, Joo SJ, Boyd RL *et al.*: **Long-term neural and physiological phenotyping of a single human**. *Nat Commun* 2015, **6**:1-15.

2. • Laumann TO, Gordon EM, Adeyemo B, Snyder AZ, Joo SJ, Chen MY, Gilmore AW, McDermott KB, Nelson SM, Dosenbach NUF *et al.*: **Functional system andareal organization of a highly sampled individual human brain**. *Neuron* 2015, **87**:657-670

Analyses and data reported in this study provided the foundation for what would become 'precision fMRI'. In particular, the authors demonstrated the benefits in reliability and anatomical specificity that could be obtained from repeatedly sampling a single participant as compared to sampling typical (small) amounts of data across a larger group. This study also highlighted the existence of individual-specific variations from typical brain organization that have since become a topic of study in their own right.

3. Gordon EM, Laumann TO, Gilmore AW, Newbold DJ, Greene DJ, Berg JJ, Ortega M, Hoyt-Drazen C, Gratton C, Sun H *et al.*: **Precision functional mapping of individual human brains**. *Neuron* 2017, **95**:791-807.e797.

4. • Braga RM, Buckner RL: **Parallel interdigitated distributed networks within the individual estimated by intrinsic functional connectivity**. *Neuron* 2017, **95**:457-471

In this study, the authors used precision fMRI to demonstrate that within single participants, the DMN seems instead to consist of two adjacent ('parallel') and highly interdigitated networks. This work therefore provided early indications that the common understanding of DMN organization—based on group-averaged data—represented a distortion of the underlying neurobiology.

5. Braga RM, Van Dijk KRA, Polimeni JR, Eldaief MC, Buckner RL: **Parallel distributed networks resolved at high resolution reveal close juxtaposition of distinct regions**. *J Neurophysiol* 2019, **121**:1513-1534.

6. • DiNicola LM, Braga RM, Buckner RL: **Parallel distributed networks dissociate episodic and social functions within the individual**. *J Neurophysiol* 2020, **123**:1144-1179

One could argue that a shortcoming of precision fMRI approaches is the small sample size. A clear solution to such a criticism is replication. In this experiment, the authors begin by identifying the DMN subsystems described by Braga and Buckner [4] and then demonstrate, in three independent (but small) cohorts, that episodic and social cognition tasks are dissociable across DMN subsystems. Future precision fMRI experiments would certainly benefit a 'discovery and replication' approach to data collection and analysis.

7. • Seitzman BA, Gratton C, Laumann TO, Gordon EM, Adeyemo B, Dworetsky A, Kraus BT, Gilmore AW, Berg JJ, Ortega M *et al.*: **Trait-like variants in human functional brain networks**. *Proc Natl Acad Sci U S A* 2019, **116**:22851-22861

This study provides an excellent example of combining precision fMRI approaches with large, publicly available datasets to answer cognitive neuroscientific questions. Observations from precision fMRI were used to formulate a specific and testable hypothesis regarding individual differences in functional brain organization, which were then tested using many hundreds of participants. Without the initial precision fMRI findings, the empirical question is unlikely to be formulated, but without the larger dataset, the meaning of differences observed across participants in an $N = 9$ dataset could not be properly interpreted.

8. Greene DJ, Marek S, Gordon EM, Siegel JS, Gratton C, Laumann TO, Gilmore AW, Berg JJ, Nguyen AL, Dierker D *et al.*: **Integrative and network-specific connectivity of the basal ganglia and thalamus defined in individuals**. *Neuron* 2020, **105**:1-17.

9. Sylvester CM, Yu Q, Srivastava AB, Marek S, Zheng A, Alexopoulos D, Smyser CD, Shimony JS, Ortega M, Dierker DL *et al.*: **Individual-specific functional connectivity of the amygdala: a substrate for precision psychiatry**. *Proc Natl Acad Sci U S A* 2020, **117**:3808-3818.

10. Marek S, Siegel JS, Gordon EM, Raut RV, Gratton C, Newbold DJ, Ortega M, Laumann TO, Adeyemo B, Miller DB *et al.*: **Spatial and temporal organization of the individual human cerebellum**. *Neuron* 2018, **100**:977-993.e977.

11. Buckner RL, DiNicola LM: **The brain's default network: updated anatomy, physiology, and evolving insights**. *Nat Rev Neurosci* 2019, **20**:593-608.

12. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL: **A default mode of brain function**. *Proc Natl Acad Sci U S A* 2001, **98**:676-682.

13. Gusnard DA: **Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function**. *Proc Natl Acad Sci U S A* 2001, **98**:4259-4264.

14. Gilmore AW, Nelson SM, McDermott KB: **A parietal memory network revealed by multiple MRI methods**. *Trends Cogn Sci* 2015, **19**:534-543.

15. McDermott KB, Gilmore AW, Nelson SM, Watson JM, Ojemann JG: **The parietal memory network activates similarly for true and associative false recognition elicited via the DRM procedure**. *Cortex* 2017, **87**:96-107.

16. Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, Raichle ME, Petersen SE: **Common blood flow changes across visual tasks: II. Decreases in cerebral cortex**. *J Cogn Neurosci* 1997, **9**:648-663.

17. McKiernan KA, Kaufman JN, Kucera-Thompson J, Binder JR: **A parametric manipulation of factors affecting task-inducted deactivation in functional neuroimaging**. *J Cogn Neurosci* 2003, **15**:394-408.

18. Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL: **Functional-anatomic fractionation of the brain's default network**. *Neuron* 2010, **65**:550-562.

19. Andrews-Hanna JR: **The brain's default network and its adaptive role in internal mentation**. *Neuroscientist* 2012, **18**:251-270.

20. Andrews-Hanna JR, Smallwood J, Spreng RN: **The default network and self-generated thought: Component processes, dynamic control, and clinical relevance**. *Ann N Y Acad Sci* 2014, **1316**:29-52.

21. Yeo BTT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zollei L, Polimeni JR: **The organization of the human cerebral cortex estimated by intrinsic functional connectivity**. *J Neurophysiol* 2011, **106**:1125-1165.

22. Hassabis D, Kumaran D, Maguire EA: **Using imagination to understand the neural basis of episodic memory**. *J Neurosci* 2007, **27**:14365-14374.

23. Bar M, Aminoff E: **Cortical analysis of visual context**. *Neuron* 2003, **38**:347-358.

24. Ritchey M, Cooper RA: **Deconstructing the posterior medial episodic memory network**. *Trends Cogn Sci* 2020, **24**:451-465.

25. Adolphs R: **The neurobiology of social cognition**. *Curr Opin Neurobiol* 2001, **11**:231-239.

26. Adolphs R: **The social brain: neural basis of social knowledge**. *Ann Rev Psychol* 2009, **60**:693-716.

27. Bar M: **A cortical mechanism for triggering top-down facilitation in visual object recognition**. *J Cogn Neurosci* 2003, **15**:600-609.

28. • Gordon EM, Laumann TO, Marek S, Raut RV, Gratton C, Newbold DJ, Greene DJ, Coalson RS, Snyder AZ, Schlaggar BL *et al.*: **Default-mode network streams for coupling to language and control systems**. *Proc Natl Acad Sci U S A* 2020, **117**:17308-17319

In this study, the authors focused on the functional connectivity of regions across the DMN using a precision fMRI approach to data collection and analysis. They found that distinct aspects of the DMN could be associated with social cognition and reconstructive memory—consistent with other work discussed in this report—but also linked smaller DMN "subsystems" with processes that included reward or language processing. This represents a proof of principle in the use of precision fMRI to improve the understanding of—and delineation of—distinct networks or subnetworks and the cognitive processes they support.

29. Woolnough O, Rollo PS, Forseth KJ, Kadipasaoglu CM, Ekstrom AD, Tandon N: **Category selectivity for face and scene recognition in human medial parietal cortex**. *Curr Biol* 2020, **30**:2707-2715.e2703.

30. Tulving E: **Episodic and semantic memory**. In *Organization of Memory.* Edited by Tulving E, Donaldson W. Academic Press; 1972:381-402.

31. Renoult L, Irish M, Moscovitch M, Rugg MD: **From knowing to remembering: the semantic–episodic distinction**. *Trends Cogn Sci* 2019, **23**:1041-1057.

32. Irish M: **On the interaction between episodic and semantic representations–constructing a unified account of imagination**. In *The Cambridge Handbook of Imagination.* Edited by Abraham A. Cambridge University Press; 2019.

33. Renoult L, Rugg MD: **An historical perspective on Endel Tulving's episodic-semantic distinction**. *Neuropsychologia* 2020, **139**:107366.

34. Gordon EM, Laumann TO, Adeyemo B, Gilmore AW, Nelson SM, Dosenbach NUF, Petersen SE: **Individual-specific features of brain systems identified with resting state functional correlations**. *NeuroImage* 2017, **146**:918-939.

35. Fedorenko E, Duncan J, Kanwisher N: **Language-selective and domain-general regions lie side by side within Broca's area**. *Curr Biol* 2012, **22**:2059-2062.

36. Kanwisher N: **Functional specificity in the human brain: a window into the functional architecture of the mind**. *Proc Natl Acad Sci U S A* 2010, **107**:11163-11170.

37. Moeller S, Freiwald WA, Tsao DY: **Patches with links: a unified system for processing faces in the macaque temporal lobe**. *Science* 2008, **320**:1355-1359.

38. Gilmore AW, Nelson SM, Laumann TO, Gordon EM, Berg JJ, Greene DJ, Gratton C, Nguyen AL, Ortega M, Coalson RS *et al.*: **High-fidelity mapping of repetition-related changes in the parietal memory network**. *NeuroImage* 2019, **199**:427-439.

39. Nelson SM, Arnold KM, Gilmore AW, McDermott KB: **Neural signatures of test-potentiated learning in parietal cortex**. *J Neurosci* 2013, **33**:11754-11762.

40. Nelson SM, McDermott KB, Wig GS, Schlaggar BL, Petersen SE: **The critical roles of localization and physiology for understanding parietal contributions to memory retrieval**. *Neuroscientist* 2013, **19**:578-591.

41. Rosen ML, Stern CE, Devaney KJ, Somers DC: **Cortical and subcortical cotributions to long-term memory-guided visuospatial attention**. *Cereb Cortex* 2018, **28**:2935-2947.

42. Brodt S, Pöhlchen D, Flanagin VL, Glasauer S, Gais S, Schönauer M: **Rapid and independent memory formation in the parietal cortex**. *Proc Natl Acad Sci U S A* 2016, **113**:13251-13256.

43. Gilmore AW, Kalinowski SE, Milleville SC, Gotts SJ, Martin A: **Identifying task-general effects of stimulus familiarity in the parietal memory network**. *Neuropsychologia* 2019, **124**:31-43.