Functional MRI Studies of Memory in Aging, Mild Cognitive Impairment, and Alzheimer's Disease

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Abbreviations

AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
APOE	Apolipoprotein E
ASL	Arterial spin labeling
BA	Brodmann's area
BOLD	Blood oxygen level dependent
CRUNCH	Compensation-related utilization of neural circuits hypothesis
DLPFC	Dorsolateral prefrontal cortex
DMN	Default-mode network
DPC	Dorsal parietal cortex
DTI	Diffusion tensor imaging
EEG	Electroencephalogram
FEF	Frontal eye fields
fMRI	Functional magnetic resonance imaging
HAROLD	Hemispheric asymmetry reduction in old adults
HDR	Hemodynamic response
HERA	Hemispheric encoding and retrieval asymmetry
HIPER	Hippocampal encoding/retrieval model
ICA	Independent component analysis
MCI	Mild cognitive impairment
mPFC	Medial prefrontal cortex
MTL	Medial temporal lobe
PASA	Posterior-anterior shift in aging
PET	Positron emission tomography
PFC	Prefrontal cortex
ROI	Regions of interest
SCD	Subjective cognitive decline
SFS	Superior frontal sulcus
SMA	Supplementary motor area
VLPFC	Ventrolateral prefrontal cortex
VPC	Ventral parietal cortex

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Introduction

In the human brain, functionally and anatomically defined systems exist for encoding, consolidating, and retrieving memories of experiences (episodic memory); accumulating and accessing factual information in a body of knowledge (semantic memory); and actively processing and manipulating information (working memory). These three memory systems can be distinguished behaviorally and neurobiologically from other nondeclarative memory systems such as procedural learning and priming [1–4]. Brain-behavior studies using a variety of approaches from lesion-based research to functional MRI (fMRI) demonstrate distinct though highly interrelated neural circuitry for episodic, semantic, and working memory [3, 5]. Each of these memory systems, despite their close interaction, is affected somewhat differently by aging and dementia.

In this chapter, the episodic, semantic, and working memory systems are each considered in turn, with special attention to changes associated with aging and with age-related memory disorders such as Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) [6], and Subjective

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Cognitive Decline (SCD) [7]. The first section explores the neuroanatomical substrates of episodic memory, as characterized by fMRI studies in healthy young adults. Next, we discuss fMRI studies of the changes in episodic memory that occur with healthy aging and in the prodromal stages of MCI and AD. Resting-state fMRI connectivity studies of episodic memory circuitry are also covered. In the final portion of the episodic memory section, we highlight studies in which fMRI probes of episodic memory have been used as biomarkers of prodromal and preclinical changes in memory and after pharmacological intervention. In the second section of this chapter, we discuss fMRI studies of semantic memory in healthy young adults, aging, and in patients with MCI and AD. In the third section, we review fMRI studies of working memory in healthy young adults, older adults, and patients with MCI and AD. We also discuss functional and resting-state connectivity studies of working memory and use of working memory fMRI studies as biomarkers. Next, we briefly cover some of the methodological considerations that are important for using fMRI techniques, particularly in older adults and patients with MCI and AD. Finally, we discuss future directions in fMRI research, including the potential for combining fMRI with other multi-modal imaging techniques, as well as some novel fMRI task paradigms to tap memory functioning across the continuum of AD. For selected reviews of fMRI studies in each of these memory systems, see Tables 30.2, 30.3, 30.4, and 30.5.

Episodic Memory

Episodic memory refers to memory for events or information encoded with respect to a particular temporal or spatial context [4]. Originally defined to encompass memory for specific information presented for example during a testing session, the concept has been reformulated over the years to have at its core the conscious recollection of previous experiences. The emphasis is on memory for experience itself, rather than knowledge about the world not tied to its context of acquisition [8]. Episodic memory can be broadly defined as three separate processes: encoding, consolidation, and retrieval. Episodic encoding and retrieval processes can be studied using fMRI, due to the limited and definable nature of the response time-course. In other words, neural responses associated with episodic encoding occur upon presentation of stimulus to be encoded, while responses associated with episodic retrieval occur upon request for recall or recognition of previously encoded information. By contrast, memory consolidation, the process that stabilizes newly formed memory traces, is less easily studied due to the fact that its exact temporal occurrence and length remain ill-defined and could vary from minutes to weeks or years after learning [9]. Other important distinctions pertaining to episodic memory function include the success with which the processes are performed (i.e., whether they result in the formation of an accurate, inaccurate, or no memory trace); the sensory modality in which the information is received (e.g., auditory, visual, olfactory, tactile, gustatory, etc.), and the nature of the material (e.g., verbal, spatial, pictorial, experiential). There are a variety of episodic memory fMRI probes, many of which are specifically designed to address or manipulate certain of these aspects of episodic memory processing; sample tasks for episodic encoding and retrieval are shown in Table 30.1a.

fMRI Studies of Episodic Memory

Both episodic encoding and retrieval processes are thought to be subserved by a similar broad network of brain regions, including the prefrontal cortex (PFC), medial temporal lobe (MTL), and parietal and temporal cortices. This similarity is not too surprising according to the "cortical reinstatement hypothesis," which posits that the neural substrates of episodic retrieval should reflect reinstatement of processes or representations active during encoding [17]. A detailed review of the literature on episodic memory and its neural bases outside of fMRI studies is beyond the scope of the present chapter, and the reader is referred to several review articles that address this topic in detail (Table 30.2).

fMRI of Episodic Encoding: The Role of the PFC

Episodic encoding studies have identified primarily left PFC, especially ventrolateral PFC (VLPFC), activations during verbal encoding tasks (novel words vs. previously presented material, association encoding of word pairs, encoding of words vs. control conditions) [10, 51–53], while nonverbal encoding tasks (similar task paradigms with encoding of objects, faces, patterns, and spatial information) show activation of the bilateral PFC [10, 51, 53–57] (Fig. 30.1). The lateralization by content type is confirmed in direct comparisons of encoding of verbal and nonverbal stimuli, with greater activation of the left PFC during word encoding relative to scene, pattern, and texture encoding [51, 53] and greater activation of the right PFC during texture encoding relative to word encoding [53]. The putative function of left VLPFC in episodic memory encoding is to support retrieval of stored knowledge from semantic memory and goal-directed selection amongst multiple semantic representations [58–61]. The left-lateralized nature of the signal associated with episodic encoding of verbal or easily verbalized material suggests an underlying association with semantic working memory sys-

Table 30.1 Sample fMRI task characteristics for episodic, semantic, and working memory

Study	Memory domain	Modality	Design	Stimuli	Control condition	Performance monitoring
(A) Episodic memory						
Kelly et al. (1998) [10]	Episodic encoding	Visual	Block	Verbal (words) and Object (line drawings)	Fixation	Recognition after scan
Wagner et al. (1998) [11]	Episodic retrieval	Visual	Block	Verbal (words)	Reading	Part of task
Hill et al. (2021) [12]	Episodic association	Visual	Event-Related	Verbal (words) paired with images (faces or scenes)	Fixation	Part of task
(B) Semantic memory						
Saykin et al. (1999) [13]	Semantic: category matching	Auditory	Block	Word pairs: category-example and category-function pairs	Nonword matching	Part of task
Martin et al. (2022) [14]	Semantic fluency	Visual	Block	Overt word generation category-examples	Oral counting	Part of task
(C) Working memory						
Rypma and D'Esposito (2000) [15]	Working: delayed response	Visual	Event-Related	Series of targets (letters, or objects and locations) encoded and retained over an unfilled interval; after interval participants respond whether target was part of retained sequence		Part of task
Wishart et al. (2006) [16]	Working: constant monitoring	Auditory (or Visual)	Block	"*N*-back" task: target letters are presented in sequence; participant must respond when a target letter is the same as a target letter either 1-back, 2-back, or 3-back in sequence		Part of task

Table 30.2 Selected review articles and meta-analyses of episodic memory for further reading

Episodic memory		
Authors	Study subjects	Article title
Fletcher et al. (1997) [18]	Young adults	The functional neuroanatomy of episodic memory. *Trends Neurosci.* May 1997;20(5):213–218.
Desgranges et al. (1998) [19]	Young adults	The functional neuroanatomy of episodic memory: The role of the frontal lobes, the hippocampal formation, and other areas. *NeuroImage.* 1998;8:198–213.
Lepage et al. (1998) [20]	Young adults	Hippocampal PET activations of memory encoding and retrieval: The HIPER model. *Hippocampus.* 1998;8:313–322.
Schacter et al. (1999) [21]	Young adults	Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus.* 1999;9(1):7–24.
Wagner et al. (1999) [22]	Young adults	When encoding yields remembering: insights from event-related neuroimaging. *Philosophical Transactions of the Royal Society of London—Series B: Biological Sciences.* 1999;354(1387):1307–1324.
Cabeza et al. (2000) [23]	Young adults	Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience.* 2000;12(1):1–47.
Grady et al. (2000) [24]	Healthy aging	Changes in memory processing with age. *Current Opinion in Neurobiology.* 2000;10:224–231.
Langley et al. (2000) [25]	Healthy aging	Functional neuroimaging of memory: implications for cognitive aging. *Microsc Res Tech.* Oct 1 2000;51(1):75–84.
Wagner (2000) [26]	MCI and AD	Early detection of Alzheimer's disease: An fMRI marker for people at risk? *Nature Neuroscience.* 2000;3(10):973–974.
Cabeza (2001) [27]	Healthy aging	Cognitive neuroscience of aging: contributions of functional neuroimaging. *Scand J Psychol.* Jul 2001;42(3):277–286.
Cabeza (2002) [28]	Healthy aging	Hemispheric asymmetry reduction in old adults: The HAROLD model. *Psychol. Aging.* 2002;17:85–100.
Cabeza et al. (2002) [29]	Healthy aging	Aging gracefully: Compensatory brain activity in high-performing older adults. *NeuroImage.* 2002;17:1394–1402.
Zakzanis et al. (2003) [30]	MCI and AD	A meta-analysis of structural and functional brain imaging in dementia of the Alzheimer's type: a neuroimaging profile. *Neuropsychol Rev.* Mar 2003;13(1):1–18.
Hedden et al. (2005) [31]	Healthy aging	Healthy and pathological processes in adult development: new evidence from neuroimaging of the aging brain. *Curr Opin Neurol.* Dec 2005; 18(6):740–747.
Rajah et al. (2005) [32]	Healthy aging	Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory. *Brain.* Sep 2005;128(Pt 9):1964–1983.

(continued)

Table 30.2 (continued)

Episodic memory		
Authors	Study subjects	Article title
Davachi (2006) [33]	Young adults	Item, context and relational episodic encoding in humans. *Curr Opin Neurobiol.* Dec 2006; 16(6):693–700.
Eichenbaum et al. (2007) [34]	Young adults	The medial temporal lobe and recognition memory. *Annu Rev Neurosci.* 2007;30:123–152.
Wierenga et al. (2007) [35]	MCI and AD	Use of functional magnetic resonance imaging in the early identification of Alzheimer's disease. *Neuropsychol Rev.* Jun 2007;17(2):127–143.
Vilberg et al. (2008) [36]	Young adults	Memory retrieval and the parietal cortex: a review of evidence from a dual-process perspective. *Neuropsychologia.* 2008;46(7):1787–1799.
Grady (2008) [37]	Healthy aging	Cognitive neuroscience of aging. *Ann N Y Acad Sci.* Mar 2008;1124:127–144.
Dickerson et al. (2008) [38]	MCI and AD	Functional abnormalities of the medial temporal lobe memory system in mild cognitive impairment and Alzheimer's disease: insights from functional MRI studies. *Neuropsychologia.* 2008;46(6):1624–1635.
Drzezga (2008) [39]	MCI and AD	Concept of functional imaging of memory decline in Alzheimer's disease. *Methods.* Apr 2008; 44(4):304–314.
Ries et al. (2008) [40]	MCI and AD	Magnetic resonance imaging characterization of brain structure and function in mild cognitive impairment: a review. *J Am Geriatr Soc.* May 2008;56(5):920–934.
Spaniol et al. (2009) [41]	Young adults	Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. *Neuropsychologia.* Jul 2009;47(8–9):1765–1779.
Han et al. (2009) [42]	MCI and AD	Functional magnetic resonance imaging of compensatory neural recruitment in aging and risk for Alzheimer's disease: review and recommendations. *Dement Geriatr Cogn Disord.* 2009;27(1):1–10.
Dickerson et al. (2009) [43]	MCI and AD	Large-scale functional brain network abnormalities in Alzheimer's disease: insights from functional neuroimaging. *Behav Neurol.* 2009;21(1):63–75.
Kim (2010) [44]	Young adults	Dissociating the roles of the default-mode, dorsal, and ventral networks in episodic memory retrieval. *Neuroimage.* May 1 2010;50(4):1648–1657.
Sperling et al. (2010) [45]	MCI and AD	Functional alterations in memory networks in early Alzheimer's disease. *Neuromolecular Med.* Mar 2010;12(1):27–43.
Kim (2011) [46]	Young adults	Neural activity that predicts subsequent memory and forgetting: A meta-analysis of 74 fMRI studies. *Neuroimage*. 2011;54(3):2446–61.
Cabeza et al. (2012) [47]	Young adults	Cognitive contributions of the ventral parietal cortex: an integrative theoretical account. *Trends Cogn Sci*. 2012;16(6):338–52.
Rugg et al. (2013) [48]	Young adults	Brain networks underlying episodic memory retrieval. *Curr Opin Neurobiol*. 2013;23(2):255–60.
Moscovitch et al. (2016) [49]	Young adults	Episodic Memory and Beyond: The Hippocampus and Neocortex in Transformation. *Annu Rev Psychol*. 2016;67(1):105–34.
Yu et al. (2021) [50]	MCI and AD	The human connectome in Alzheimer disease—relationship to biomarkers and genetics. *Nat Rev Neurol*, 2021. 17(9): p. 545–563.

tems in Broca's area (BA45) [62, 63]. This theory is supported by a study by Otten and Rugg [64] which found that words encoded with semantic associations show significantly greater activation in the left PFC than those encoded with phonological associations [64].

While the VLPFC contributes to long-term memory through the maintenance, retrieval, and selection of information, the dorsolateral PFC (DLPFC) enhances memory via its capability to manipulate and organize multiple pieces of information in working memory [65]. Indeed, Blumenfeld et al. [66] demonstrated that DLPFC helped form relationships among items to support associative memory, but did not promote memory for item-specific information. The distinction between the roles of VLPFC and DLPFC in memory encoding also fits well with the generic "what/how" axis specified by a generic model of PFC organization, proposing that VLPFC determines what features should be processed/extracted depending on the ongoing goals, whereas DLPFC determines how operations should be carried on given execution rules [67].

fMRI of Episodic Encoding: The Role of the MTL

The role of the MTL in episodic memory has been well-established from lesion cases (e.g., the famous patient H.M. who had bilateral MTL surgical excisions for the treatment of medically refractory epilepsy [68]) and numerous fMRI studies of episodic encoding [20, 21, 27, 54, 55, 69–74]. The MTL is defined by a circuit of regions, including the hippocampal formation (dentate gyrus, CA1, CA2 and CA3 fields, and subiculum), entorhinal cortex, perirhinal cortex, parahippocampal complex, and the amygdala [19, 23, 75, 76]. Activation of the hippocampus is especially sensitive to

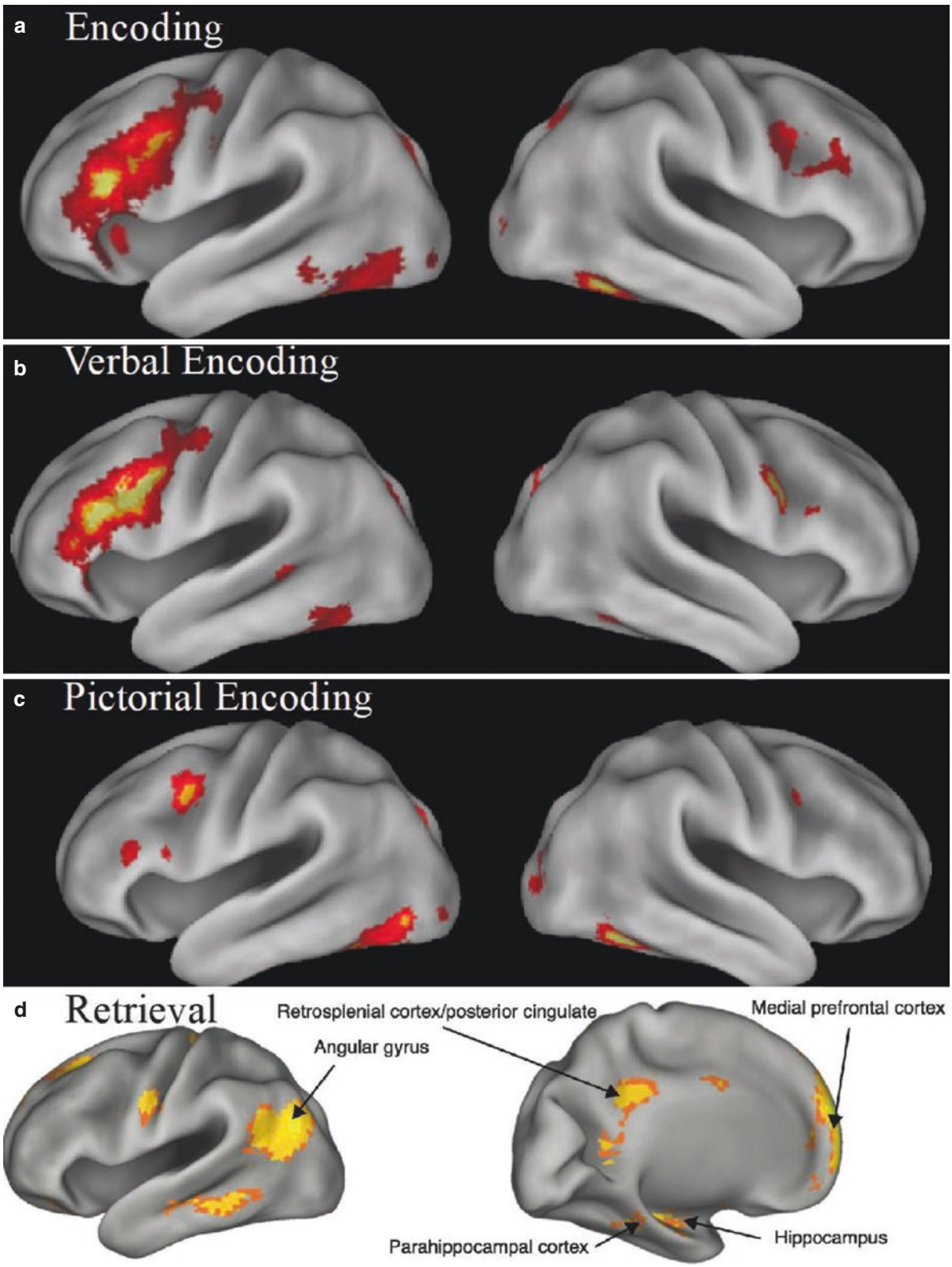

Fig. 30.1 Brain regions showing activation during episodic encoding and retrieval. A broad pattern of regions including the bilateral prefrontal cortex (PFC; BA47) and medial temporal lobe (MTL) were activated to support successful episodic encoding, according to a recent meta-analysis of 74 fMRI studies (**a**). The meta-analysis also showed that verbal items (**b**) preferentially engage left PFC compared with pictorial (**c**) items (adopted from Kim 2011 [29]). The putative episodic memory retrieval network (**d**) partially overlaps with the midline structures of the "default mode network," such as the mPFC and retrosplenial cortex/posterior cingulate. The MTL (hippocampus and parahippocampus) and parietal cortex (angular gyrus) also serve memory retrieval. (Reproduced with permission from Rugg and Vilberg 2013 [31])

novel information, with repetition suppression or decreasing activation associated with repeated exposure to a stimulus [55, 74, 77]. Similar to activations in the PFC, episodic encoding activations in the MTL show content-based or material-specific laterality [78]. Episodic encoding of verbal material shows activation in the left MTL [10, 77, 79], whereas encoding of nonverbal material typically leads to bilateral MTL activation [10, 55, 73, 74, 80]. Furthermore, earlier studies have shown that MTL activation is associated with successful memory formation [22, 54, 79], presumably through binding different aspects of an event into a durable memory representation [29, 81]. By synthesizing previous theoretical accounts and modern evidence from fMRI multivoxel pattern analysis, an overarching framework of hippocampal organization has been proposed. This framework suggests that the hippocampus functions as a general hub for associative information (e.g., face-name pairing), temporal sequences (a series of events intrinsic to episodic memory), and hierarchy of schematic concepts (e.g., factual knowledge related to semantic memory, for more discussion see the Semantic Memory section), thus unifying other seemingly divergent views about the role of hippocampus in cognitive maps and spatial navigation [82].

fMRI Studies of Episodic Retrieval

Episodic retrieval has also been shown to involve many of the same brain regions as those activated by episodic encoding, including the PFC, MTL, and temporal and parietal cortices. Episodic retrieval paradigms typically test verbal or nonverbal information retrieval, in the forms of free/cued recall and recognition (e.g., [83]). A special distinction between recollection and familiarity is usually drawn for recognition memory, with recollection or "remembering" referring to the detailed retrieval of a previously experienced event and familiarity or "knowing" referring to the personal feeling that the event occurred but the details could not be memorized at the moment [31]. Although alternate models have been proposed [84–86], there is evidence that these two types of recognition reflect qualitatively distinct processes with different yet overlapping contributions from MTL and parietal cortex [31, 32].

fMRI Studies of Episodic Retrieval: The Role of the PFC

Verbal and nonverbal episodic retrieval tasks demonstrate significant activation in the right and/or bilateral PFC, including regions of the posterior ventrolateral (BA45/47), frontopolar (BA10), and dorsal PFC (BA8/9) [11, 53, 87, 88]. The predominately right-lateralized nature of this response, relative to the previously discussed left-lateralized PFC responses during episodic encoding, led to the development of a general theory called the "hemispheric encoding and retrieval asymmetry" (HERA) model [59, 89, 90]. Specifically, the HERA model posits that left PFC regions are involved primarily in retrieval from semantic memory and encoding into episodic memory, whereas right PFC regions are involved in the retrieval of information from episodic memory [23, 90–92]. Although initially proposed in response to functional PET imaging studies, results supporting the HERA model have repeatedly been observed in studies using fMRI [10, 27, 53, 70, 93–96].

The medial PFC (mPFC) and the posterior cingulate cortex along the midline are part of the resting-state/default-mode network (DMN, [97]), that is typically activated during rest conditions and deactivated upon tasks [69, 98, 99]. The activation of DMN regions at encoding is predictive of subsequent forgetting [29, 100]. On the other hand, other research (e.g., [101]) has demonstrated overlaps between encoding failure and retrieval success activity within these DMN midline areas. The discrepancy between memory encoding and retrieval could be explained by a common self-referential processing occurring in the midline brain regions (including mPFC): at encoding it reflects mind-wandering or momentary lapse of attention to external learning items, which could lead to encoding impairment; at retrieval it indicates active search through one's internal memory storage. Finally, research also suggests a special yet unclear role of mPFC in remote (vs. recent) memories [102].

fMRI Studies of Episodic Retrieval: The Role of the MTL

The MTL, including the hippocampus, parahippocampal, entorhinal, and perirhinal cortex, has also been implicated in episodic retrieval [25, 69, 103, 104]. Studies using fMRI have identified bilateral hippocampal activations during episodic retrieval, with retrieval of verbal information primarily showing left hippocampal activation and nonverbal retrieval demonstrating right-lateralized or bilateral hippocampal activations [21, 27, 55, 86, 93, 105–107]. This asymmetry is superimposed on a historical, lesion-based, material-specificity model [108] which posits a left MTL specialization for verbal memory and a right MTL specialization for nonverbal material that is not readily verbally coded. Early brain insults also appear to moderate this model [109–111].

Additional fMRI studies of episodic encoding have also attempted to parse whether topographic sub-divisions within the MTL mediate separate episodic memory functions. Initial studies of hippocampal activation in episodic memory using functional PET imaging techniques suggested a rostrocaudal gradient of hippocampal activity during episodic encoding and retrieval [20]. Although some event-related fMRI studies have been supportive of this hippocampal encoding/retrieval (HIPER) model [112], other studies have suggested a more nuanced pattern of findings regarding hippocampal organization for episodic memory processes [21, 69]. A more recent model regarding the topographic organization of hippocampus along the long axis in humans proposes that the posterior hippocampus processes specific associative information, whereas the anterior represents generalized contextual features of memories [113].

The neural correlates of two types of recognition memory, that is, recollection and familiarity, is partially mediated by MTL regions, such as the parahippocampus, which forms the "where" stream and supports recollection through the encoding of contextual or relational information [25], and the perirhinal cortex, which forms the "what" stream and is specifically activated during the encoding of memories for specific learned items [71, 72, 114] producing the experience of familiarity. The two streams converge in the hippocampus to represent items embedded in the internal and/or external context where they were initially experienced [25].

fMRI Studies of Episodic Retrieval: The Role of the Parietal Cortex

Similar to MTL and prefrontal regions, the parietal cortex can also be further divided into at least two sub-regions by the intra-parietal sulcus: the dorsal parietal cortex (DPC) and ventral parietal cortex (VPC, which includes the supramarginal gyrus and angular gyrus) [30]. The DPC shows greater activation for "familiar" or "new" items relative to "old" items during episodic retrieval [115, 116]. However, the signal is unaffected by modality or task difficulty. Therefore, the bilateral superior parietal regions are thought to be involved in attentional processing and focus on behaviorally relevant stimuli rather than playing a specific role in episodic memory [26, 117]. Activation in the VPC has been posited to reflect sensory and perceptual information associated with recollection [118, 119], because the VPC shows specific association with successful recollection and greater activation to "remembered" relative to "known" items [86, 107]. Likewise, the VPC also supports source monitoring and high-confidence responses during recognition memory [120]. Regardless of the different theoretical accounts that have been given to interpret the function of the VPC, such as attentional reorientation and episodic buffer [30], the VPC seems more related to subjective experience of retrieval or metacognition but not memory accuracy per se [31].

fMRI Studies to Identify the Neural Correlates of the Component Processes of Episodic Retrieval

To evaluate the roles of specific regions showing activation in retrieval studies, a number of studies have attempted to parse out the elements of episodic retrieval. Retrieval of episodic information can be broadly divided into three general stages, including (1) preparation and attention to the task requests and probes (i.e., "retrieval preparation"); (2) search and accuracy monitoring of retrieved information ("retrieval mode"); and (3) successful recollection of content or context ("retrieval success"). These separate steps appear to be neurally represented in overlapping and distributed anatomic locations. Using high temporal resolution task paradigms, such as jittering of probes and null trials, the bilateral frontopolar regions have been shown to mediate the "retrieval preparation" [121–124]. Specifically, a study by Dobbins and Han [121] used variable delays between task initiation and presentation of the target recognition probe to demonstrate that right frontopolar activation occurred prior to presentation of the delayed probes [121]. Frontopolar regions, along with the dorsal PFC, have also been implicated in "retrieval mode" functions [57, 125]. A number of reports suggest that the left frontopolar and bilateral dorsal PFC are activated regardless of the type of retrieval task (item/content retrieval vs. contextual retrieval) or the content of the retrieved information (verbal or nonverbal) [126, 127]. Furthermore, this activation has a sustained and tonic pattern of response during retrieval blocks, suggesting involvement in the general process of episodic retrieval instead of activation in response to specific retrieval probes [125, 127]. Finally, "retrieval success" has been primarily linked to activation of the MTL, suggesting this region is important for the recall of specific items and contextual information associated with successful retrieval [128]. Alternatively, a simpler two-stage model has been proposed that characterizes hippocampus-mediated rapid unconscious and obligatory retrieval, as well as a slower conscious experience of a memory episode, presumably subserved by VPC and controlled by prefrontal regions [32].

Age-Related Changes in Episodic Memory

A large body of literature suggests that episodic memory processes, particularly encoding and retrieval, decline with age [33, 129–133]. Whether this is related to "normal aging" of the brain or to an accumulation of age-related diseases remains a topic of debate [134–136]. There is some evidence to suggest relatively selective age-related atrophy of prefrontal cortical areas is involved in episodic memory circuitry [137], with preservation of MTL structures [137–139], though this too is debatable [140–142].

Much of the research on normal cognitive aging preceded the development of amyloid and tau PET and other biomarkers that can identify and quantitate specific in vivo brain pathophysiology prior to onset of MCI or dementia. Furthermore, regenerative processes and reorganization in the adult human brain may help allay development of cognitive problems despite structural brain changes [143, 144]. Therefore, significant questions remain as to the neural and cognitive basis of episodic memory decline in aging, especially independent of accumulated pathophysiological changes. For reviews of episodic memory processes in aging see Table 30.2.

fMRI Studies of Episodic Encoding and Retrieval in Normal Aging

A number of functional neuroimaging, electrophysiological, and behavioral studies suggest that the typical prefrontal functional asymmetries for memory processes in younger adults are diminished or absent in older adults. Healthy older adults demonstrate reduced left PFC activation and increased right PFC activation during intentional and incidental encoding [36, 37, 145] (Fig. 30.2). Additionally, older adults show diminished right PFC activation and enhanced left PFC activation in episodic retrieval [36, 37, 145, 147–151]. In other

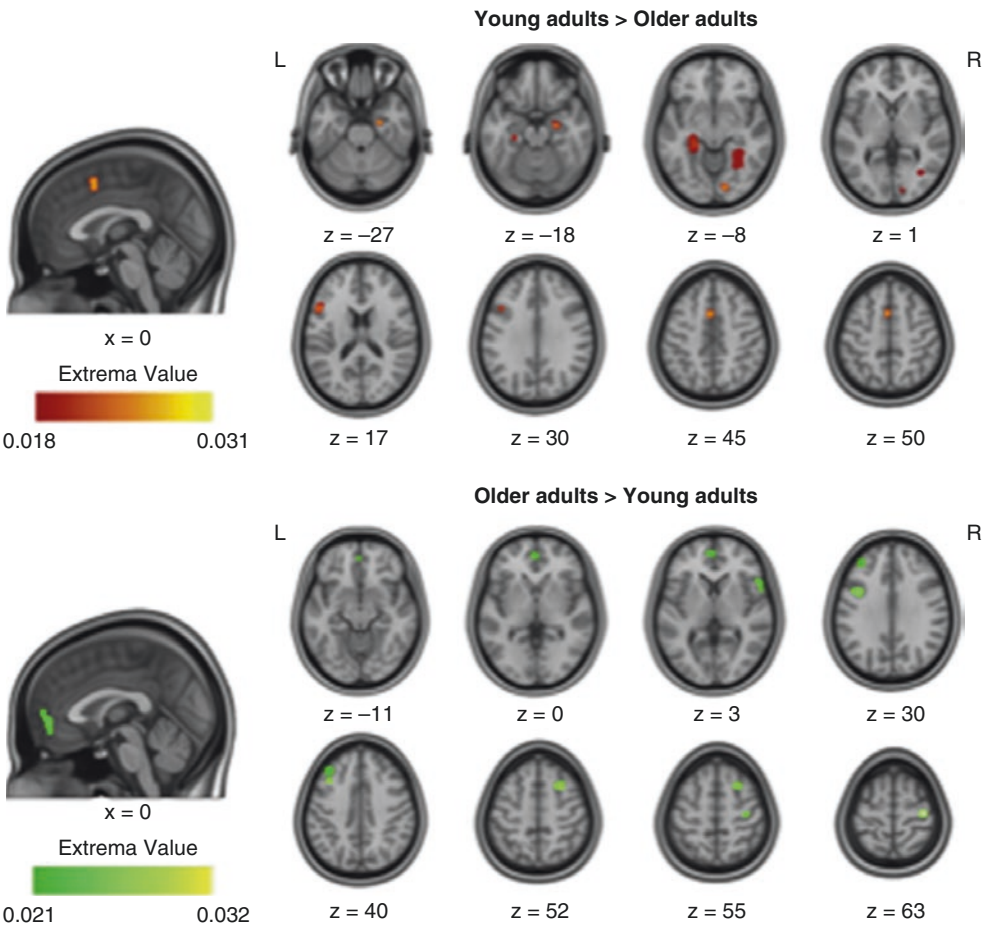

Fig. 30.2 Brain regions demonstrating age-related differences in activity across a wide spectrum of memory and nonmemory tasks. A meta-analysis on a total of 114 fMRI studies (ranging from memory encoding and retrieval, semantic and working memory, to motor and perception tasks) revealed age-related decreases in brain activity primarily in posterior regions (including parahippocampal and fusiform gyri, lingual gyrus, certain frontal gyri, and middle cingulate gyrus) and increases primarily in anterior regions (including middle and medial frontal gyri, and anterior cingulate gyrus), supporting the "posterior-anterior shift in aging" (PASA) model of an increased engagement of frontal activity to compensate for deficits in processing served by the posterior cortices. (Reproduced with permission from Li et al. 2015 [146])

words, research suggests that the above-mentioned HERA model in young adults does not hold in normal aging. This concept has been articulated in the HAROLD (*H*emispheric *A*symmetry *R*eduction in *Old* Adults) model [36]. This model has repeatedly been shown in studies utilizing a wide variety of both verbal and nonverbal episodic encoding and retrieval tasks in older adults. Interestingly, the decreasing asymmetry of PFC responses to episodic encoding and retrieval in older adults is at least somewhat dependent on cognitive strategy. In fact, a few studies have shown that older adults show more symmetrical PFC responses during successful encoding and retrieval when taught to use deep (vs. shallow) encoding strategies [152–154]. These findings suggest that the regional deficit in activation in older adults during encoding is related to altered recruitment of available brain resources, rather than an irreversible loss of the underlying tissue due to cell death or dysfunction.

The reduced PFC lateralization and other age-related activity changes observed in older adults have been interpreted from the perspective of "compensation" and "dedifferentiation" [36, 39, 148, 149, 155–157]. The compensatory hypothesis posits that increased bilateral representation of cognitive functions in older adults may reflect a form of compensatory brain reorganization that helps maintain normal cognitive function [36, 37, 39, 155]. In fact, increased task complexity leads to bilateral activation in young adults, suggesting that bilateral representation assists with difficult processing [158]. Furthermore, increased bilateral PFC activation has been associated with better performance in older adults [36, 37, 144], although not all studies support this association [159].

The interaction between the task demand and age is actually more complicated: at low cognitive load, old adults recruit large neural resources that are only required by young adults at high cognitive load. One study showed the recruitment of bilateral PFC during a difficult episodic memory condition among young adults but the same recruitment among old adults for both the easy and difficult task conditions [160]. This pattern of an earlier engagement of additional brain regions for easy tasks has been captured by the "compensation-related utilization of neural circuits hypothesis" (CRUNCH) model [161, 162]. The CRUNCH model might also explain the decreased activation that sometimes occurs in conjunction with increased activation in other areas [156].

On the other hand, bilateral hemispheric representation may simply reflect diminished selectivity or "dedifferentiation" of the neural substrate of cognition in older adults [37, 154]. Previous reports have demonstrated a strong intercorrelation among different measures of cognitive ability in older adults, even across cognitive domains [163]. For example, in one study, young adults recruited the MTL to learn a list of words, but by contrast they recruited the striatum to learn a sequence of repeated open circles, demonstrating expected brain specificity for explicit and implicit memory [164]. Older adults, in contrast, showed no preferential regional activation during the two tasks. Of note, the dedifferentiation and compensation theories may not be mutually exclusive, with the dedifferentiation theory reflecting a type of compensation, depending on investigators' use of these terms [35].

Structural degeneration of the PFC has been reported in healthy aging, while the MTL is relatively spared [137]. However, some studies have suggested a decreased magnitude and extent of hippocampal activation during episodic encoding and retrieval tasks in older individuals relative to young controls [148, 150, 165–167]. Small and colleagues used the BOLD fMRI signal obtained at rest to estimate regional basal metabolism and examine the integrity of hippocampal subregions in healthy controls and individuals with dementia [168, 169]. This method rests on the assumption that basal deoxyhemoglobin levels reflect hemodynamic variables, such as oxygen extraction, that are related to basal metabolism. Using this method, Small examined hippocampal circuitry in 70 individuals ranging in age from 20 to 88 years. In two hippocampal subregions, the subiculum and the dentate gyrus, decline in resting BOLD fMRI signal appeared to occur as a linear function of age. However, decline in the entorhinal cortex was more variable, present only in a subset of older adults. This was interpreted as evidence that the entorhinal change was not a normal age-related change but rather an indicator of a pathological process.

In addition to decreased PFC asymmetry and altered MTL activation, older adults show a posterior to anterior activation shift during episodic retrieval called the "posterior-anterior shift in aging" (PASA) [170, 171]. This consistent pattern has been proposed to result from a shift in processing, in which the PFC is increasingly engaged to compensate for deficits in sensory processing mediated by the occipital cortex. The PASA has been shown to be a specific effect of aging rather than task difficulty and generalizable across different types of cognitive tasks, including episodic retrieval [170].

Though structural brain changes may well play a role in inducing age-related changes in activity of episodic memory circuitry, the studies that compared deep to shallow encoding offer preliminary evidence that age-related differences in the approach to a task may also contribute [70, 154]. This under-

scores the importance of incorporating both structural and functional brain imaging methods in studies of cognition and aging, and of carefully monitoring participants' cognitive strategy use or approach to the task in addition to other aspects of their task performance.

Episodic Memory in Alzheimer's Disease and Related Conditions

Impairment of episodic memory is a core feature of neurodegenerative disorders such as AD and amnestic MCI, which is considered to be a prodromal stage of AD. Amnestic MCI, the most commonly studied subtype of MCI, is characterized by relatively isolated impairment of episodic memory in the context of otherwise normal daily functioning and an absence of dementia [172–175]. For reviews and diagnostic criteria for MCI see [172–176]. MCI and mild AD patients show significant structural neurodegeneration, with the earliest atrophic changes occurring in the hippocampus and entorhinal cortex (EC), followed by progressive atrophy of the frontal, parietal, and temporal lobes [177–181]. This pattern is distinct from that of the process of normal aging, which shows accentuated frontal atrophy and relative preservation of hippocampal regions, suggesting that AD does not reflect merely an accelerated aging but instead entails a qualitatively different diseased state [182]. Patients with amnestic MCI are significantly more likely to progress to mild AD, with an annualized conversion rate of 10–15%, relative to only 1–2% annual conversion of healthy elders to AD [175]. Neurodegenerative changes assessed using structural MRI techniques have been shown to accurately predict the rate of MCI to AD progression, suggesting these measures may provide sensitive biomarkers for therapeutic trials [183–186]. For additional information regarding the role of structural MRI in MCI and AD, the reader is directed to relevant reviews [42, 187–196].

fMRI Studies of Episodic Memory in Patients with AD

In addition to the structural changes associated with AD, patients also show altered brain function during cognitive tasks, including episodic encoding and retrieval. Studies utilizing fMRI have shown that patients with AD have reduced MTL activation relative to healthy older adults, including decreased activation of the hippocampus, entorhinal cortex, and parahippocampal gyri, during episodic memory encoding of verbal and nonverbal material [167, 197–203] (Fig. 30.3). The extent of hippocampal activation is associated with successful encoding in healthy older adults and patients with AD, suggesting that the reduced MTL activation is related to the observed impairments in encoding in AD [197, 205]. Furthermore, entorhinal cortex activation patterns have been shown to be particularly good at discriminating AD patients from healthy older adult controls [201]. In addition to the reduced MTL activation, episodic encoding was associated with increased activation in frontal and parietal cortical areas in AD relative to age-matched controls [167, 198, 203, 206]. These regions of increased activation may suggest compensatory changes, dedifferentiation, or altered strategies for encoding in patients with AD. Finally, patients with AD also show alterations in episodic retrieval, with reduced PFC and MTL activations [207, 208]. The extent of PFC activation has been shown to be directly associated with retrieval success in AD patients [205]. Additionally, the extent of PFC activation during episodic retrieval within the AD patients was significantly associated with hippocampal volume, a marker of disease severity [208]. This finding is also consistent with a network conceptualization that the MTL and frontal regions form an integrated circuitry underlying episodic memory, and that damage in one part of the circuitry may be reflected in altered activation of other regions.

fMRI Studies of Episodic Memory in Patients with MCI

In contrast to the consistent findings from fMRI studies of AD patients, studies of episodic encoding and retrieval in patients with MCI have been equivocal. Some reports have demonstrated increased MTL activation in MCI patients relative to healthy older adults during episodic tasks [209–212] (Figs. 30.3 and 30.4), while other studies have demonstrated significantly reduced MTL activations [202, 209, 214]. Further inspection of the results from these studies, as well as longitudinal follow-up studies of patients with MCI, has led to the formulation of a general pattern of MTL activation along the spectrum from healthy aging to AD [197, 209, 213]. Very mild early MCI patients show increased MTL activation during episodic tasks, which may reflect functional compensatory effects in attempt to maintain memory performance and overcome abnormal pathology and neurodegeneration. In fact, fMRI studies of these mild MCI patients often show near normal levels of performance on the functional episodic tasks. However, later stage MCI patients show significantly reduced MTL activation in episodic tasks associated with impaired memory performance. Late MCI participants also show a reduced "adaptation" response to repeated presentation of stimuli during encoding [215]. The increased MTL

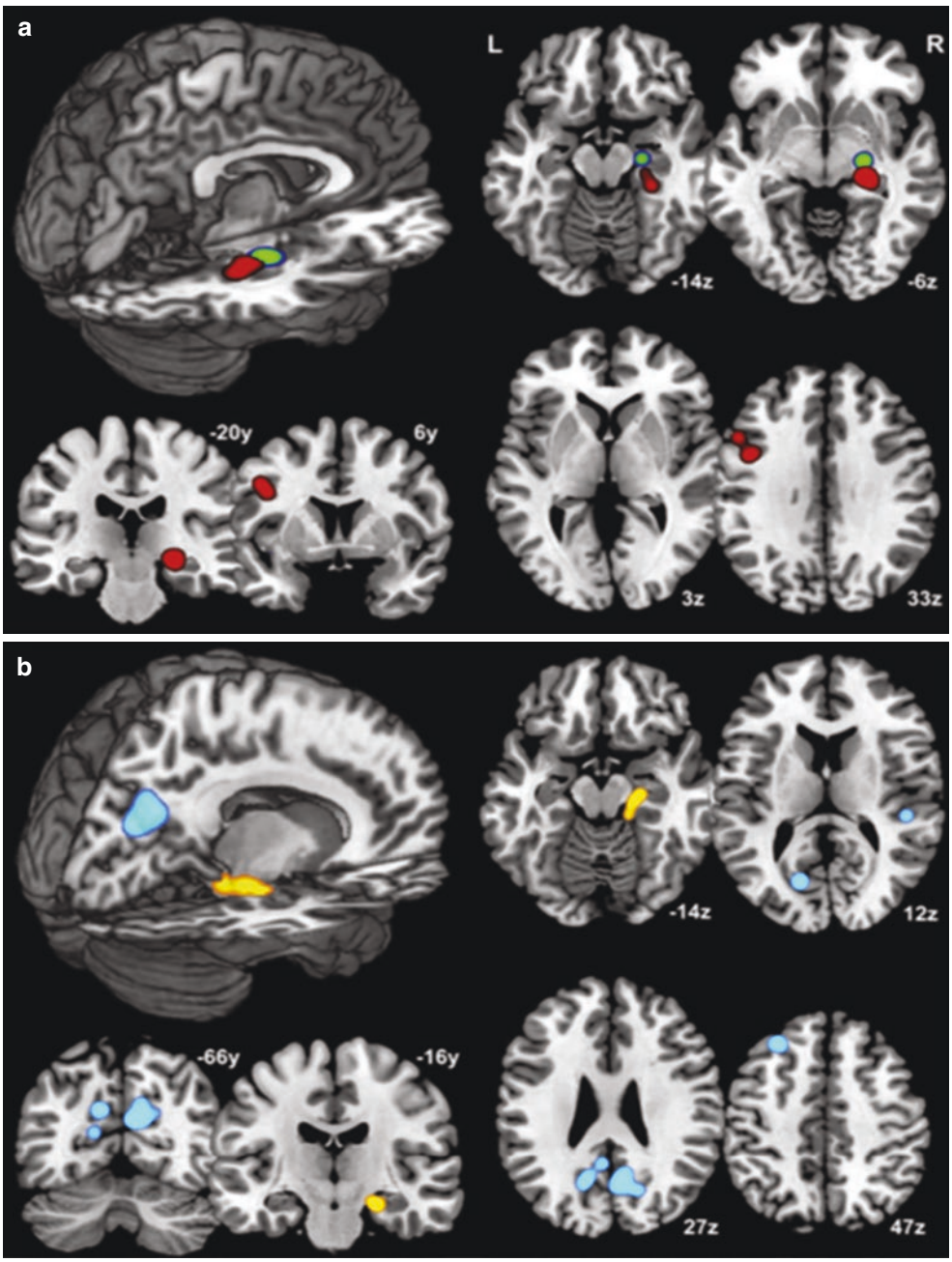

Fig. 30.3 Alterations in fMRI activations during episodic encoding in patients with mild cognitive impairment and Alzheimer's disease. Mild cognitive impairment (MCI) patients have decreased activity (indicated in red color) in left inferior frontal gyrus (BA 9) and right anterior parahippocampal gyrus (~BA 28), and an increased activity (indicated in green color) in a different sub-region of anterior parahippocampal gyrus (~BA 35) relative to cognitively healthy older adults (**a**). Alzheimer's disease (AD) patients show less brain activation (indicated in yellow color) in right anterior parahippocampal gyrus (~BA 28) and more brain activation (indicated in blue color) in cuneus (BA 18), precuneus (BA 31), superior temporal gyrus (BA 41) and superior frontal gyrus (BA 6/8) than cognitively healthy older adults (**b**). (Reproduced with permission from a meta-analysis by Browndyke et al. 2013 [204])

activation observed in mild MCI patients may be a sensitive predictor of future progression to AD, such that early MCI patients who had the highest baseline level of MTL activation during an episodic encoding task demonstrated a faster rate of decline over 2–6 years [213, 216]. As shown in Fig. 30.4, patients who progressed most quickly or "fast-progressors" had significantly greater hippocampal activity during an episodic encoding task at baseline relative to healthy older adults, stable early MCI patients, and even MCI patients who progressed at a slower rate ("slow-progressors") [213]. Furthermore, after 2 years fast-progressors showed a significantly greater loss of hippocampal activation during an episodic memory task. In fact, fast-progressors demonstrated significantly reduced hippocampal activation during episodic encoding relative to healthy older adults, stable MCI patients, and slow-progressors [213]. In addition to the variable MTL responses across the spectrum of MCI severity, differences in response may also be evident within the MTL sub-structures. A high-resolution fMRI study suggested that patients with mild MCI show increased activation in the CA3 and dentate gyrus of the hippocampal formation and decreased activation in the entorhinal cortex [217].

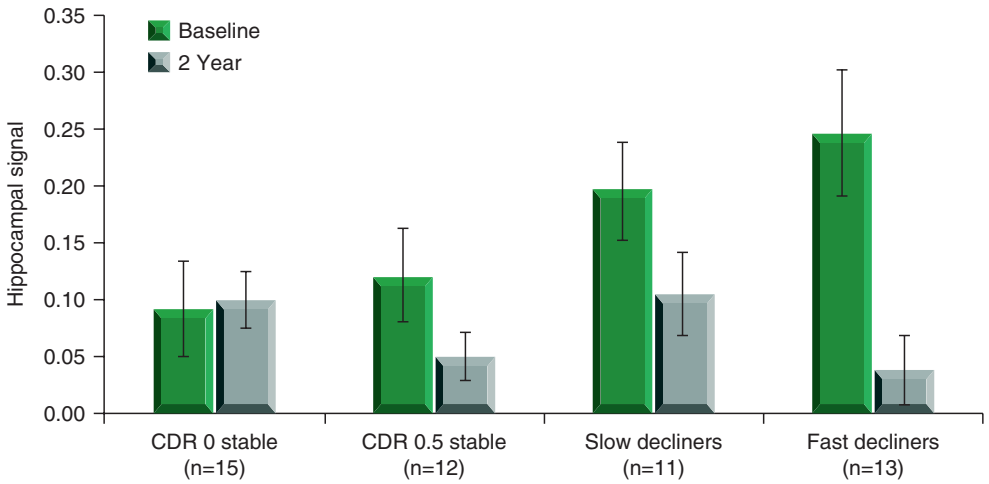

Fig. 30.4 Increased hippocampal activation at baseline is association with faster decline in cognition over 2 years. A longitudinal study of cognitively healthy older adults and older adults with mild impairment demonstrated that increased hippocampal activation in an fMRI study of episodic encoding at baseline is associated with faster decline in cognition over 2 years. Furthermore, the difference between baseline and 2-year hippocampal activation was significantly greater in participants who demonstrated the greatest decline in cognition, relative to participants who remained stable or had a slower decline. (Reproduced from O'Brien et al. 2010, with permission [213])

Functional and Resting State Connectivity Associated with Episodic Memory

Traditionally, fMRI and other types of functional neuroimaging studies have focused on specific regions of activation associated with a task independently. However, complex cognitive tasks usually require a network of regions working together [218, 219]. Therefore, a number of recent reports have focused on the connection between fMRI signals in anatomically distinct regions, during task-induced activations ("functional connectivity") [219], and during periods in the absence of functional tasks ("resting state connectivity") [69, 220].

fMRI Studies of Episodic Associated Connectivity in Healthy Young Adults

Memory research has long proposed the idea that the frontal, parietal, and temporal brain regions work together in support of episodic memory [82, 221–223]. For example, successful episodic encoding activates a functional network that includes the hippocampus and other MTL regions, the medial and lateral parietal lobe, lateral temporal cortical regions, and the PFC [222]. Additionally, a study by Burianova and colleagues suggested that a common functional network that includes the MTL, lateral temporal cortex, PFC, and cingulate underlies autobiographical, episodic, and semantic memory systems [223]. As a more specific example, previous research has directly demonstrated a functional connection between the left inferior frontal gyrus and left middle temporal gyrus during language comprehension at the sentence level [224], thus suggesting that the prefrontal modulation of posterior cortical representations might be critical to word–word associative learning. Structurally, this left frontotemporal connection seems to arise from two direct anatomical circuits between them—dorsally via the arcuate fasciculus and ventrally via the extreme capsule [225]. On the other hand, after an item has already been successfully learned, the frontotemporal neural coupling becomes weakened during restudying the item, highlighting the importance of this connectivity to memory encoding [226]. Functional connectivity analyses have also identified networks associated with episodic retrieval. A network connecting frontal and parietal cortical regions has been implicated in successful episodic retrieval [227, 228], although the activity of this network may be dependent on the depth of episodic encoding [228].

fMRI Studies of Episodic Associated Connectivity in Healthy Older Adults

Functional and resting connectivity techniques have also been applied to investigate episodic memory function in older adults. Greater prefrontal connectivity, inferior parietal connectivity, and decreased hippocampal connectivity during episodic encoding and retrieval in older adults compared to younger adults has been reported using structural equation modeling of fMRI and PET data [3, 229–231], mirroring the compensatory role of prefrontal lobes observed in regional activity findings. A study by Daselaar et al. [165] suggested similar alterations in functional connectivity during a verbal episodic memory task, including a reduction in the hippocampal–parietotemporal functional network and an increase in the rhinal–frontal network in older adults relative to younger participants [165]. The strength of hippocampal–

medial parietal connectivity has also been shown to be associated with episodic retrieval performance in older adults [232]. Interestingly, the structural integrity of distal MTL regions might determine the effectiveness of compensation by the increased frontal connectivity [233].

Alterations in the DMN or "resting state" network have also been reported in older participants [234–236]. Specifically, older adults show reduced deactivation of the DMN upon episodic task initiation relative to young controls, including impaired deactivation of the precuneus and posterior cingulate. Furthermore, older adults with high performance on a postscan recognition test demonstrated significantly greater deactivation of the precuneus relative to older adults who performed poorly [237]. Thus, the DMN and functional networks demonstrate age-related alterations, which may lead to memory dysfunction and/or serve as biomarkers for future cognitive decline.

fMRI Studies of Episodic Associated Connectivity in Patients with MCI and AD

In addition to alterations in regional activations during episodic tasks, patients with MCI and AD show altered functional and resting state connectivity (Fig. 30.5). Patients with AD show impaired functional connectivity between the left and right hippocampus [238], as well as impairment in connectivity of an episodic encoding network that includes the hippocampus, inferior PFC, fusiform gyrus, and visual-association cortex [209]. Impairment of connectivity in patients with MCI may be dependent on stage of disease, with late-stage MCI patients showing greater impairment of the hippocampal-PFC-parietal network than early-stage MCI patients. Patients with AD may also engage additional networks in order to accomplish tasks relative to those used by healthy older adults [206]. More recent work suggests from the network perspec-

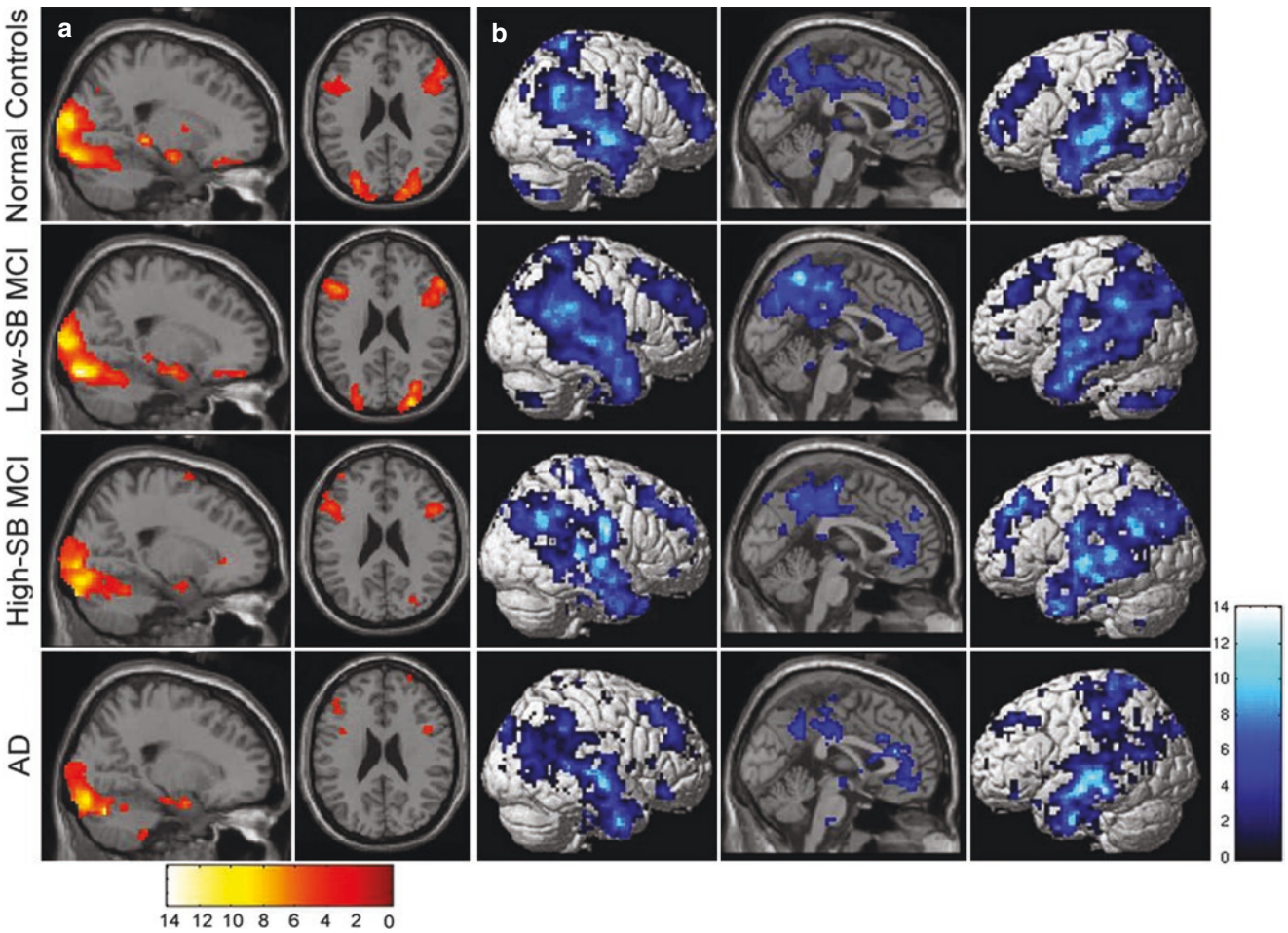

Fig. 30.5 Functional and resting-state connectivity associated with episodic memory is altered in mild cognitive impairment and Alzheimer's disease relative to cognitively healthy older adults. A functional network (**a**, yellow-red) between the visual cortex, hippocampus, and inferior prefrontal cortex (PFC) was observed during an episodic encoding task in all participants. Deactivation of the resting-state network (**b**, blue), including the medial parietal, lateral temporal, and PFC, was also observed upon task initiation in all participants. However, mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients demonstrated altered activation and deactivation of both of these networks. Early (low Clinical Dementia Rating Scale—Sum of Boxes (Low-SB)) MCI patients demonstrated increased connectivity of both the functional and resting-state networks. However, late (High-SB) MCI and AD patients showed decreased functional and resting-state connectivity relative to early MCI and cognitively healthy older adults. (Adapted from Celone et al. 2006 [209], with permission)

tive a unique role of left frontal cortex (LFC) as a hub region showing, among MCI patients, higher connectivity to the key memory networks (e.g., default mode network and dorsal attention network) during successful episodic memory [239, 240]. Furthermore, this higher LFC connectivity was associated with more education [239, 240], contributing to a potential neural foundation for cognitive reserve [241].

A number of studies have also shown impaired "deactivation" of the DMN in patients with MCI and AD [209, 242–245]. Specifically, AD and late-stage MCI patients showed impaired deactivation of the DMN, including the precuneus, posterior cingulate, lateral parietal cortex, temporal cortices, anterior cingulate, and medial frontal cortices. However, early-stage MCI patients showed a "greater" deactivation of the DMN relative to late-stage MCI, AD, and healthy older adults. The greatest differences between patients and healthy older adults occurred in the earliest phase of deactivation in the anterior frontal cortex, including the anterior cingulate and medial frontal lobe [243]. Furthermore, the extent of deactivation in the anterior frontal cortex could successfully classify healthy older adults vs. MCI patients and MCI vs. AD patients, while the extent of deactivation in the precuneus successfully classified healthy older adults from both patient groups [243]. Alterations in the DMN function have also been shown to be highly associated with alterations in MTL activity and connectivity, suggesting a specific association between these impairments and episodic memory function [209, 216, 242].

fMRI of Episodic Memory Function as a Biomarker: Patients At-Risk for AD and after Therapeutic Intervention

Recently researchers have been shifting their focus to even earlier stages of AD, as the first pathological changes have been shown to occur decades before AD clinical diagnosis [246, 247]. One type of preclinical or asymptomatic stage of AD, prior to MCI, was initially conceptualized as cognitive complaints [248], and more recently as subjective cognitive decline (SCD), and features a self-perceived decline in memory and/or other cognitive capabilities despite no evidence of objective performance impairment on standard neuropsychological assessment or deterioration in activities of daily living [249–251]. SCD is associated with an elevated risk to develop MCI and AD, especially when the cognitive complaints are also corroborated by an informant [252–256]. A meta-analysis concluded that the annual conversion rate to MCI among older adults who reported SCD was 6.6%, and they were twice as likely to develop AD as those who did not report during a 4-year follow-up period [257]. Therefore, SCD may represent an early manifestation of AD while normal cognitive functioning is still relatively well maintained, and therefore offers a unique time window for effective intervention and treatment to delay or even prevent further structural and functional neural degeneration before the progressive and irreversible changes have occurred [258, 259].

Briefly, a wide spectrum of AD-related biomarkers have already shown alterations in SCD, including elevated tau pathology [260], increased amyloid-β burden [261], low cerebrospinal fluid Aβ42 [262], temporal and parietal cortical thinning [248, 263], and altered resting functional connectivity [264–266]. Some of these biomarker effects are modulated by a variant in the apolipoprotein E gene [ApoE ε4, a well-established genetic risk for AD; see 242], such that SCD *ApoE* ε4+ (carriers) showed higher CSF tau and p-tau, greater amyloid deposition, and lower CSF Aβ42 than SCD *ApoE* ε4− (noncarriers) [267].

SCD participants also show significant alterations in brain activation during episodic memory probes relative to age-matched controls. In a report by Rodda and colleagues, patients with cognitive complaints showed significantly increased activation of the left PFC during an episodic encoding task relative to age-matched controls without complaints [268]. Furthermore, the magnitude of the left PFC response was positively associated with successful retrieval within the group with complaints and across all participants. Similarly, another study found a reduction in right hippocampal activation during episodic memory recall in SCD, but also an increase in the right PFC activation in the SCD versus the control group [269]. The two groups did not differ in their memory behavioral performance. ApoE ε4 genotype, SCD symptoms and hippocampal volume may jointly influence episodic memory [270]. A more recent study showed that SCD participants also had less deactivation relative to the control group of part of the DMN, including in the posterior cingulate cortex, precuneus, and ventromedial PFC during memory formation, despite no difference in task performance [271]. The authors suggest that such a pattern presumably reflects decreased task-directed attention in SCD. Rami and colleagues also showed a similar pattern of less deactivation of precuneus and posterior cingulate cortex during encoding among a preclinical AD group, defined by a lower cerebrospinal fluid levels of Aβ42 rather than SCD [272]. Together, these results indicate that neuroimaging is sensitive to subtle changes in this sub-clinical stage of AD in the absence of obvious objective impairment. However, additional studies are needed to further characterize this population cross-sectionally and longitudinally.

Cognitively intact, middle-aged to older individuals who are at-risk for AD by virtue of their *ApoE* genotype also show altered fMRI activations during episodic tasks [273]. In an early study, Bookheimer and colleagues found increased intensity and spatial extent of activation in temporal, parietal, and prefrontal regions during episodic encoding and retrieval in middle-aged to older adult individuals who were *ApoE* ε4 positive compared to those without the ε4 allele [274]. Baseline activation patterns predicted memory decline over the next 2 years. The fact that these individuals were recruiting broader areas of brain tissue to accomplish

the episodic memory task suggests that changes in activation may occur very early during the course of memory disorders such as AD. These changes may play a compensatory role and may represent an early marker for subsequent cognitive decline. Subsequently, a follow-up study reported no differences between *ApoE* ε4 positive and negative groups in fMRI brain activation patterns on an attention/working memory task [275]. This was interpreted as evidence that compensatory brain activation in *ApoE* ε4 carriers is specific to the episodic memory system. Similar results were also reported in a separate cohort of older adults, with *ApoE* ε4 positive participants demonstrating greater brain response during novel picture encoding in the bilateral fusiform gyri, superior parietal lobe, and the frontal cortex relative to *ApoE* ε4 negative participants [276]. In contrast, other studies have shown reduced MTL and PFC activation in *ApoE* ε4 positive participants at-risk for AD during episodic memory tasks [277, 278].

In addition to potential utility as an early marker of disease, activations during episodic encoding tasks have been used in studies to evaluate the effect of acetylcholinesterase inhibitor (AChEI) treatments on brain function in patients with MCI and AD. In a preliminary study of seven patients with mild AD, Rombouts and colleagues investigated the effects of rivastigmine, a cholinesterase inhibitor, on brain activity patterns during episodic memory performance (and working memory, as described below) [279]. A single dose of the medication led to a bilateral increase in activation in the fusiform gyrus during face encoding, suggesting that rivastigmine affects activity in regions associated with cholinergic circuitry. Additional studies to investigate other AChEI treatments, including galantamine and donepezil, have demonstrated similar increased activation and normalized MTL functional connectivity associated with task performance improvement in patients with MCI and/or AD [280–282]. The effects of anti-cholinergic medications such as scopolamine and/or mecamylamine have also been investigated using fMRI studies of episodic memory [283, 284]. A study by Dumas and colleagues demonstrated modulation of MTL and cortical activations after administration of scopolamine or mecamylamine, including decreased activation in the left parietal and occipital cortices, insula and parahippocampal gyrus, but increased activation in the right hippocampus [283]. Overall, these studies suggest that activations measured using fMRI may be sensitive to the effects of pharmacological treatments on cognition in patients with MCI and AD, and thus, may be useful in therapeutic trials to assess both efficacy and mechanism of action.

Summary

fMRI studies of episodic memory have implicated a network of brain regions involved with both episodic encoding and retrieval, including the bilateral PFC and MTL. In young adults, episodic encoding and retrieval appear to be lateralized in the frontal cortex with encoding localized to the left PFC and retrieval localized in the right PFC. However, in older adults this hemispheric lateralization appears to be reduced or absent. Patients with MCI and AD show altered activation during episodic encoding and retrieval, which may be dependent on disease stage. Early MCI patients show increased MTL activation during episodic tasks, while late MCI and AD patients show decreased activation in the MTL. Furthermore, increased hippocampal activation at baseline may be a biomarker of progression. fMRI studies of task-related connectivity studies have implicated networks that include frontal, parietal, and temporal cortices in episodic memory function. Resting-state networks that include the medial parietal and frontal cortex have also been identified in fMRI studies of episodic memory. Both functional and resting-state networks are altered in normal aging, as well as MCI and AD. Finally, the use of fMRI studies of episodic memory as a biomarker have shown promise in detecting preclinical and prodromal altered activation patterns in individuals at risk for dementia and in pharmacological intervention studies.

Semantic Memory

Semantic memory is broadly defined as knowledge about the world and includes the set of ideas, words, and symbols that are generally shared by individuals within a culture [23, 285]. Unlike episodic memories, semantic memories are divested of contextual details. Semantic memory consists of knowledge about the meaning of words, the properties of objects, and general facts. For example, remembering the movie you saw last week depends on episodic memory, but remembering the meaning of the word "movie," the knowledge that "movies are often made in Hollywood," and the fact that "Hollywood is in the state of California in the USA" are examples of semantic memory. For selected reviews of fMRI studies of semantic memory see Table 30.3.

fMRI of the Neuroanatomical Substrates of Semantic Memory

The first studies regarding the neural networks associated with semantic memory were in patients with brain damage, neurodegenerative disorders, and brain lesions. More recently, functional neuroimaging techniques have been utilized in patients with selective deficits in semantic memory, as well as healthy participants engaging in semantic memory retrieval (Fig. 30.6). Functional semantic memory studies primarily access the semantic network through tasks focused on naming, categorization, or generation of concepts, words, or objects. Sample fMRI measures of semantic memory are presented in Table 30.1b.

Table 30.3 Selected review articles of semantic memory for further reading

Semantic memory		
Authors	Study subjects	Article title
Cabeza et al. (2000) [23]	Young adults	Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience.* 2000;12(1):1–47.
Grady et al. (2000) [24]	Healthy aging	Changes in memory processing with age. *Current Opinion in Neurobiology.* 2000;10:224–231.
Langley et al. (2000) [25]	Healthy aging	Functional neuroimaging of memory: implications for cognitive aging. *Microsc Res Tech.* Oct 1 2000;51(1):75–84.
Cabeza (2001) [27]	Healthy aging	Cognitive neuroscience of aging: contributions of functional neuroimaging. *Scand J Psychol.* Jul 2001;42(3):277–286.
Hedden et al. (2005) [31]	Healthy aging	Healthy and pathological processes in adult development: new evidence from neuroimaging of the aging brain. *Curr Opin Neurol.* Dec 2005;18(6):740–747.
Vigneau et al. (2006) [286]	Young adults	Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing. *Neuroimage.* May 1 2006;30(4):1414–1432.
Wingfield et al. (2006) [287]	Healthy aging	Language and the aging brain: patterns of neural compensation revealed by functional brain imaging. *J Neurophysiol.* Dec 2006;96(6):2830–2839.
Wierenga (2007) [35]	MCI and AD	Use of functional magnetic resonance imaging in the early identification of Alzheimer's disease. *Neuropsychol Rev.* Jun 2007;17(2):127–143.
Cappa (2008) [288]	Young adults	Imaging studies of semantic memory. *Curr Opin Neurol.* Dec 2008;21(6):669–675.
Grady (2008) [37]	Healthy aging	Cognitive neuroscience of aging. *Ann N Y Acad Sci.* Mar 2008;1124:127–144.
Drzezga (2008) [39]	MCI and AD	Concept of functional imaging of memory decline in Alzheimer's disease. *Methods.* Apr 2008;44(4):304–314.
Binder et al. (2009) [289]	Young adults	Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb Cortex.* Dec 2009;19(12):2767–2796.
Grady (2012) [156]	Healthy aging	The cognitive neuroscience of ageing. *Nat Rev Neurosci*. 2012;13(7):491–505.
Scheller et al. (2014) [155]	Healthy aging	Attempted and successful compensation in preclinical and early manifest neurodegeneration—a review of task FMRI studies. *Front Psychiatry*. 2014;5:132.
Lambon Ralph et al. (2017) [290]	Young adults	The neural and computational bases of semantic cognition. *Nat Rev Neurosci*. 2017;18(1):42–55.
Xu et al. (2017) [291]	Young adults	A Tri-network Model of Human Semantic Processing. *Front Psychol*. 2017;8:2025–12.
Ralph et al. (2017) [290]	MCI and AD	The neural and computational bases of semantic cognition. *Nat Rev Neurosci*, 2017. 18(1): p. 42–55.
Taler et al. (2019) [292]	MCI and AD	Semantic Function in Mild Cognitive Impairment. *Front Psychol*, 2019. 10: p. 3041.

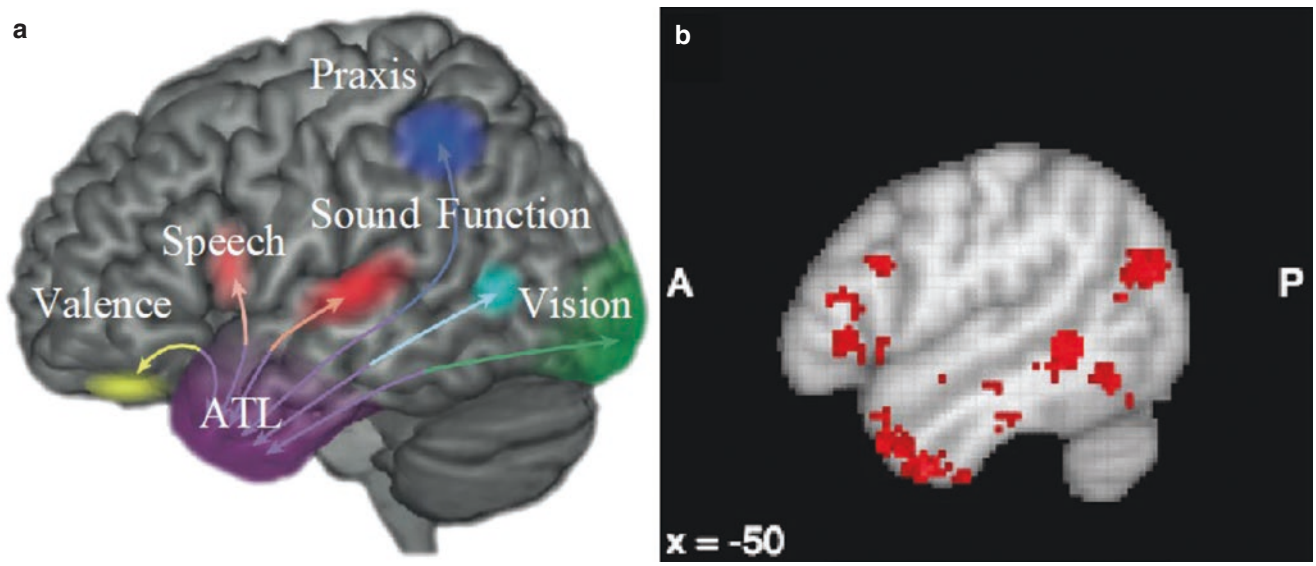

Fig. 30.6 fMRI activations during semantic processing. According to a model proposed by Lambon Ralph et al. 2017 [289], anterior temporal lobes (ATL) are a transmodal convergence zone to promote verbal and nonverbal knowledge generalization and connect with modality-specific regions where representations of semantic attributes (e.g., shape, sound, color, motion, and valence) are stored separately (**a**) (reproduced with permission from Lambon Ralph et al. (2017) [289]). The empirical activation pattern obtained from an automated meta-analysis of 123 semantic memory studies (retrieved from http://neurosynth.org/analyses/terms/semantic%20memory/ on March 14, 2019) fits the proposed model (**b**). *ATL* anterior temporal lobes, *A* anterior, *P* posterior

As might be expected given the rich associative and inferential processes that can be invoked for the recollection of even simple factual information and words, fMRI studies of semantic memory suggest a broad-based neural circuitry [23, 286, 288, 293–295]. According to one model, the semantic brain network could be categorized into two sub-networks: one involved in actual conceptual representation and the other responsible for higher-order semantic control [289].

Specifically, representations of semantic attributes (e.g., shape, sound, color, motion, and valence) are stored in corresponding sensorimotor cortices in a modality-specific manner [296]. The posterior temporal cortex is particularly implicated in long-term storage of tool and action concepts [297], while the fusiform gyrus is thought to have a role in storage of visual attributes of semantic knowledge [298]. The ventromedial PFC, including the rostral and subgenual cingulate gyrus, gyrus rectus, and medial orbitofrontal cortex, are thought to be involved in storage and retrieval of the emotional attributes of semantic concepts [286, 299]. This region has also been linked with motivation, the affective nature of semantic concepts, reward processing, and self-knowledge or semantic self-awareness [300, 301].

Meanwhile, bilateral anterior temporal lobes are a transmodal convergence zone to promote verbal and nonverbal knowledge generalization [302, 303]. As an illustration, semantic dementia, a progressive neurodegenerative form of frontotemporal dementia (FTD), is associated with extensive atrophy of the anterior temporal lobes [304–306]. Patients with semantic dementia often show global (across all modalities) deficits in semantic knowledge with relative sparing of other types of memory (i.e. episodic, working, procedural memory) [305].

Moreover, corroborating evidence points to the existence of distributed semantic control network that is largely distinct from the above network for semantic representations and that exerts influence on the retrieval and manipulation of semantic knowledge according to task contexts and goals. This network includes the PFC, posterior middle temporal gyrus, intraparietal sulcus, presupplementary motor area, and the anterior cingulate-ventromedial PFC [289]. For instance, the dorsal mPFC is also thought to play a role in semantic integration and is particularly implicated in self-guided and motivated retrieval [307] and formulation of semantic concepts [286]. Patients with damage to this area have difficulty with generation of new speech (i.e. category lists) and unique responses during discourse [286, 308]. The inferior frontal lobe, including the pars orbitalis, is thought to play a similar role to the dorsal mPFC and is associated with task difficulty and complex planning of semantic articulations. Interestingly, damage to this area does not affect the accuracy of semantic processing but instead impairs processing "efficiency" or "speed" [286, 309].

Whether the hippocampus plays a role in semantic memory is controversial. One school of thought posits that episodic and semantic memory are dissociable with the former depending largely on hippocampal formation (see section on "Episodic Memory") and the latter requiring adjacent cortices, such as entorhinal, perirhinal, and parahippocampal cortices [310]. Another view holds that hippocampus is also important to semantic memory: lesions restricted to hippocampal region not only impair previously stored semantic memory in a temporally limited fashion such that only remote ones remains intact, but also negatively affect the formation of new factual knowledge [311]. Besides, although it is possible for hippocampus patients to acquire new vocabulary, such learning through explicit relational association is ineffective [312]. Furthermore, category fluency, traditionally testing semantic memory, could also engage MTL activity to retrieve contextual experience under certain conditions (e.g., imaging one's own kitchen when being asked to list kitchen utensils) [313]. Finally, more recent evidence may help reconcile the discrepancy showing that amnesic patients with profoundly damaged hippocampi were able to acquire associative knowledge through a mechanism called "fast mapping," likely supported by the left polar temporal neocortex and left perirhinal and entorhinal cortices [314]. Fast mapping also applies to the learning of normal controls to help rapidly integrate novel information into existing knowledge [315]. Thus, there seems to exist multiple pathways leading to semantic memory mediated by hippocampus or nonhippocampal regions.

fMRI of Semantic Memory in Normal Aging

An important component of semantic memory, knowledge or "crystallized intellect," is thought to be preserved and possibly even enhanced in normal aging [134, 316]. However, the efficiency and accuracy with which information is retrieved from semantic memory can be affected in older adults [317–319]. Functional neuroimaging studies exploring changes in semantic memory processing in normal aging have found similar alterations as observed in the studies of episodic memory in older adults (see section on "fMRI of Episodic Memory in Normal Aging"). Specifically, older adults show reduced lateralization of semantic retrieval, which has been posited in the "HAROLD" model, as previously discussed [36, 145]. This reduction in hemispheric asymmetry may represent compensation, reductions in processing efficacy, or dedifferentiation of cognitive function. fMRI studies of semantic memory have demonstrated increased bilateral activations in older adults relative to young adults using a variety of semantic paradigms, including naming tasks with multiple semantic categories, semantic memory for famous people, as well as sentence processing and comprehension [320–325]. Despite having equivalent performance to the younger participants, older adults show a significant positive association between greater bilateral activation and performance on the semantic tasks [324]. Tyler and colleagues also demonstrated a significant association between greater atro-

phy in the left inferior frontal gyrus, as measured by reduced grey matter density, and increased activation in the right inferior and middle frontal gyri during a sentence comprehension task [326]. These authors suggested that the bilateral activation in older adults during semantic processing compensates for reduced GM density in the frontal lobe associated with aging. However, the role for the age-related engagement of right frontal activation is inconclusive as some studies have found negative correlations with task performance [327] or no correlation at all [328]. The inconsistency in the literature might be related to "successful" vs. "attempted" compensation [155].

In addition to reduced lateralization, older adults demonstrate other alterations in fMRI studies of semantic memory relative to young controls. Studies utilizing both naming and semantic processing tasks suggested a greater magnitude and extent of activation in older adults relative to young adults [323, 325, 326]. Specifically, older adults showed greater activation in the bilateral medial, inferior, and dorsal lateral PFC, lateral temporal cortex, posterior lateral temporoparietal regions, and fusiform gyrus than young adults. Additionally, a study by Wierenga et al. [324] demonstrated an altered hemodynamic response (HDR) during semantic tasks in older adults relative to younger controls [324]. Specifically, older adults had a different HDR time-course in regions of interest (ROIs) in the frontal and temporal lobes with a delayed rise to peak activation and return to baseline.

fMRI Studies of Semantic Memory in MCI and AD

Like episodic memory, semantic memory is affected in MCI and AD, though the more profound changes typically occur later in the disease course. Eventually, profound deficits in identification and knowledge can emerge [135]. AD patients can show category-specific impairments (i.e., "living things" more impaired than "artifacts") and category-independent deficits [329–331], while MCI patients often show minimal or no deficits in semantic memory [332]. fMRI studies of patients with MCI and AD have shown significant alterations in activations associated with semantic memory paradigms, including semantic classification, category-matching, naming, and other semantic tasks [13, 333–336]. In simple semantic tasks where performance of AD patients and healthy older adults is similar, AD patients show primarily reduced activation relative to healthy controls during task performance in the lateral frontal and temporoparietal cortices [333–336]. These regions are primarily implicated in category-independent processing and integration of semantic knowledge, thus suggesting particular impairment in higher-level semantic processing in patients with AD [336]. On the other hand, other studies have found increased activations in patients with MCI and AD relative to healthy older adults in both the frontal and temporal lobes during both simple and more difficult semantic tasks [13, 335]. For example, in an early study examining these issues, Saykin and colleagues demonstrated that two semantic category-matching tasks activated left lateral prefrontal and temporal regions, whereas a phonologic control task activated only temporal areas [13]. In patients with mild AD, the spatial extent of left frontal activation on the semantic task was greater than in older adult controls, although accuracy was lower in the patient group. Figure 30.7 shows a surface render of brain activation during semantic decision making for category–function pairs (e.g., match: beverage-sip, compared to mismatch: vehicle-sip). Similar to the increased activation seen in older adults relative to young adults, this increased activation was thought to be compensatory. In fact, the extent of increased activation in the lateral frontal cortex during semantic processing was shown to be significantly correlated with the extent of atrophy in the frontal lobe in AD patients [334], suggesting that an increased extent and amplitude brain activation may help offset disease-related structural changes in the brain. Yet to complicate matters further, another study found that the MCI group had both decreased activation compared with controls in a network of occipitotemporal regions and inferior frontal cortex and increased activation in bilateral anterior cingulate cortex during a lexical decision task [337]. The activation differences could not be attributable to task performance, which were comparable between groups, or brain structure, which showed no cerebral atrophy in these regions in MCI patients.

The mixed results from different studies may result from the different semantic tasks employed and differences in task performance between patients with AD and healthy older adult controls. Additionally, the extent and magnitude of activation during semantic memory tasks may depend on disease stage and clinical severity, similar to the results from patients with MCI and AD in episodic memory studies [333, 335]. In fact, patients with MCI show increased activation during semantic memory tasks, particularly in the DLPFC, inferior parietal lobe, and temporoparietal regions [332, 333].

fMRI Studies of Semantic Memory Associated Connectivity in Healthy Young Adults

In order to determine the functional networks involved in semantic memory processing, studies employing fMRI functional connectivity analysis techniques have been implemented in studies with semantic tasks in healthy young adults. One study utilized an independent component analysis (ICA) technique to analyze fMRI activations during a semantic decision task and identified seven unique and independent networks [338]. Left and right lateralized hemispheric networks connecting the inferior and middle frontal gyri, inferior parietal lobule, middle temporal, as well as

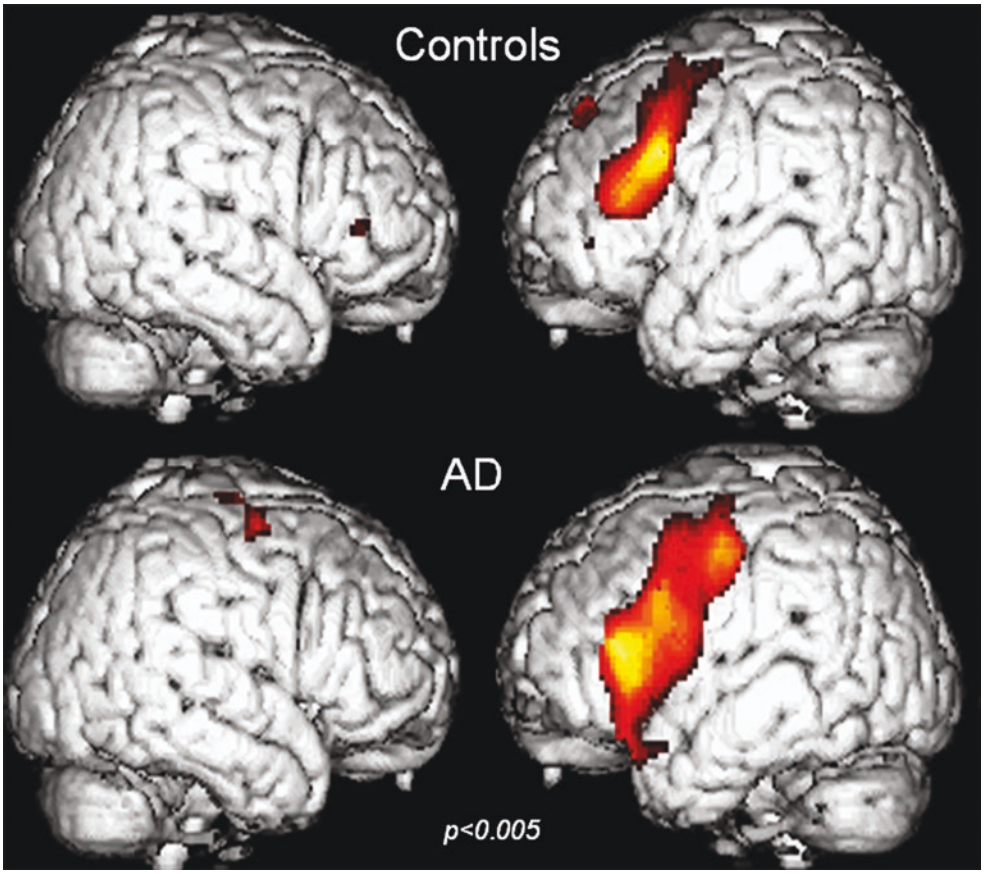

Fig. 30.7 Expanded region of activation in the PFC in a semantic decision task in Alzheimer's disease patients. Upper panel is fMRI brain activation during semantic decision making (match vs. mismatch) for category-function pairs (e.g., beverage-sip, vehicle-sip) for the cognitively healthy older adult group, while the bottom panel is the activation for the mild Alzheimer's disease group. Note the expanded spatial extent of activation in the patient group in the left frontal region in the AD patients. (Based on a further analysis of data published in Saykin et al. 1999 [13])

other regions were identified and thought to be involved in task-specific semantic processing. The remaining five functional networks included two additional task-specific networks, the "presupplementary motor area (SMA)-thalamus" network and the "parietal-frontal" network, which are involved in the integration of multiple features and mental imagery, respectively; two networks involved in basic sensory processing, the "temporal-frontal" network for auditory processing and the "occipital-motor" network, which is involved in visual functioning; and, the resting-state "default mode network (DMN)." The DMN, which included the angular gyri, posterior cingulate, ventromedial PFC, and dorsomedial PFC, was also shown in an independent study to be "deactivated" upon initiation of a perceptual task but not a semantic task [339]. The results of this study suggest that the lack of "deactivation" of the DMN upon initiation of a semantic task is due to on-going semantic processing as part of the "at-rest" activity.

A study by Vitali and colleagues examined whether different semantic categories showed separate or overlapping functional networks [340]. The results from healthy young adults demonstrated the presence of an expansive functional network for the processing of tools, which included a left-lateralized network connecting the DLPFC, premotor regions (including the pre-SMA), inferior parietal lobule, and temporoparietal regions. Semantic processing of tools also demonstrated increased activation of two functional connections including a connection between the inferior frontal and superior occipital gyri, and a network connecting the inferior frontal gyri, lateral fusiform gyri, and the temporoparietal junction. On the other hand, semantic processing of animals showed a much more limited left-lateralized functional network connecting the visual association areas (lateral and medial fusiform gyri with the superior and inferior occipital gyri). Two other functional connections for the semantic processing of animals were observed, including a network connecting the inferior frontal gyri and medial fusiform gyri, and a network connecting the inferior frontal gyri and inferior occipital gyri. The results of this study suggest independent and minimally overlapping functional networks are involved in the processing of separate semantic categories (tools and animals), with overlap in only the inferior frontal and fusiform gyri.

fMRI of Semantic Memory in Patients At-Risk for AD and after Therapeutic Intervention

Some studies have suggested minimal deficits in semantic memory performance in patients with early forms of MCI and AD [332, 333], while others show measurable impairments in MCI patients [341–343]. However, alterations in brain activation during semantic memory tasks has been observed in patients with MCI and AD, as well as patients

at-risk for developing AD due to genetic status and/or a family history of illness. A number of studies have shown increased activation in frontal and temporoparietal regions during semantic memory task performance in participants at-risk for AD due to *ApoE* genotype and/or family history of AD, even in the absence of performance differences [324, 344]. However, reduced activation in the inferior parietal and bilateral anterior cingulate during semantic categorization in *ApoE* ε4 positive participants has also been reported [345]. Likewise, participants with the presence of *ApoE* ε4 and/or family history of AD had a greater response to famous names in the posterior cingulate/precuneus, temporoparietal junction, and PFC, whereas controls had a larger activation to unfamiliar names in regions of the frontal and parietal lobes [346]. Due to the presence of alterations observed in fMRI studies of semantic memory in the absence of clinical deficits in performance, these paradigms may provide a useful biomarker for early AD.

Pharmacological intervention studies have also been performed using fMRI of semantic memory performance in patients with AD. A study by McGeown and colleagues measured fMRI activation pattern during a semantic association task in AD patients both before and after treatment with rivastigmine, a cholinesterase inhibitor and treatment for AD [347]. These results were compared with fMRI results during the same task in healthy older adults. After treatment with a cholinesterase inhibitor, patient with AD showed "more normal" activation patterns as compared to healthy older adults. Specifically, treatment with rivastigmine resulted in increased activation in the temporal and frontal lobes, as well as the bilateral fusiform gyri, relative to baseline in patients with AD. These results support the potential use of semantic memory fMRI activation changes as a biomarker for early diagnosis and treatment efficacy in patients with AD.

Summary

Semantic memory retrieval has primarily been linked to activations of the PFC, lateral temporal cortex, and posterior inferior parietal lobe using fMRI studies in young adults. In young adults, activations associated with semantic retrieval are primarily left-lateralized, while cognitively healthy older adults show decreased lateralization in the PFC. Similar to reports in episodic memory, patients with MCI and AD show altered activation during fMRI studies of semantic memory. The direction and magnitude of the alterations associated with MCI and AD may be dependent on disease severity. Functional connectivity studies in young adults have implicated a variety of functional semantic networks connecting the frontal, temporal, and parietal cortices. Finally, fMRI studies of semantic memory have also been utilized as biomarkers, with alterations in activation reported in patients at-risk for AD and after pharmacological interventions.

Working Memory

Working memory can be defined as the means by which small amounts of information are maintained in active stores and available for other cognitive processes. These other operations may include such processes as language comprehension, problem-solving, memory encoding, and many others. Working memory is distinct from short-term memory, which involves retaining information in mind but not engaging in other cognitive processes and not engaging the dorsolateral PFC [348, 349]. Working memory belongs to a broad concept of executive functions (also known as executive control or cognitive control). Other types of executive functions include inhibition and cognitive flexibility that are more or less tied to working memory [350].

Baddeley and colleagues proposed a model in which the working memory system has a central executive that, together with an episodic buffer, allocates limited attentional resources to separate subsystems for verbal and nonverbal information, referred to as the "phonological loop" and "visuospatial sketchpad," respectively [1, 2, 351]. Working memory subsystems, including the "phonological loop" and "visuospatial sketchpad" are thought to include two basic mechanisms: (1) a phonological or visuospatial store where the information in working memory is stored during use; and (2) an articulatory or coordinate system rehearsal process through which information in the storage is repeatedly updated and refreshed. For detailed reviews of models of working memory, see [2, 352, 353] and Table 30.4.

fMRI Studies of the Neural Basis for Working Memory

Although lesion studies provided the earliest mapping of the neural representations of working memory, functional neuroimaging studies have provided convincing evidence for the involvement of a broad network of brain areas in working memory processes. A number of different tasks are employed to measure working memory in functional neuroimaging studies, including paradigms featuring continuous monitoring of information (e.g. "*n*-back" tasks), delayed response, temporal ordering of material, and manipulation of information. Sample working memory fMRI probes that contrast or emphasize different processing demands are presented in Table 30.1c.

One theory of the neural representations of the subsystems of working memory proposes that like visual cortex for visual processing, unique discrete brain regions exist for different component of working memory [354, 365, 366]. Alternatively,

Table 30.4 Selected review articles of working memory

Working memory		
Authors	Study subjects	Article title
Smith et al. (1998) [354]	Young adults	Neuroimaging analyses of human working memory. *Proc Natl Acad Sci U S A.* Sep 29 1998;95(20):12061–12068.
Smith et al. (1998) [355]	Young adults	Components of verbal working memory: evidence from neuroimaging. *Proc Natl Acad Sci U S A.* Feb 3 1998;95(3):876–882.
Cabeza et al. (2000) [23]	Young adults	Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience.* 2000;12(1):1–47.
Grady et al. (2000) [24]	Healthy aging	Changes in memory processing with age. *Current Opinion in Neurobiology.* 2000;10:224–231.
Langley et al. (2000) [25]	Healthy aging	Functional neuroimaging of memory: implications for cognitive aging. *Microsc Res Tech.* Oct 1 2000;51(1):75–84.
Cabeza (2001) [27]	Healthy aging	Cognitive neuroscience of aging: contributions of functional neuroimaging. *Scand J Psychol.* Jul 2001;42(3):277–286.
Wager et al. (2003) [356]	Young adults	Neuroimaging studies of working memory: a meta-analysis. *Cogn Affect Behav Neurosci.* Dec 2003;3(4):255–274.
Hedden et al. (2005) [31]	Healthy aging	Healthy and pathological processes in adult development: new evidence from neuroimaging of the aging brain. *Curr Opin Neurol.* Dec 2005;18(6):740–747.
Rajah et al. (2005) [32]	Healthy aging	Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory. *Brain.* Sep 2005;128(Pt 9):1964–1983.
D'Esposito (2007) [357]	Young adults	From cognitive to neural models of working memory. *Philos Trans R Soc Lond B Biol Sci.* May 29 2007;362(1481):761–772.
Grady (2008) [37]	Healthy aging	Cognitive neuroscience of aging. *Ann N Y Acad Sci.* Mar 2008;1124:127–144.
Drzezga (2008) [39]	MCI and AD	Concept of functional imaging of memory decline in Alzheimer's disease. *Methods.* Apr 2008;44(4):304–314.
Han et al. (2009) [42]	MCI and AD	Functional magnetic resonance imaging of compensatory neural recruitment in aging and risk for Alzheimer's disease: review and recommendations. *Dement Geriatr Cogn Disord.* 2009;27(1): 1–10.
Baddeley (2010) [358]	Young adults	Working memory. *Curr Biol.* Feb 23 2010; 20(4):R136–140.
Turner et al. (2012) [359]	Healthy aging	Executive functions and neurocognitive aging: dissociable patterns of brain activity. *Neurobiol Aging*. 2012;33(4):826.e1–13
Diamond (2013) [350]	Young adults	Executive functions. *Annu Rev Psychol*. 2013;64:135–68
D'Esposito (2015) [360]	Young adults	The cognitive neuroscience of working memory. *Annu Rev Psychol*. 2015;66(1):115–42.
Lara et al. (2015) [361]	Young adults	The Role of Prefrontal Cortex in Working Memory: A Mini Review. *Front Syst Neurosci*. 2015;9:173.
Farras-Permanyer et al. (2015) [362]	MCI and AD	Mild cognitive impairment and fMRI studies of brain functional connectivity: the state of the art. *Front Psychol*, 2015. 6: p. 1095.
Kirova et al. (2015) [363]	MCI and AD	Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. *Biomed Res Int*, 2015. 2015: p. 748212.
Chai et al. (2018) [364]	Young adults	Working Memory From the Psychological and Neurosciences Perspectives: A Review. *Front Psychol*. 2018;9:401.

the storage of verbal and nonverbal material in working memory may occur in regions conventionally responsible for sensorimotor processing of this material, and connections with the central executive may provide selective attention on these sources of information during working memory tasks; once the task ends, this temporary brain coordination dissembles [367, 368]. Studies have provided evidence supporting the latter of these theories, although debate about the neural seats of working memory continues [355] (Table 30.5).

Initial functional imaging studies of healthy young adults engaging in working memory tasks suggested that a number of regions are involved in the various subsystems falling into two broad categories: the posterior sensorimotor and frontal executive recruitment (Fig. 30.8). Specifically, storage and maintenance of spatial material in working memory has primarily been mapped to the frontal eye fields (FEF), superior frontal sulcus (SFS), and intraparietal sulcus [374–376], which are regions known to be involved in the motor and functional aspects of eye movement. Activations of the primary visual cortex have also been reported in studies of spatial working memory [377]. Studies suggest that the representation of saccade eye movements and oculomotor coordinates may be stored in FEF, with rehearsal of the spatial saccade vector to the spatial target location involving communication between the FEF and intraparietal sulcus [376].

On the contrary, the storage and maintenance of verbal working memory information involves activity in the inferior posterior parietal cortex, precuneus, the lateral PFC (Broca's area), regions involved in the motor aspects of speech production (SMA and cerebellum), and subcortical regions (thalamus and striatum) [356, 357, 378–380]. Functional

Table 30.5 Additional selected review articles and meta-analyses for further reading

Authors	Article title	Significance
D'Esposito et al. (2003) [369]	Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. *Nat Rev Neurosci.* Nov 2003;4(11):863–872.	Alterations in BOLD with aging
Dickerson (2006) [370]	Functional magnetic resonance imaging of cholinergic modulation in mild cognitive impairment. *Curr Opin Psychiatry.* May 2006;19(3):299–306.	Functional MRI of cholinergic alterations
Greicius (2008) [371]	Resting-state functional connectivity in neuropsychiatric disorders. *Curr Opin Neurol.* Aug 2008;21(4):424–430.	Functional and resting-state connectivity
Rasch et al. (2010) [372]	Imaging genetics of cognitive functions: Focus on episodic memory. *Neuroimage.* Jan 11 2010.	Imaging genetics of memory
Loewenstein et al. (2018) [373]	Novel Cognitive Paradigms for the Detection of Memory Impairment in Preclinical Alzheimer's Disease. *Assessment*. 2018;25(3):348–59.	Novel memory paradigms related to AD
Stern et al. (2020) [241]	Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimers Dement*. 2020;16(9):1305–11.	Comprehensive update on cognitive reserve and related concepts
Yu et al. (2021) [50]	The human connectome in Alzheimer disease—relationship to biomarkers and genetics. *Nat Rev Neurol*, 2021. 17(9): p. 545–563.	Structural and functional connectome in MCI and AD

imaging studies have suggested that the inferior parietal cortex may be the site of phonological storage with sub-vocal rehearsal of verbal information in working memory involving coordination between the lateral PFC and SMA.

Nonspatial and nonverbal (i.e., objects, faces, etc.) information has been proposed to be stored primarily in posterior cortical areas, particularly along the inferior temporal lobe, during working memory processing [358, 381, 382]. For example, working memory processing of faces has been shown to be specifically associated with activations in the fusiform gyrus [383].

Finally, different frontal sub-regions may play different roles in working memory [355, 384, 385], with VLPFC (BA 45, 47) being involved in the selection, inspection, and comparison of stimuli held in short-term and long-term memory, DLPFC (BA 9, 46) in strategic reorganization and control of working memory contents, and frontal pole (BA 10) in the integration of results of multiple cognitive operations (e.g., monitor, update, maintain, and compare) to fulfill the higher behavioral goal [386].

Overall, the broad network of frontal and parietal lobar regions involved in working memory has been theorized to be divided into separate streams of information processing by the material type and/or the type and amount of executive functioning. Functional imaging studies have suggested material-specific hemispheric specialization in both the parietal cortex and the PFC, with left lateralization for processing of verbal information and right lateralization for both object and spatial information [23, 358, 387]. However, the lateralization by material type in the PFC is dependent on the amount of executive processing with tasks with greater executive demand showing more bilateral representation for all type of material. General divisions by material type based on dorsal/ventral information streams have also been proposed [349, 358]. For example, separate yet overlapping neural representations for visual working memory processes associated with spatial ("where") information following a dorsal stream of processing in the superior parietal lobe and object ("what") information following a ventral stream of processing in the inferior parietal temporal lobes have been observed in functional imaging studies [374]. This separation of neural representations in working memory is analogous to the dissociation in the visual system between dorsal occipitoparietal pathways thought to be involved in the processing of spatial locations and relations among objects, and the ventral occipitotemporal pathways that are involved in the processing of the perceptual characteristics that are important for recognition of objects [388, 389].

Of note, because early studies (e.g., [390]) of single neuron recording in primates showed that PFC activity still persists after the external stimuli is removed from visual fields, the pattern in PFC has been interpreted as mirroring the maintenance of relevant information for the completion of working memory task [359]. However, this prevailing view that PFC reflects temporary information storage in working memory has been challenged. Studies with fMRI multi-voxel pattern analysis show that specific stimulus information is not encoded by persistent PFC activity during the delay period in working memory [391], but instead by activity in posterior sensory areas [392]. These novel findings raise the possibility that delay-period PFC activity does not signify information maintenance, but rather serve as a top-down signal that biases sensorimotor processing in the posterior cortical regions [360, 361].

fMRI Studies of Working Memory in Healthy Aging

Behavioral and functional neuroimaging studies indicate the presence of age-related changes in working memory [393, 394]. Many of the functional neuroimaging studies of working

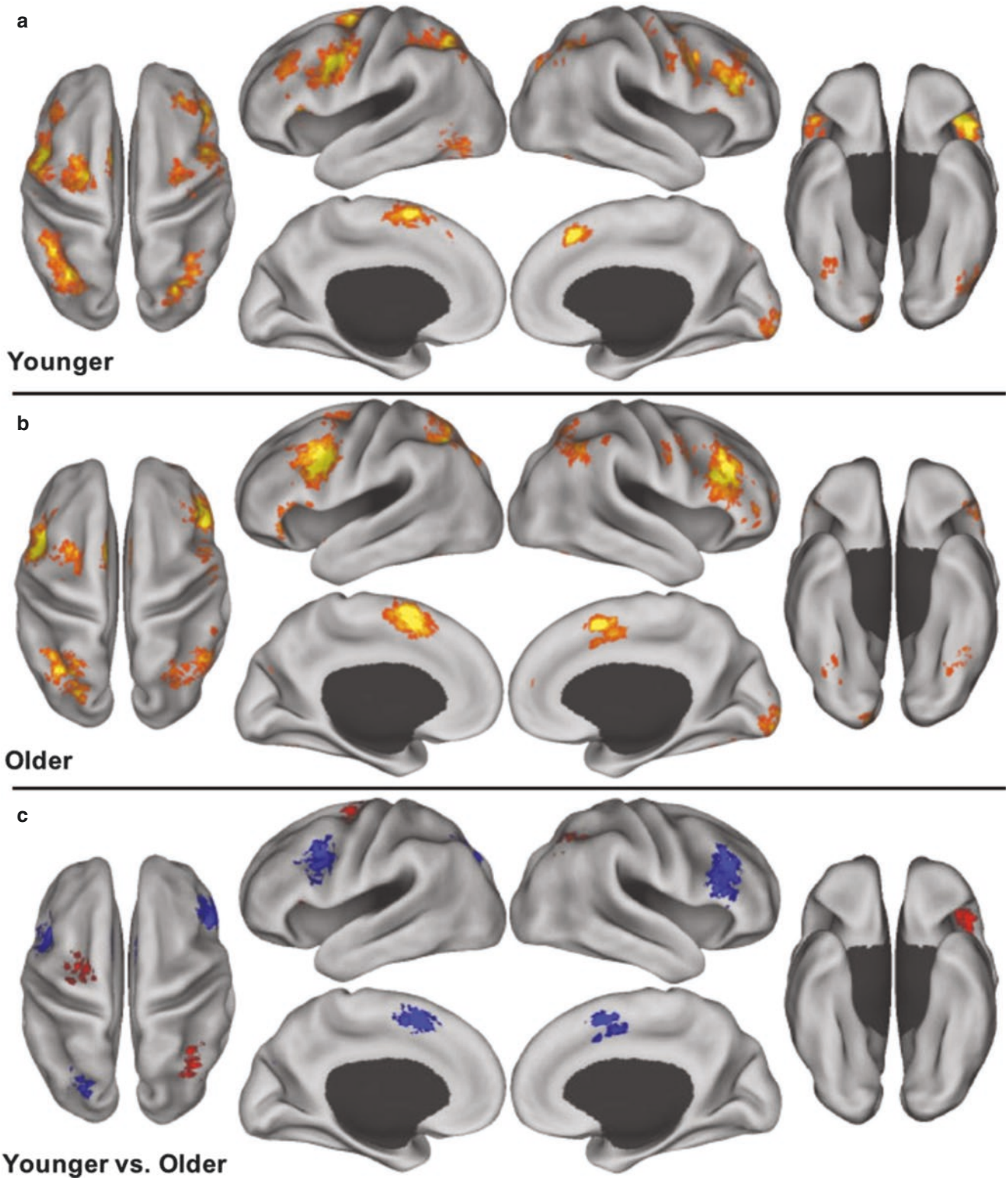

Fig. 30.8 Altered patterns of activation in working memory tasks with normal aging. Based on 19 studies of working memory, a reliable recruitment of lateral PFC and posterior parietal brain regions is revealed in both younger (**a**) and older (**b**) adults. However, younger adults recruit more posterior regions (red color in **c**) including frontal eye fields, whereas older adults show bilateral frontal activation (blue color in **c**), a pattern consistent with the Hemispheric Asymmetry Reduction in Old Adults ("HAROLD") model. (Reproduced with permission from Turner and Spreng 2012 [362])

memory in normal aging have reported increased activity in older adults relative to younger controls, as well as increased bilateral activations, similar to that seen in other types of memory (i.e., "HAROLD" model in episodic memory) [144, 395]. Studies in older adults utilizing working memory paradigms with all material types (spatial, verbal, and nonverbal, nonspatial) have reported similar increases in activity in the PFC, parietal lobe, and other regions relative to healthy young adults [33, 39, 151, 395–398]. Age-related deficiencies in hippocampal activation have also been demonstrated for feature-binding in working memory, the process whereby individual elements of experience are bound together [399].

A meta-analysis by Rajah and D'Esposito [39] suggests that age-related changes in PFC activity are region specific [39]. For the ventral PFC, there are mixed results, with some studies showing greater activation in older adults relative to young controls and others showing the reverse [325, 400]. However, activity in the dorsal PFC during working memory tasks has consistently been reported to be greater in healthy older adults relative to young adults [148, 325], which was confirmed by another meta-analysis [362] that found the engagement of bilateral dorsal PFC (together with supplementary motor cortex and left inferior parietal lobe) in older adults. Finally, the anterior PFC shows bilateral activation during working memory tasks in older adults, while young adults show only unilateral activation [325, 399]. The increased activity and bilateral representation may be a compensatory change in older adults, as there are age-associated structural changes in PFC [137]. Interestingly, increased activation appears to be selective for paradigms in which the performance of older adults is equivalent to young controls [151, 401]. Studies in which older adults show impaired performance relative to young controls demonstrate a different pattern of activation, with older adults showing equal or less activation in the PFC relative to younger participants [396] (Fig. 30.8).

fMRI Studies of Working Memory in MCI and AD

In addition to assessing changes in older adults, fMRI studies have been used to measure alterations in brain activity during working memory tasks in patients with MCI and AD. Patients with AD show marked deficits in working memory [402], while patients with MCI show subtler changes in working memory. fMRI studies of working memory processes in patients with AD have shown mixed results, which may be dependent on the severity of the working memory deficit during the task [403–405]. A study by Yetkin et al. [405] suggested that patients with AD showed increased activation in the right superior frontal gyrus, bilateral middle frontal gyri, bilateral anterior cingulate, bilateral middle temporal gyri, and bilateral fusiform gyri relative to age-matched controls [405]. Importantly, in this study, AD patients did not show significantly impaired performance. In another fMRI study of verbal working memory in patients with AD, patients showed significantly reduced performance, along with reduced activation in the left frontal pole, left ventrolateral PFC, left insula, as well as the right premotor cortex and increased activation in only the left precuneus [403]. In a related study, Firbank et al. [406] found that AD patients had similar but greater activation of the fronto-parieto-occipital network (without engagement of additional brain regions) particularly under difficult vs. easy conditions of an attentional and executive task, in comparison to healthy controls. AD patients also had slower reaction times. Together, these results suggest that the extent of activation during working memory tasks is potentially associated with the level of performance in AD patients and may support a compensatory role for the observed increases in activation.

Patients with MCI also show alterations in activation during working memory tasks relative to healthy older adult controls. Converging evidence across studies seems to suggest that MCI patients engage frontal regions in a compensatory fashion to accomplish working memory tasks ([405, 407–409], cf. [410]). For example, one study [408] demonstrated that MCI hyperactivation in the left frontal areas predicted better task performance in MCI relative to controls and that those MCI patients with low performance tended to show frontal hypoactivation. Additionally, less task-related deactivation in the insula and lingual gyrus has been reported in MCI [411]. When interpreting these sometimes inconsistent results, one should consider that brain activation also varies as a function of working memory load [412]. At lower working memory loads, greater activity was observed in MCI in comparison to controls, whereas at higher levels, reduced activation in similar regions were instead observed in MCI [412]. Structural integrity of these regions is also an important factor, as cortical thickness in bilateral parietal, temporal, and frontal cortices has been shown to be associated with executive function [413].

Functional neuroimaging studies of working memory have also been shown to be useful in contrasting different types of dementia and may one day assist in differential diagnosis of dementia type. In a study comparing patients with AD to individuals with early FTD on a working memory task, both groups showed activation of frontal, parietal, and thalamic regions [414]. However, patients with FTD showed less frontal and parietal activation and greater cerebellar activation than those with AD. The authors suggested that fMRI may be useful for differentiating AD and FTD early in the disease course.

Investigations of working memory function in patients with AD have also been useful in characterizing the brain regions that are involved in working memory subsystems. Patients with AD often show a particularly significant impairment in the episodic buffer subsystem of working memory, as proposed by Baddeley and colleagues. In order to investigate the neural substrate of the episodic memory buffer, Berlingeri et al. [415] compared atrophy on structural MRI between AD patients showing significant impairments in the episodic buffer and patients with AD who show relative sparing of this subsystem [415]. Patients with impaired episodic buffer processing showed significantly greater atrophy of the left anterior hippocampus relative to those with intact episodic buffer processing. The authors suggest that the anterior hippocampus may be an important region for this working memory subsystem, given the known role for the MTL in episodic memory processing. Results from an fMRI study by Luck and colleagues also support the importance of the MTL as the neural seat of the episodic buffer. In healthy young adults, activation in the MTL was observed during encoding and maintenance of episodic material in working memory, but not for retrieval [416].

fMRI Studies of Working Memory Associated Connectivity in Healthy Young Adults

The distributed neural activity associated with working memory tasks represents a set of functionally connected networks including multiple brain regions. A number of reports have addressed the functional connectivity of fMRI activations in anatomically distinct brain regions during working memory tasks in healthy young adults [417–419]. Using a delayed face recognition working memory task, two functional networks connecting the fusiform gyrus and right inferior frontal gyrus, as well as the fusiform gyrus and hippocampus were identified [419]. The strength of these connections was dependent on working memory load. Protzner and colleagues investigated whether the modality of working memory input would activate different functional networks [418]. Three unique functional networks were identified, including a modality-independent network which included the ventrolateral PFC, DLPFC, occipitoparietal cortex, and temporal pole, an auditory-input network connecting the left superior temporal gyrus, frontal operculum, and bilateral superior parietal cortex, and a visual-input network including the primary visual cortex and right anterior PFC. A number of studies have also implicated the DMN in working memory tasks [417, 420, 421]. Deactivation of this network, including the posterior cingulate, medial frontal cortex, was significantly associated with the performance on working memory tasks, as well as task difficulty.

fMRI Studies of Working Memory Associated Connectivity in Healthy Aging, MCI, and AD

Alterations in working memory associated functional connectivity have also been reported in cognitively healthy older adults, as well as in patients with MCI and AD. Healthy older adults show increased functional connectivity in working memory task-related networks, including a functional network connecting the superior and inferior parietal cortex, inferior frontal gyri, DLPFC, premotor cortex, and occipital cortex [422]. However, other data suggests reduced functional connectivity of working memory networks in older adults, particularly reduced activity of parietal-PFC networks [423]. Similarly, although MCI showed decreased frontal (among other regions) activity during visuospatial working memory, there was an increased local efficiency in the background/task-residual network, suggesting additional efforts to maintain the cognitive state [424]. However, other studies found deficits in the background network in MCI relative to controls [425, 426].

The DMN shows decreased connectivity in healthy older adults relative to younger controls, suggesting altered resting state activity with aging [235, 422, 427]. Furthermore, patients with MCI and AD show more significant impairment of the DMN [243, 407, 428]. However, one related study [429] found, using a network measurement based on the graph theory (i.e., eigencentrality), that AD patients had increased resting-state connectivity relative to controls in the anterior cingulate and paracingulate gyrus, two regions potentially linked to executive function. In another recent study, AD patients were found to have hyperconnectivity between DMN and the dorsal attention network during an attentional and executive task, which may, according to the authors, reflect a compensation for DMN dysfunction [430]. These findings underlying altered working memory networks may be related to structural integrity and connectivity [431].

fMRI Studies of Working Memory in Patients At-Risk for AD and After Pharmacological Intervention

Though SCD is generally thought to show no impairment on standard neuropsychological tests, behavioral research seems to suggest that SCD is associated with poorer performance on executive function tasks that particularly require inhibition and time-sensitive goal achievement (e.g., Stroop color naming) [432]. One fMRI study also found that the SCD group showed poorer performance than controls on visual working memory tasks, and that this impairment was potentially linked to lower average resting-state functional

connectivity within a posterior memory system [433]. In a related study involving only middle-aged women, women who had subjective cognitive complaints showed greater activation in the working memory network than women without complaints during an *n*-back task [434]. Additionally, women with complaints recruited additional regions related to working memory as the task load increased. This hyperactivation is likely compensatory in nature, given that no group difference in task performance was found. Another study involving divided attention supported this conclusion by showing that SCD engaged increased activation in left MTL, bilateral thalamus, posterior cingulate and caudate, regions whose activation was reportedly decreased in AD during the same task [435]. Thus, the relative maintenance of working memory task performance as observed in early stages of AD, such as SCD, is likely mediated by brain hyperactivation. As the disease progresses, such compensatory activation is no longer effective and instead the hyperactivation reverses to hypoactivation, reflecting potential underlying neuronal losses.

Similar to reports utilizing episodic and semantic memory paradigms, fMRI studies of working memory have been performed in patients at increased risk for developing AD due to genetic background (i.e. *ApoE* ε4 positive) and/or family history of dementia. Young adults with an increased risk for AD due to the presence of an *ApoE* ε4 allele show greater activity in widespread frontal, parietal, temporal, and other regions during an fMRI working memory challenge than those who are *ApoE* ε4 negative [436]. Similar results have been shown in older adults who are cognitively healthy but *ApoE* ε4 positive [16], although some mixed reports have emerged [275]. Wishart and colleagues found that *ApoE* ε4 positive older adults show greater activation during an *n*-back working memory task in the bilateral medial frontal gyri, bilateral medial parietal regions, right DLPFC, and right anterior cingulate gyrus relative to older adults without an *ApoE* ε4 allele [16]. The identification of fMRI patterns of altered activation during working memory tasks provides an early biomarker of functional changes that may be predictive of future progression to dementia, but longitudinal studies are needed.

Similar to fMRI studies of episodic memory, anticholinergic therapies have been investigated using fMRI of working memory tasks in healthy young and adults [437, 438]. Reduced extent and amplitude of PFC activation after administration of scopolamine or mecamylamine was reported in studies with young and older women [437, 438]. Several studies have also investigated working memory related activation patterns on fMRI in response to cholinergic interventions in patients with MCI and AD. Goekoop and colleagues in a one group design evaluated whether an 8-week treatment with galantamine could cause alterations in fMRI activation patterns and magnitude in patients with MCI [439]. Relative to baseline, patients with MCI showed increased activation in the right precuneus and middle frontal gyrus in response to a working memory task. Furthermore, the extent of increased activation was significantly associated with increased performance on the working memory task. Saykin et al. [410] examined the effects of a 10-week treatment with donepezil in patients with MCI relative to untreated but rescanned healthy older adult controls and found similar treatment-induced increases in activation during a working memory task relative to baseline [410]. In this study, patients with MCI showed reduced frontal and parietal activation during a working memory task at baseline relative to healthy older adult controls, despite similar performance. However, after treatment, MCI patients demonstrated a significant increase in activation in the left superior frontal gyrus, DLPFC, temporal lobe, and occipital lobe. After treatment with donepezil, patients with MCI demonstrated nearly equivalent brain activation and performance to controls, suggesting a "normalization" of working memory processes after treatment. The extent of increased activity in the frontal lobe was also significantly associated with both increased performance and baseline hippocampal volume, suggesting different treatment responsiveness based on severity of baseline MTL atrophy.

Other studies have assessed the effects of cholinergic therapies on working memory related activations in patients with AD. Rombouts and colleagues examined the effect of acute cholinergic enhancement on brain activity during working memory in a sample of patients with mild AD [279]. After a single dose of rivastigmine, activity in the PFC cortex, including the left middle and superior frontal gyri, was enhanced during the basic working memory condition. When the working memory demands were increased, both increases and decreases in activation in different regions were seen. Specifically, increased working memory load led to rivastigmine-related increased activation in the left middle frontal gyrus, as well as the right inferior and superior frontal gyri. Increased working memory load was also associated with a decrease in right middle and superior frontal gyri activation. McGeown et al. [347] assessed the effects of chronic administration (20-weeks) of rivastigmine on working memory associated brain activation in patients with mild AD, as well as untreated age-matched controls [347]. Patients with AD showed increased activation during a working memory task in the right inferior, middle, and superior frontal gyri, as well as the right medial frontal and precentral gyri after chronic treatment with rivastigmine relative to baseline. Treatment with rivastigmine also led to decreased activation during a working memory task in AD patients in the left middle frontal, precentral and cingulate gyri, as well as the left insula and thalamus, relative to baseline. Older adult controls demonstrated primarily right frontal and insular activation during this working memory task. These results suggest that

chronic treatment with rivastigmine leads to increased right lateralization of working memory activation in patients with AD, which leads to a more "normal" pattern of activation. However, the extent to which these changes are task-dependent remains to be determined.

The results of studies with cognitively healthy individuals with high genetic risk for AD suggest that fMRI studies of working memory may be a particularly sensitive biomarker for sub-clinical alterations in cognitive functioning and future disease progression. Additionally, studies assessing the effects of acute and chronic treatment with cholinergic interventions in healthy elders and patients with MCI and AD indicate that fMRI techniques can be useful in determining the brain regions in which a medication exerts its functional effects. Overall, fMRI studies of working memory are well suited for measuring changes in brain function even in the absence of measurable behavioral and cognitive deficits. These techniques may also be useful when employed before and after drug treatment to monitor mechanisms and efficacy.

Summary

fMRI studies of working memory in young adults have shown a pattern of bilateral frontal, parietal, and temporal activation, although differences in the particular regions identified varies with the type of information being processed (i.e. verbal, object, spatial, etc.). Older adults show increased activation and increased bilateral representation, while patients with MCI and AD show either increased or decreased activations depending on the severity of working memory impairment. Connectivity studies in young adults have shown functional networks including the parietal, frontal, and temporal cortices associated with working memory, as well as deactivation of the DMN. Healthy older adults and patients with MCI and AD show alterations in functional and resting-state connectivity. fMRI studies of working memory have also shown altered activation patterns in individuals at-risk for dementia and after pharmacological interventions, suggesting utility of this measure as a biomarker.

Methodological Issues in the Use of fMRI in Aging and Dementia Research

A number of methodological considerations must be addressed when conducting and interpreting fMRI research in aging and dementia. For example, there is evidence to suggest that normal aging affects some aspects of the coupling of the hemodynamic response with neural activity [369, 440]. Using a simple reaction time task (one known to evoke similar electrical potentials in young and old adults), D'Esposito and colleagues found in excess of fourfold more activated voxels in sensorimotor cortex in young than older participants [441]. Other aspects of the hemodynamic response, such as the shape of the curve and the within-group variance, did not significantly differ as a function of age. On the contrary, Huettel and colleagues found age differences in the shape of the hemodynamic response, its within-group variability, and the number of activated voxels on a visual task [442]. The younger adults showed a later time to peak, less variability, and twice as many activated voxels as the older adults, though both groups activated similar regions of visual cortex. However, age-related prolongation of the time lag in signal change on fMRI has also been reported [443]. Other groups have observed smaller areas [444, 445] or larger areas [446] of activation in older adults compared to younger individuals, or no significant differences between groups [322]. Buckner and colleagues observed similar summation of the hemodynamic response across brain regions examined with a sensorimotor task and suggested that even if absolute measurement differences exist between age groups, there should be preservation of relative task-related changes in activation [447]. Furthermore, the type of task performed could have different BOLD signal variability resulting from different vascular variability [448]. These issues indicate the need for sophisticated experimental design, postprocessing, and interpretation of fMRI data in aging research in relation to performance, strategy, reaction time, and other variables to ensure that reported findings are not spurious effects of basic physiological or artefactual signal differences between young and older groups.

Many fMRI studies in young and older controls, as well as patients with MCI and AD, utilize subtraction methods to determine regions of activation associated with a task. In other words, activation patterns during a cognitive task of interest are compared to those elicited by a control task. The control task can take a wide variety of forms, including other attention or cognitive tasks which are not of interest (i.e. episodic memory task vs. reading words), responding to a similar task paradigm but with pseudo-stimuli (i.e. semantic task vs. pseudo-words), or a resting state (i.e. fixation). However, it is a very large assumption to consider the difference between a task of interest and even a well-designed control task to be specific to only activations associated with the cognitive process of interest [449, 450]. Event-related fMRI designs may be useful in addressing some of these concerns.

Further technical and scientific issues are encountered when using fMRI to study patients with disease states, including MCI and AD. Currently, the conditions and importance of alterations in brain activity in patients with AD are not well understood. For example, does increased activation in patients relative to controls reflect compensation, de-differentiation, or both? Could expanded activation represent

a disinhibition in some cases? Here, fMRI methods beyond the standard univariate averaged activations might be able to provide more evidence to support one explanation over the other. For example, one recent fMRI study using model-based multivariate analysis challenged the conception of PFC compensation by suggesting that the age-related increase in frontal activity during memory processing did not carry additional information and simply reflected reduced efficiency or specificity [451]. In the same vein, effective connectivity such as dynamic causal modeling can allow the directionality of brain connectivity to be inferred, affording insights into the compensation for disease-related deficits that are not available from functional connectivity [452, 453]. Alternatively, brain stimulation techniques (e.g., transcranial magnetic stimulation, transcranial direct current stimulation) could potentially offer more definite answers through the direct manipulation of potential "compensatory" regions such that a disruption or enhancement of behavioral performance could be observed correspondingly. Also, if patients perform abnormally on an activation task, how should the resulting activation maps be compared to those of healthy controls with no performance deficits? How should atrophy and vascular function be taken into account when interpreting fMRI data? Approaches that integrate structural neuroimaging, carefully designed activation tasks, as well as close monitoring of in-scanner task performance will likely help address such questions [176]. Finally, the use of well-designed event-related fMRI techniques can help to address issues of performance by allowing comparison of only successful task responses as well as analysis of errors. An ideal task should also avoid either the floor or ceiling effects among both patients and controls; this is not a trivial criterion in light of the significant cognitive decline associated with AD.

Future Directions

Multi-Modal Imaging Studies and Technological Advancements in MRI

Approaches that have been increasingly used in recent research and likely in the future involve combining fMRI with other imaging techniques, including electroencephalogram (EEG), PET imaging (e.g., amyloid and tau—two hallmarks of AD), arterial spin labeling (ASL), an MR-based technique to measure changes in cerebral blood flow, and diffusion tensor imaging (DTI), a technique to measure white matter integrity [454–463]. Multi-modal methods, by evaluating participants with two or more types of imaging, can add other dimensions to improve characterization of the neural substrates of memory in healthy and disease states, provide insights into underlying neural mechanism, and reconcile mixed findings in functional MRI studies.

In an early study featuring five in vivo imaging modalities, Buckner et al. found that amyloid deposition, cerebral atrophy, decreased glucose metabolism occurred in posterior cingulate, retrosplenial, and lateral parietal cortex in AD [464]. The alteration in these posterior cortical regions helps explain memory impairment as a prominent symptom of AD, because these areas were also active during resting and successful memory retrieval in young adults. In a series of studies, Sperling and colleagues found that amyloid deposition, as measured by PET, was associated with impaired DMN function in pre-MCI [457], aberrant entorhinal activity during an episodic memory task in cognitively normal older adults [465], and hippocampal hyperactivity during memory encoding cross-sectionally and longitudinally in MCI [466]. One study [467] also uncovered a relationship between reduced intrinsic functional connectivity in the medial parietal cortex and increased regional amyloid in MCI. Another study demonstrated that increased amyloid burden was related to higher posterior left middle temporal gyrus activation during a semantic memory task in normal adults [468]. Amyloid positive normal older adults also had more hippocampal activation during face-name episodic memory task [469]. It is possible that hippocampal hyperactivity may precede amyloid deposition [470], in that accumulation of amyloid is associated with memory task-related greater hippocampal hyperactivity and more importantly mediates subsequent memory decline [471].

With the recent advent of in vivo tau PET tracers [461–463], researchers have started to examine the interplay between tau, amyloid, and functional activation during memory tasks in patients with or at risk for AD. For example, one preliminary study [472] showed that tau pathology particularly in the MTL, but not amyloid, was associated with the amnestic variant of AD, older age, *ApoE* ε4 genotype, and memory performance on neuropsychological tests in AD patients. MTL tau was also related to aberrant functional MTL activity during memory encoding in the normal older adults [473] and predicted episodic memory performance independent of amyloid status [474]. Tau deposition also had an overall negative association with resting-state functional connectivity, whereas amyloid had a positive association in cognitively normal older adults [475]. Another study found an interaction between tau and amyloid to affect functional connectivity [476]. Recent studies are focusing on the impact of specific pathophysiology in MCI and dementia, including amyloid and tau deposition as assessed by PET or cerebrospinal fluid biomarkers, on the structural and functional brain connectome. Yu et al. [50] provide a detailed review of this topic including the role of genetic factors.

Novel fMRI Memory Paradigms

Although the utilization of the common fMRI memory paradigms tapping human episodic, semantic, and working memory systems has been fairly fruitful in helping us understand memory impairment, there are several reasons why new paradigms are needed [373]. First, given the growing research interests in SCD (see section on "Patients At-Risk for AD"), more sensitive and potentially cognitively challenging memory tests may be able to detect these early subtle memory alterations reported by SCD participants in terms of behavior and fMRI activation. Second, the recent development and emphasis of a vast array of AD biomarkers, such as PET imaging, fluid-based markers, and genetics, among others, demand clinically meaningful end points with which to assess their specificity and sensitivity [477]. Under these circumstances, more subtle memory dysfunction in preclinical AD, as could be potentially detected by newer tasks, is one of the viable and relevant candidates. Third, a memory paradigm with high test–retest reliability and low inter-individual variability could provide ideal cognitive targets and fMRI indices to examine and track the effects of any disease-modifying treatments and intervention. Therefore, the following is a brief survey of fMRI memory paradigms that are less common in the AD literature but have been employed to investigate different aspects or types of memory related to AD, in the hope that additional novel paradigms would be inspired by and derived from the existing ones.

One crucial facet of episodic memory is termed pattern separation, which was proposed as a computational processing to account for our ability to distinguish complex and similar items from each other (e.g., similar faces) [32, 478]. It is thought to be instantiated in and limited to the CA3/dentate gyrus subfields of hippocampus to orthogonalize similar items or memories into highly dissimilar, nonoverlapping representations [479]. One study suggested that hypoactivity in the anterolateral entorhinal cortex and hyperactivity in the CA3/dentate gyrus underlie deficits in pattern separation in older adults [480]. In addition, other hippocampus-based cognitive functions that have been studied in AD include topographical memory (spatial navigation) [481], category learning (hippocampal-mediated semantic learning) [482], and prospective memory (remembering an action in the future) [483]. Two studies explored the self-reference effect (better information encoding when referring to oneself) and found reduced activity in angular gyrus during encoding in early AD patients [484] and retrieval failure associated with reduced grey matter density in the lateral PFC in AD patients [485]. AD anosognosia, the unawareness of one's own illness and a concept related to metacognition and metamemory [486], was inspected in two studies which point to the importance of medial PFC in this effect [487, 488]. Finally, it is important to note that some forms of memory are relatively preserved in AD, such as priming effect (the facilitation of the response to a stimuli by a previous exposure to an earlier stimuli) [489] and musical memory (presumably subserved by anterior cingulate cortex and pre-supplementary motor cortex) [490].

Conclusion

Episodic, semantic, and working memory processes are mediated by widely distributed cortical and subcortical networks. Frontal, parietal, and temporal cortices are functionally connected as part of multiple networks that are essential for successful memory encoding and retrieval. Many age-related changes in neural functions associated with memory have been reported, including reduced prefrontal asymmetry, altered MTL, and frontal activations during memory tasks, and changes in connectivity between frontal, parietal, and temporal lobe functional and resting-state networks. These changes may be a direct effect of structural and physiological changes in the aging brain and may also reflect age-related differences in cognitive strategy or approach to task performance. In individuals with MCI and AD, further disease stage-dependent alterations are observed. Early MCI and other preclinical and prodromal stages often are associated with increased activation during memory tasks, which has been conceptualized as a compensatory response. However, late-stage MCI and AD dementia patients have shown significantly reduced activations, likely resulting from neurodegeneration of MTL and PFC regions involved in memory processing. MCI and AD patients also show significantly disrupted functional and resting-state memory networks reflecting degeneration and disconnection of key regions.

Despite significant technical challenges, research using fMRI and other neuroimaging techniques is advancing knowledge of the effects of aging and dementia on the brain's memory circuitry. These findings have major potential implications for early detection of prodromal stages of neurodegenerative dementias and treatment monitoring, especially if used in combination with genetic testing and PET-based methods for in vivo detection of amyloid plaque and tau tangle burden in AD [462, 491–496]. fMRI has already demonstrated promise in imaging genomics studies of memory-related variants, reflecting its unique sensitivity and applicability to subtle alterations in memory function. Advances in MRI technology and combining fMRI with other multi-modal imaging techniques will permit enhanced characterization of the neuroanatomic and physiological substrates of memory both in healthy individuals and in disease processes. Early detection of disease and treatment

monitoring are especially important at this time because many disease modifying medications to slow the progression of neurodegeneration and cognitive decline are under development [497]. In 2021, the FDA granted accelerated approval to aducanumab (Aduhelm), the first putatively disease modifying anti-amyloid agent. The approval was highly controversial as the ability to clear amyloid from the brain was not accompanied by clear evidence of efficacy in terms of slowing clinical progression [498]. Results from trials of several other anti-amyloid monoclonal antibodies are expected to read out in the next year or two, which may clarify whether the amyloid hypothesis will lead to an effective treatment. As treatment development progresses, trials of therapeutic agents could greatly benefit from more sensitive and disease-specific functional techniques for detecting and monitoring the progression of disease, as well as treatment response. fMRI techniques, coupled with amyloid and tau biomarkers, hold potential as sensitive biomarkers but further optimization of resting state or task-based methods for clinical trials is needed to realize the potential.

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References

1. Baddeley A. Working memory. In: Gazzaniga MS, editor. The cognitive neurosciences. Cambridge, MA: MIT Press; 1995.
2. Baddeley A. Recent developments in working memory. Curr Opin Neurobiol. 1998;8(2):234–8.
3. Krause JB, Taylor JG, Schmidt D, Hautzel H, Mottaghy FM, Muller-Gartner HW. Imaging and neural modeling in episodic and working memory processes. Neural Netw. 2000;13(8–9):847–59.
4. Tulving E, Donaldson W. The organization of memory. New York, NY: Academic Press; 1972.
5. Nyberg L, Marklund P, Persson J, Cabeza R, Forkstam C, Petersson KM, et al. Common prefrontal activations during working memory, episodic memory, and semantic memory. Neuropsychologia. 2003;41(3):371–7.
6. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004;256(3):183–94.
7. Jessen F, Amariglio RE, Buckley RF, van der Flier WM, Han Y, Molinuevo JL, et al. The characterisation of subjective cognitive decline. Lancet Neurol. 2020;19(3):271–8.
8. Tulving E, Markowitsch HJ. Episodic and declarative memory: role of the hippocampus. Hippocampus. 1998;8(3):198–204.
9. Dudai Y. The neurobiology of consolidations, or, how stable is the engram? Annu Rev Psychol. 2004;55:51–86.
10. Kelley WM, Miezin FM, McDermott KB, Buckner RL, Raichle ME, Cohen NJ, et al. Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. Neuron. 1998;20(5):927–36.
11. Wagner AD, Desmond JE, Glover GH, Gabrieli JD. Prefrontal cortex and recognition memory. Functional-MRI evidence for context-dependent retrieval processes. Brain. 1998;121(Pt 10):1985–2002.
12. Hill PF, King DR, Rugg MD. Age differences in retrieval-related reinstatement reflect age-related dedifferentiation at encoding. Cereb Cortex. 2021;31(1):106–22.
13. Saykin AJ, Flashman LA, Frutiger SA, Johnson SC, Mamourian AC, Moritz CH, et al. Neuroanatomic substrates of semantic memory impairment in Alzheimer's disease: patterns of functional MRI activation. J Int Neuropsychol Soc. 1999;5(5):377–92.
14. Martin S, Saur D, Hartwigsen G. Age-dependent contribution of domain-general networks to semantic cognition. Cereb Cortex. 2022;32(4):870–90.
15. Rypma B, D'Esposito M. Isolating the neural mechanisms of age-related changes in human working memory. Nat Neurosci. 2000;3(5):509–15.
16. Wishart HA, Saykin AJ, Rabin LA, Santulli RB, Flashman LA, Guerin SJ, et al. Increased brain activation during working memory in cognitively intact adults with the APOE epsilon4 allele. Am J Psychiatry. 2006;163(9):1603–10.
17. Johnson JD, Rugg MD. Recollection and the reinstatement of encoding-related cortical activity. Cereb Cortex. 2007;17(11):2507–15.
18. Fletcher PC, Frith CD, Rugg MD. The functional neuroanatomy of episodic memory. Trends Neurosci. 1997;20(5):213–8.
19. Desgranges B, Baron JC, Eustache F. The functional neuroanatomy of episodic memory: the role of the frontal lobes, the hippocampal formation, and other areas. NeuroImage. 1998;8(2):198–213.
20. Lepage M, Habib R, Tulving E. Hippocampal PET activations of memory encoding and retrieval: the HIPER model. Hippocampus. 1998;8(4):313–22.
21. Schacter DL, Wagner AD. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus. 1999;9(1):7–24.
22. Wagner AD, Koutstaal W, Schacter DL. When encoding yields remembering: insights from event-related neuroimaging. Phil Trans R Soc Lond Ser B Biol Sci. 1999;354(1387):1307–24.
23. Cabeza R, Nyberg L. Imaging cognition II: An empirical review of 275 PET and fMRI studies. J Cogn Neurosci. 2000;12(1):1–47.
24. Davachi L. Item, context and relational episodic encoding in humans. Curr Opin Neurobiol. 2006;16(6):693–700.
25. Eichenbaum H, Yonelinas AP, Ranganath C. The medial temporal lobe and recognition memory. Annu Rev Neurosci. 2007;30:123–52.
26. Vilberg KL, Rugg MD. Memory retrieval and the parietal cortex: a review of evidence from a dual-process perspective. Neuropsychologia. 2008;46(7):1787–99.
27. Spaniol J, Davidson PS, Kim AS, Han H, Moscovitch M, Grady CL. Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. Neuropsychologia. 2009;47(8–9):1765–79.
28. Kim H. Dissociating the roles of the default-mode, dorsal, and ventral networks in episodic memory retrieval. NeuroImage. 2010;50(4):1648–57.
29. Kim H. Neural activity that predicts subsequent memory and forgetting: a meta-analysis of 74 fMRI studies. NeuroImage. 2011;54(3):2446–61.
30. Cabeza R, Ciaramelli E, Moscovitch M. Cognitive contributions of the ventral parietal cortex: an integrative theoretical account. Trends Cogn Sci. 2012;16(6):338–52.
31. Rugg MD, Vilberg KL. Brain networks underlying episodic memory retrieval. Curr Opin Neurobiol. 2013;23(2):255–60.
32. Moscovitch M, Cabeza R, Winocur G, Nadel L. Episodic memory and beyond: the hippocampus and neocortex in transformation. Annu Rev Psychol. 2016;67(1):105–34.
33. Grady CL, Craik FI. Changes in memory processing with age. Curr Opin Neurobiol. 2000;10(2):224–31.

34. Langley LK, Madden DJ. Functional neuroimaging of memory: implications for cognitive aging. Microsc Res Tech. 2000;51(1):75–84.
35. Cabeza R. Cognitive neuroscience of aging: contributions of functional neuroimaging. Scand J Psychol. 2001;42(3):277–86.
36. Cabeza R. Hemispheric asymmetry reduction in old adults: the HAROLD model. Psychol Aging. 2002;17:85–100.
37. Cabeza R, Anderson ND, Locantore JK, McIntosh AR. Aging gracefully: compensatory brain activity in high-performing older adults. NeuroImage. 2002;17(3):1394–402.
38. Hedden T, Gabrieli JD. Healthy and pathological processes in adult development: new evidence from neuroimaging of the aging brain. Curr Opin Neurol. 2005;18(6):740–7.
39. Rajah MN, D'Esposito M. Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory. Brain. 2005;128(Pt 9):1964–83.
40. Grady CL. Cognitive neuroscience of aging. Ann N Y Acad Sci. 2008;1124:127–44.
41. Wagner AD. Early detection of Alzheimer's disease: an fMRI marker for people at risk? Nat Neurosci. 2000;3(10):973–4.
42. Zakzanis KK, Graham SJ, Campbell Z. A meta-analysis of structural and functional brain imaging in dementia of the Alzheimer's type: a neuroimaging profile. Neuropsychol Rev. 2003;13(1):1–18.
43. Wierenga CE, Bondi MW. Use of functional magnetic resonance imaging in the early identification of Alzheimer's disease. Neuropsychol Rev. 2007;17(2):127–43.
44. Dickerson BC, Sperling RA. Functional abnormalities of the medial temporal lobe memory system in mild cognitive impairment and Alzheimer's disease: insights from functional MRI studies. Neuropsychologia. 2008;46(6):1624–35.
45. Drzezga A. Concept of functional imaging of memory decline in Alzheimer's disease. Methods. 2008;44(4):304–14.
46. Han SD, Bangen KJ, Bondi MW. Functional magnetic resonance imaging of compensatory neural recruitment in aging and risk for Alzheimer's disease: review and recommendations. Dement Geriatr Cogn Disord. 2009;27(1):1–10.
47. Dickerson BC, Sperling RA. Large-scale functional brain network abnormalities in Alzheimer's disease: insights from functional neuroimaging. Behav Neurol. 2009;21(1):63–75.
48. Ries ML, Carlsson CM, Rowley HA, Sager MA, Gleason CE, Asthana S, et al. Magnetic resonance imaging characterization of brain structure and function in mild cognitive impairment: a review. J Am Geriatr Soc. 2008;56(5):920–34.
49. Sperling RA, Dickerson BC, Pihlajamaki M, Vannini P, LaViolette PS, Vitolo OV, et al. Functional alterations in memory networks in early Alzheimer's disease. NeuroMolecular Med. 2010;12(1):27–43.
50. Yu M, Sporns O, Saykin AJ. The human connectome in Alzheimer disease - relationship to biomarkers and genetics. Nat Rev Neurol. 2021;17(9):545–63.
51. Harrington GS, Tomaszewski Farias S, Buonocore MH, Yonelinas AP. The intersubject and intrasubject reproducibility of fMRI activation during three encoding tasks: implications for clinical applications. Neuroradiology. 2006;48(7):495–505.
52. Shallice T, Fletcher P, Frith CD, Grasby P, Frackowiak RS, Dolan RJ. Brain regions associated with acquisition and retrieval of verbal episodic memory. Nature. 1994;368(6472):633–5.
53. Wagner AD, Poldrack RA, Eldridge LL, Desmond JE, Glover GH, Gabrieli JD. Material-specific lateralization of prefrontal activation during episodic encoding and retrieval. Neuroreport. 1998;9(16):3711–7.
54. Brewer JB, Zhao Z, Desmond JE, Glover GH, Gabrieli JD. Making memories: brain activity that predicts how well visual experience will be remembered. Science. 1998;281(5380):1185–7.
55. Gabrieli JD, Brewer JB, Desmond JE, Glover GH. Separate neural bases of two fundamental memory processes in the human medial temporal lobe. Science. 1997;276(5310):264–6.
56. Roland PE, Zilles K. Structural divisions and functional fields in the human cerebral cortex. Brain Res Brain Res Rev. 1998;26(2–3):87–105.
57. McDermott KB, Buckner RL, Petersen SE, Kelley WM, Sanders AL. Set- and code-specific activation in frontal cortex: an fMRI study of encoding and retrieval of faces and words. J Cogn Neurosci. 1999;11(6):631–40.
58. Badre D, Wagner AD. Left ventrolateral prefrontal cortex and the cognitive control of memory. Neuropsychologia. 2007;45(13):2883–901.
59. Habib R, Nyberg L, Tulving E. Hemispheric asymmetries of memory: the HERA model revisited. Trends Cogn Sci. 2003;7(6):241–5.
60. Wagner AD, Pare-Blagoev EJ, Clark J, Poldrack RA. Recovering meaning: left prefrontal cortex guides controlled semantic retrieval. Neuron. 2001;31(2):329–38.
61. Thompson-Schill SL, D'Esposito M, Aguirre GK, Farah MJ. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. Proc Natl Acad Sci U S A. 1997;94(26):14792–7.
62. Busatto G, Howard RJ, Ha Y, Brammer M, Wright I, Woodruff PW, et al. A functional magnetic resonance imaging study of episodic memory. Neuroreport. 1997;8(12):2671–5.
63. Otten LJ, Henson RN, Rugg MD. Depth of processing effects on neural correlates of memory encoding: relationship between findings from across- and within-task comparisons. Brain. 2001;124(Pt 2):399–412.
64. Otten LJ, Rugg MD. Task-dependency of the neural correlates of episodic encoding as measured by fMRI. Cereb Cortex. 2001;11(12):1150–60.
65. Blumenfeld RS, Ranganath C. Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. The Neuroscientist: a review journal bringing neurobiology, neurology and psychiatry. 2007;13(3):280–91. https://doi.org/10.1177/1073858407299290.
66. Blumenfeld RS, Parks CM, Yonelinas AP, Ranganath C. Putting the pieces together: the role of dorsolateral prefrontal cortex in relational memory encoding. J Cogn Neurosci. 2011;23(1):257–65. https://doi.org/10.1162/jocn.2010.21459.
67. O'Reilly RC. The What and How of prefrontal cortical organization. Trends in neurosciences. 2010;33(8):355–61. https://doi.org/10.1016/j.tins.2010.05.002.
68. Squire LR, Wixted JT. The cognitive neuroscience of human memory since H.M. Annu Rev Neurosci. 2011;34(1):259–88.
69. Greicius MD, Krasnow B, Boyett-Anderson JM, Eliez S, Schatzberg AF, Reiss AL, et al. Regional analysis of hippocampal activation during memory encoding and retrieval: fMRI study. Hippocampus. 2003;13(1):164–74.
70. Daselaar SM, Veltman DJ, Rombouts SA, Raaijmakers JG, Jonker C. Neuroanatomical correlates of episodic encoding and retrieval in young and elderly subjects. Brain. 2003;126(Pt 1):43–56.
71. Davachi L, Mitchell JP, Wagner AD. Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. Proc Natl Acad Sci U S A. 2003;100(4):2157–62.
72. Davachi L, Wagner AD. Hippocampal contributions to episodic encoding: insights from relational and item-based learning. J Neurophysiol. 2002;88(2):982–90.
73. Rombouts SA, Machielsen WC, Witter MP, Barkhof F, Lindeboom J, Scheltens P. Visual association encoding activates the medial temporal lobe: a functional magnetic resonance imaging study. Hippocampus. 1997;7(6):594–601.
74. Stern CE, Corkin S, Gonzalez RG, Guimaraes AR, Baker JR, Jennings PJ, et al. The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. Proc Natl Acad Sci U S A. 1996;93(16):8660–5.

75. Braak H, Braak E, Yilmazer D, Bohl J. Functional anatomy of human hippocampal formation and related structures. J Child Neurol. 1996;11(4):265–75.
76. Van Hoesen GW. Anatomy of the medial temporal lobe. Magn Reson Imaging. 1995;13(8):1047–55.
77. Dolan RJ, Fletcher PC. Dissociating prefrontal and hippocampal function in episodic memory encoding. Nature. 1997;388(6642):582–5.
78. Golby AJ, Poldrack RA, Brewer JB, Spencer D, Desmond JE, Aron AP, et al. Material-specific lateralization in the medial temporal lobe and prefrontal cortex during memory encoding. Brain. 2001;124(Pt 9):1841–54.
79. Wagner AD, Schacter DL, Rotte M, Koutstaal W, Maril A, Dale AM, et al. Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. Science. 1998;281(5380):1188–91.
80. Aguirre GK, Detre JA, Alsop DC, D'Esposito M. The parahippocampus subserves topographical learning in man. Cereb Cortex. 1996;6(6):823–9.
81. Cooper RA, Ritchey M. Progression from feature-specific brain activity to hippocampal binding during episodic encoding. J Neurosci. 2020;40(8):1701–9.
82. Eichenbaum H. Memory: organization and control. Annu Rev Psychol. 2017;68(1):19–45.
83. Zhu J, Olechowski A, Habib R. The re-encoding processes of restudy and testing are equally susceptible to the impairment of divided attention. Cogn Brain Behav. 2017;21(2):65–84.
84. Yonelinas AP. The nature of recollection and familiarity: a review of 30 years of research. J Mem Lang. 2002;46(3):441–517.
85. Yonelinas AP, Aly M, Wang WC, Koen JD. Recollection and familiarity: examining controversial assumptions and new directions. Hippocampus. 2010;20(11):1178–94.
86. Yonelinas AP, Otten LJ, Shaw KN, Rugg MD. Separating the brain regions involved in recollection and familiarity in recognition memory. J Neurosci. 2005;25(11):3002–8.
87. Buckner RL, Koutstaal W, Schacter DL, Dale AM, Rotte M, Rosen BR. Functional-anatomic study of episodic retrieval. II. Selective averaging of event-related fMRI trials to test the retrieval success hypothesis. NeuroImage. 1998;7(3):163–75.
88. Buckner RL, Koutstaal W, Schacter DL, Wagner AD, Rosen BR. Functional-anatomic study of episodic retrieval using fMRI. I. Retrieval effort versus retrieval success. NeuroImage. 1998;7(3):151–62.
89. Lepage M, Ghaffar O, Nyberg L, Tulving E. Prefrontal cortex and episodic memory retrieval mode. Proc Natl Acad Sci U S A. 2000;97(1):506–11.
90. Nyberg L, Cabeza R, Tulving E. PET studies of encoding and retrieval: the HERA model. Psychon Bull Rev. 1996;3(2):135–48.
91. Nyberg L, McIntosh AR, Cabeza R, Habib R, Houle S, Tulving E. General and specific brain regions involved in encoding and retrieval of events: what, where, and when. Proc Natl Acad Sci U S A. 1996;93(20):11280–5.
92. Tulving E, Kapur S, Craik FI, Moscovitch M, Houle S. Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. Proc Natl Acad Sci U S A. 1994;91(6):2016–20.
93. Wagner K, Frings L, Quiske A, Unterrainer J, Schwarzwald R, Spreer J, et al. The reliability of fMRI activations in the medial temporal lobes in a verbal episodic memory task. NeuroImage. 2005;28(1):122–31.
94. Henson RN, Shallice T, Dolan RJ. Right prefrontal cortex and episodic memory retrieval: a functional MRI test of the monitoring hypothesis. Brain. 1999;122(Pt 7):1367–81.
95. Gilbert SJ, Spengler S, Simons JS, Steele JD, Lawrie SM, Frith CD, et al. Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. J Cogn Neurosci. 2006;18(6):932–48.
96. McDermott KB, Ojemann JG, Petersen SE, Ollinger JM, Snyder AZ, Akbudak E, et al. Direct comparison of episodic encoding and retrieval of words: an event-related fMRI study. Memory. 1999;7(5–6):661–78.
97. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci. 2008;1124(1):1–38.
98. Gusnard DA, Raichle ME, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. Nat Rev Neurosci. 2001;2(10):685–94.
99. 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(2):676–82.
100. Rugg MD, Johnson JD, Park H, Uncapher MR. Encoding-retrieval overlap in human episodic memory: a functional neuroimaging perspective. Prog Brain Res. 2008;169:339–52.
101. Kim H, Daselaar SM, Cabeza R. Overlapping brain activity between episodic memory encoding and retrieval: roles of the task-positive and task-negative networks. NeuroImage. 2010;49(1):1045–54.
102. Frankland PW, Bontempi B. The organization of recent and remote memories. Nat Rev Neurosci. 2005;6(2):119–30.
103. Henson RN, Hornberger M, Rugg MD. Further dissociating the processes involved in recognition memory: an fMRI study. J Cogn Neurosci. 2005;17(7):1058–73.
104. Henson R. A mini-review of fMRI studies of human medial temporal lobe activity associated with recognition memory. Q J Exp Psychol B. 2005;58(3–4):340–60.
105. Daselaar SM, Fleck MS, Cabeza R. Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. J Neurophysiol. 2006;96(4):1902–11.
106. Dolcos F, LaBar KS, Cabeza R. Remembering one year later: role of the amygdala and the medial temporal lobe memory system in retrieving emotional memories. Proc Natl Acad Sci U S A. 2005;102(7):2626–31.
107. Montaldi D, Spencer TJ, Roberts N, Mayes AR. The neural system that mediates familiarity memory. Hippocampus. 2006;16(5):504–20.
108. Milner B. Psychological aspects of focal epilepsy and its neurosurgical management. Adv Neurol. 1975;8:299–321.
109. Hermann BP, Seidenberg M, Haltiner A, Wyler AR. Relationship of age at onset, chronologic age, and adequacy of preoperative performance to verbal memory change after anterior temporal lobectomy. Epilepsia. 1995;36(2):137–45.
110. Saykin AJ, Gur RC, Sussman NM, O'Connor MJ, Gur RE. Memory deficits before and after temporal lobectomy: effect of laterality and age of onset. Brain Cogn. 1989;9:191–200.
111. Saykin AJ, Robinson LJ, Stafiniak P, et al. Neuropsychological effects of temporal lobectomy: acute changes in memory, language, and music. In: Bennett T, editor. Neuropsychology of epilepsy. New York, NY: Plenum Press; 1992.
112. Saykin AJ, Johnson SC, Flashman LA, McAllister TW, Sparling M, Darcey TM, et al. Functional differentiation of medial temporal and frontal regions involved in processing novel and familiar words: an fMRI study. Brain. 1999;122(Pt 10):1963–71.
113. Collin SH, Milivojevic B, Doeller CF. Memory hierarchies map onto the hippocampal long axis in humans. Nat Neurosci. 2015;18(11):1562–4.
114. Ranganath C, Yonelinas AP, Cohen MX, Dy CJ, Tom SM, D'Esposito M. Dissociable correlates of recollection and familiarity within the medial temporal lobes. Neuropsychologia. 2004;42(1):2–13.
115. Henson RN, Rugg MD, Shallice T, Josephs O, Dolan RJ. Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. J Neurosci. 1999;19(10):3962–72.

116. Woodruff CC, Johnson JD, Uncapher MR, Rugg MD. Content-specificity of the neural correlates of recollection. Neuropsychologia. 2005;43(7):1022–32.
117. Corbetta M, Kincade JM, Shulman GL. Neural systems for visual orienting and their relationships to spatial working memory. J Cogn Neurosci. 2002;14(3):508–23.
118. Kahn I, Davachi L, Wagner AD. Functional-neuroanatomic correlates of recollection: implications for models of recognition memory. J Neurosci. 2004;24(17):4172–80.
119. Gottfried JA, Smith AP, Rugg MD, Dolan RJ. Remembrance of odors past: human olfactory cortex in cross-modal recognition memory. Neuron. 2004;42(4):687–95.
120. Cabeza R. Role of parietal regions in episodic memory retrieval: the dual attentional processes hypothesis. Neuropsychologia. 2008;46(7):1813–27.
121. Dobbins IG, Han S. Cue- versus probe-dependent prefrontal cortex activity during contextual remembering. J Cogn Neurosci. 2006;18(9):1439–52.
122. Dobbins IG, Han S. Isolating rule- versus evidence-based prefrontal activity during episodic and lexical discrimination: a functional magnetic resonance imaging investigation of detection theory distinctions. Cereb Cortex. 2006;16(11):1614–22.
123. Simons JS, Owen AM, Fletcher PC, Burgess PW. Anterior prefrontal cortex and the recollection of contextual information. Neuropsychologia. 2005;43(12):1774–83.
124. Simons JS, Gilbert SJ, Owen AM, Fletcher PC, Burgess PW. Distinct roles for lateral and medial anterior prefrontal cortex in contextual recollection. J Neurophysiol. 2005;94(1):813–20.
125. Velanova K, Jacoby LL, Wheeler ME, McAvoy MP, Petersen SE, Buckner RL. Functional-anatomic correlates of sustained and transient processing components engaged during controlled retrieval. J Neurosci. 2003;23(24):8460–70.
126. Dobbins IG, Foley H, Schacter DL, Wagner AD. Executive control during episodic retrieval: multiple prefrontal processes subserve source memory. Neuron. 2002;35(5):989–96.
127. Dobbins IG, Wagner AD. Domain-general and domain-sensitive prefrontal mechanisms for recollecting events and detecting novelty. Cereb Cortex. 2005;15(11):1768–78.
128. Cabeza R, Rao SM, Wagner AD, Mayer AR, Schacter DL. Can medial temporal lobe regions distinguish true from false? An event-related functional MRI study of veridical and illusory recognition memory. Proc Natl Acad Sci U S A. 2001;98(8):4805–10.
129. Anderson ND, Craik FIM. Memory in the aging brain. In: Craik FIM, editor. The Oxford handbook of memory. New York, NY: Oxford; 2000. p. 411–25.
130. Balota DA, Dolan PO, Duchek JM. Memory changes in healthy older adults. In: Craik FIM, editor. The oxford handbook of memory. New York, NY: Oxford; 2000. p. 395–409.
131. Nyberg L, Backman L, Erngrund K, Olofsson U, Nilsson LG. Age differences in episodic memory, semantic memory, and priming: relationships to demographic, intellectual, and biological factors. J Gerontol B Psychol Sci Soc Sci. 1996;51(4):234–40.
132. Park DC, Smith AD, Lautenschlager G, Earles JL, Frieske D, Zwahr M, et al. Mediators of long-term memory performance across the lifespan. Psychol Aging. 1996;11:621–37.
133. Zacks RT, Hasher L, Li KZH. Human memory. In: Salthouse TA, editor. The handbook of aging and cognition. Mahwah, NJ: Erlbaum; 1999. p. 200–30.
134. Baltes PB. The aging mind: potential and limits. Gerontologist. 1993;33(5):580–94.
135. Flashman LA, Wishart HA, Saykin AJ. Boundaries between normal aging and dementia: perspectives from neuropsychological and neuroimaging investigations. In: Oxman TE, editor. Dementia: presentations, differential diagnosis and nosology. 2nd ed. Baltimore, MD: Johns Hopkins University Press; 2003.
136. Schroots JJF, Birren JE. Theoretical issues and basic questions in the planning of longitudinal studies of health and aging. In: Schroots JJF, editor. Aging, health and competence: the next generation of longitudinal studies. Amsterdam: Elsevier; 1993. p. 4–34.
137. Raz N, Gunning FM, Head D, Dupuis JH, McQuain J, Briggs SD, et al. Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. Cereb Cortex. 1997;7(3):268–82.
138. Bigler ED, Blatter DD, Anderson CV, Johnson SC, Gale SD, Hopkins RO, et al. Hippocampal volume in normal aging and traumatic brain injury. AJNR Am J Neuroradiol. 1997;18(1):11–23.
139. DeCarli C, Murphy DG, Gillette JA, Haxby JV, Teichberg D, Schapiro MB, et al. Lack of age-related differences in temporal lobe volume of very healthy adults. AJNR Am J Neuroradiol. 1994;15(4):689–96.
140. Greenwood PM. The frontal aging hypothesis evaluated. J Int Neuropsychol Soc. 2000;6(6):705–26.
141. Greenwood PM. Reply to west. J Int Neuropsychol Soc. 2000;6:730.
142. West R. In defense of the frontal lobe hypothesis of cognitive aging. J Int Neuropsychol Soc. 2000;6(6):727–9; discussion 30.
143. Kempermann G, Gage FH. New nerve cells for the adult brain. Sci Am. 1999;280(5):48–53.
144. Reuter-Lorenz PA, Stanczak L, Miller AC. Neural recruitment and cognitive aging: two hemispheres are better than one, especially as you age. Psychol Sci. 1999;10(6):494–500.
145. Stebbins GT, Carrillo MC, Dorfman J, Dirksen C, Desmond JE, Turner DA, et al. Aging effects on memory encoding in the frontal lobes. Psychol Aging. 2002;17(1):44–55.
146. Li HJ, Hou XH, Liu HH, Yue CL, Lu GM, Zuo XN. Putting age-related task activation into large-scale brain networks: a meta-analysis of 114 fMRI studies on healthy aging. Neurosci Biobehav Rev. 2015;57:156–74.
147. Anderson KE, Perera GM, Hilton J, Zubin N, Dela Paz R, Stern Y. Functional magnetic resonance imaging study of word recognition in normal elders. Prog Neuro-Psychopharmacol Biol Psychiatry. 2002;26(4):647–50.
148. Cabeza R, Daselaar SM, Dolcos F, Prince SE, Budde M, Nyberg L. Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. Cereb Cortex. 2004;14(4):364–75.
149. Grady CL. Age-related differences in face processing: a meta-analysis of three functional neuroimaging experiments. Can J Exp Psychol. 2002;56(3):208–20.
150. Morcom AM, Good CD, Frackowiak RS, Rugg MD. Age effects on the neural correlates of successful memory encoding. Brain. 2003;126(Pt 1):213–29.
151. Morcom AM, Li J, Rugg MD. Age effects on the neural correlates of episodic retrieval: increased cortical recruitment with matched performance. Cereb Cortex. 2007;17(11):2491–506.
152. Grady CL, McIntosh AR, Rajah MN, Beig S, Craik FI. The effects of age on the neural correlates of episodic encoding. Cereb Cortex. 1999;9(8):805–14.
153. Mandzia JL, Black SE, McAndrews MP, Grady C, Graham S. fMRI differences in encoding and retrieval of pictures due to encoding strategy in the elderly. Hum Brain Mapp. 2004;21(1):1–14.
154. Logan JM, Sanders AL, Snyder AZ, Morris JC, Buckner RL. Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. Neuron. 2002;33(5):827–40.
155. Scheller E, Minkova L, Leitner M, Kloppel S. Attempted and successful compensation in preclinical and early manifest neurodegeneration - a review of task fMRI studies. Front Psychiatry. 2014;5:132.

156. Grady C. The cognitive neuroscience of ageing. Nat Rev Neurosci. 2012;13(7):491–505.
157. Sala-Llonch R, Bartres-Faz D, Junque C. Reorganization of brain networks in aging: a review of functional connectivity studies. Front Psychol. 2015;6:663.
158. Belger A, Banich MT. Costs and benefits of integrating information between the cerebral hemispheres: a computational perspective. Neuropsychology. 1998;12(3):380–98.
159. Erickson KI, Colcombe SJ, Wadhwa R, Bherer L, Peterson MS, Scalf PE, et al. Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. Neurobiol Aging. 2007;28(2):272–83.
160. Spaniol J, Grady C. Aging and the neural correlates of source memory: over-recruitment and functional reorganization. Neurobiol Aging. 2012;33(2):425.e3–18.
161. Reuter-Lorenz PA, Cappell KA. Neurocognitive aging and the compensation hypothesis. Curr Dir Psychol Sci. 2008;17(3):177–82.
162. Schneider-Garces NJ, Gordon BA, Brumback-Peltz CR, Shin E, Lee Y, Sutton BP, et al. Span, CRUNCH, and beyond: working memory capacity and the aging brain. J Cogn Neurosci. 2010;22(4):655–69.
163. Baltes PB, Lindenberger U. Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? Psychol Aging. 1997;12(1):12–21.
164. Dennis NA, Cabeza R. Age-related dedifferentiation of learning systems: an fMRI study of implicit and explicit learning. Neurobiol Aging. 2011;32(12):2318.e17–30.
165. Daselaar SM, Fleck MS, Dobbins IG, Madden DJ, Cabeza R. Effects of healthy aging on hippocampal and rhinal memory functions: an event-related fMRI study. Cereb Cortex. 2006;16(12):1771–82.
166. Dennis NA, Daselaar S, Cabeza R. Effects of aging on transient and sustained successful memory encoding activity. Neurobiol Aging. 2007;28(11):1749–58.
167. Sperling RA, Bates JF, Chua EF, Cocchiarella AJ, Rentz DM, Rosen BR, et al. fMRI studies of associative encoding in young and elderly controls and mild Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2003;74(1):44–50.
168. Small SA, Tsai WY, DeLaPaz R, Mayeux R, Stern Y. Imaging hippocampal function across the human life span: is memory decline normal or not? Ann Neurol. 2002;51(3):290–5.
169. Small SA, Wu EX, Bartsch D, Perera GM, Lacefield CO, DeLaPaz R, et al. Imaging physiologic dysfunction of individual hippocampal subregions in humans and genetically modified mice. Neuron. 2000;28(3):653–64.
170. Davis SW, Dennis NA, Daselaar SM, Fleck MS, Cabeza R. Que PASA? The posterior-anterior shift in aging. Cereb Cortex. 2008;18(5):1201–9.
171. Dennis NA, Hayes SM, Prince SE, Madden DJ, Huettel SA, Cabeza R. Effects of aging on the neural correlates of successful item and source memory encoding. J Exp Psychol Learn Mem Cogn. 2008;34(4):791–808.
172. Petersen RC. Aging, mild cognitive impairment, and Alzheimer's disease. Neurol Clin. 2000;18(4):789–806.
173. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, et al. Current concepts in mild cognitive impairment. Arch Neurol. 2001;58(12):1985–92.
174. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001;56(9):1133–42.
175. Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, et al. Mild cognitive impairment: ten years later. Arch Neurol. 2009;66(12):1447–55.
176. Saykin AJ, Wishart HA. Mild cognitive impairment: conceptual issues and structural and functional brain correlates. In: Ovsiew F, editor. Seminars in clinical neuropsychiatry; 2003.
177. Braak H, Braak E, Bohl J. Staging of Alzheimer-related cortical destruction. Eur Neurol. 1993;33(6):403–8.
178. Chetelat G, Desgranges B, De La Sayette V, Viader F, Eustache F, Baron JC. Mapping gray matter loss with voxel-based morphometry in mild cognitive impairment. Neuroreport. 2002;13(15):1939–43.
179. de Leon MJ, Convit A, DeSanti S, Golomb J, Tarshish C, Rusinek H, et al. The hippocampus in aging and Alzheimer's disease. Neuroimaging Clin N Am. 1995;5(1):1–17.
180. de Leon MJ, Convit A, George AE, Golomb J, de Santi S, Tarshish C, et al. In vivo structural studies of the hippocampus in normal aging and in incipient Alzheimer's disease. Ann N Y Acad Sci. 1996;777:1–13.
181. Jack CR Jr, Petersen RC, O'Brien PC, Tangalos EG. MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. Neurology. 1992;42(1):183–8.
182. Toepper M. Dissociating normal aging from Alzheimer's disease: a view from cognitive neuroscience. J Alzheimers Dis. 2017;57(2):331–52.
183. Jack CR Jr, Shiung MM, Gunter JL, O'Brien PC, Weigand SD, Knopman DS, et al. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. Neurology. 2004;62(4):591–600.
184. Jack CR Jr, Shiung MM, Weigand SD, O'Brien PC, Gunter JL, Boeve BF, et al. Brain atrophy rates predict subsequent clinical conversion in normal elderly and amnestic MCI. Neurology. 2005;65(8):1227–31.
185. Risacher SL, Saykin AJ, West JD, Shen L, Firpi HA, McDonald BC, et al. Baseline MRI predictors of conversion from MCI to probable AD in the ADNI cohort. Curr Alzheimer Res. 2009;6(4):347–61.
186. Devanand DP, Liu X, Tabert MH, Pradhaban G, Cuasay K, Bell K, et al. Combining early markers strongly predicts conversion from mild cognitive impairment to Alzheimer's disease. Biol Psychiatry. 2008;64(10):871–9.
187. Risacher SL, Saykin AJ. Neuroimaging of Alzheimer's disease, mild cognitive impairment, and other dementias. In: Cohen RA, Sweet LH, editors. Brain imaging in behavioral medicine and clinical neuroscience. New York, NY: Springer; 2011. p. 309–39.
188. de Leon MJ, DeSanti S, Zinkowski R, Mehta PD, Pratico D, Segal S, et al. MRI and CSF studies in the early diagnosis of Alzheimer's disease. J Intern Med. 2004;256(3):205–23.
189. de Leon MJ, Mosconi L, Blennow K, DeSanti S, Zinkowski R, Mehta PD, et al. Imaging and CSF studies in the preclinical diagnosis of Alzheimer's disease. Ann N Y Acad Sci. 2007;1097:114–45.
190. DeCarli C. The role of neuroimaging in dementia. Clin Geriatr Med. 2001;17(2):255–79.
191. Good CD. Dementia and ageing. Br Med Bull. 2003;65:159–68.
192. Weiner MW. Imaging and biomarkers will be used for detection and monitoring progression of early Alzheimer's disease. J Nutr Health Aging. 2009;13:332.
193. Whitwell JL, Jack CR Jr. Neuroimaging in dementia. Neurol Clin. 2007;25(3):843–57, viii.
194. Wolf H, Hensel A, Kruggel F, Riedel-Heller SG, Arendt T, Wahlund LO, et al. Structural correlates of mild cognitive impairment. Neurobiol Aging. 2004;25(7):913–24.
195. Wolf H, Jelic V, Gertz HJ, Nordberg A, Julin P, Wahlund LO. A critical discussion of the role of neuroimaging in mild cognitive impairment. Acta Neurol Scand Suppl. 2003;179:52–76.
196. Wolk DA, Price JC, Saxton JA, Snitz BE, James JA, Lopez OL, et al. Amyloid imaging in mild cognitive impairment subtypes. Ann Neurol. 2009;65(5):557–68.

197. Dickerson BC, Salat DH, Greve DN, Chua EF, Rand-Giovannetti E, Rentz DM, et al. Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. Neurology. 2005;65(3):404–11.
198. Pariente J, Cole S, Henson R, Clare L, Kennedy A, Rossor M, et al. Alzheimer's patients engage an alternative network during a memory task. Ann Neurol. 2005;58(6):870–9.
199. Kato T, Knopman D, Liu H. Dissociation of regional activation in mild AD during visual encoding: a functional MRI study. Neurology. 2001;57(5):812–6.
200. Rombouts SA, Barkhof F, Veltman DJ, Machielsen WC, Witter MP, Bierlaagh MA, et al. Functional MR imaging in Alzheimer's disease during memory encoding. AJNR Am J Neuroradiol. 2000;21(10):1869–75.
201. Small SA, Perera GM, DeLapaz R, Mayeux R, Stern Y. Differential regional dysfunction of the hippocampal formation among elderly with memory decline and Alzheimer's disease. Ann Neurol. 1999;45(4):466–72.
202. Machulda MM, Ward HA, Borowski B, Gunter JL, Cha RH, O'Brien PC, et al. Comparison of memory fMRI response among normal, MCI, and Alzheimer's patients. Neurology. 2003;61(4):500–6.
203. Gron G, Bittner D, Schmitz B, Wunderlich AP, Riepe MW. Subjective memory complaints: objective neural markers in patients with Alzheimer's disease and major depressive disorder. Ann Neurol. 2002;51(4):491–8.
204. Browndyke JN, Giovanello K, Petrella J, Hayden K, Chiba-Falek O, Tucker KA, et al. Phenotypic regional functional imaging patterns during memory encoding in mild cognitive impairment and Alzheimer's disease. Alzheimers Dement. 2013;9(3):284–94.
205. Corkin S. Functional MRI for studying episodic memory in aging and Alzheimer's disease. Geriatrics. 1998;53(Suppl 1):S13–5.
206. Grady CL, McIntosh AR, Beig S, Keightley ML, Burian H, Black SE. Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. J Neurosci. 2003;23(3):986–93.
207. Golby A, Silverberg G, Race E, Gabrieli S, O'Shea J, Knierim K, et al. Memory encoding in Alzheimer's disease: an fMRI study of explicit and implicit memory. Brain. 2005;128(Pt 4):773–87.
208. Saykin AJ, Flashman LA, Johnson S, Santulli R, Wishart HA, Baxter L, et al. Frontal and hippocampal memory circuitry in early Alzheimer's disease: relation of structural and functional MRI changes. NeuroImage. 2000;11(5):S123.
209. Celone KA, Calhoun VD, Dickerson BC, Atri A, Chua EF, Miller SL, et al. Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: an independent component analysis. J Neurosci. 2006;26(40):10222–31.
210. Trivedi MA, Murphy CM, Goetz C, Shah RC, Gabrieli JD, Whitfield-Gabrieli S, et al. fMRI activation changes during successful episodic memory encoding and recognition in amnestic mild cognitive impairment relative to cognitively healthy older adults. Dement Geriatr Cogn Disord. 2008;26(2):123–37.
211. Dickerson BC, Salat DH, Bates JF, Atiya M, Killiany RJ, Greve DN, et al. Medial temporal lobe function and structure in mild cognitive impairment. Ann Neurol. 2004;56(1):27–35.
212. Hamalainen A, Pihlajamaki M, Tanila H, Hanninen T, Niskanen E, Tervo S, et al. Increased fMRI responses during encoding in mild cognitive impairment. Neurobiol Aging. 2007;28(12):1889–903.
213. O'Brien JL, O'Keefe KM, LaViolette PS, DeLuca AN, Blacker D, Dickerson BC, et al. Longitudinal fMRI in elderly reveals loss of hippocampal activation with clinical decline. Neurology. 2010;74(24):1969–76.
214. Johnson SC, Schmitz TW, Moritz CH, Meyerand ME, Rowley HA, Alexander AL, et al. Activation of brain regions vulnerable to Alzheimer's disease: the effect of mild cognitive impairment. Neurobiol Aging. 2006;27(11):1604–12.
215. Johnson SC, Baxter LC, Susskind-Wilder L, Connor DJ, Sabbagh MN, Caselli RJ. Hippocampal adaptation to face repetition in healthy elderly and mild cognitive impairment. Neuropsychologia. 2004;42(7):980–9.
216. Miller SL, Fenstermacher E, Bates J, Blacker D, Sperling RA, Dickerson BC. Hippocampal activation in adults with mild cognitive impairment predicts subsequent cognitive decline. J Neurol Neurosurg Psychiatry. 2008;79(6):630–5.
217. Yassa MA, Stark SM, Bakker A, Albert MS, Gallagher M, Stark CE. High-resolution structural and functional MRI of hippocampal CA3 and dentate gyrus in patients with amnestic Mild Cognitive Impairment. NeuroImage. 2010;51(3):1242–52.
218. McIntosh AR. Towards a network theory of cognition. Neural Netw. 2000;13(8–9):861–70.
219. Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. NeuroImage. 1997;6(3):218–29.
220. Greicius MD, Menon V. Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. J Cogn Neurosci. 2004;16(9):1484–92.
221. Nyberg L, Persson J, Habib R, Tulving E, McIntosh AR, Cabeza R, et al. Large scale neurocognitive networks underlying episodic memory. J Cogn Neurosci. 2000;12(1):163–73.
222. Ranganath C, Heller A, Cohen MX, Brozinsky CJ, Rissman J. Functional connectivity with the hippocampus during successful memory formation. Hippocampus. 2005;15(8):997–1005.
223. Burianova H, McIntosh AR, Grady CL. A common functional brain network for autobiographical, episodic, and semantic memory retrieval. NeuroImage. 2010;49(1):865–74.
224. Snijders TM, Petersson KM, Hagoort P. Effective connectivity of cortical and subcortical regions during unification of sentence structure. NeuroImage. 2010;52(4):1633–44.
225. Papoutsi M, Stamatakis EA, Griffiths J, Marslen-Wilson WD, Tyler LK. Is left fronto-temporal connectivity essential for syntax? Effective connectivity, tractography and performance in left-hemisphere damaged patients. NeuroImage. 2011;58(2):656–64.
226. Zhu J, LaMontagne PJ, Habib R. Neural signatures of test-depressed encoding: dynamic modulations in the memory encoding network and anterior cingulate cortex. Cogn Brain Behav. 2018;22(3):127–46.
227. Takahashi E, Ohki K, Kim DS. Dissociated pathways for successful memory retrieval from the human parietal cortex: anatomical and functional connectivity analyses. Cereb Cortex. 2008;18(8):1771–8.
228. Iidaka T, Matsumoto A, Nogawa J, Yamamoto Y, Sadato N. Frontoparietal network involved in successful retrieval from episodic memory. Spatial and temporal analyses using fMRI and ERP. Cereb Cortex. 2006;16(9):1349–60.
229. Cabeza R, Grady CL, Nyberg L, McIntosh AR, Tulving E, Kapur S, et al. Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. J Neurosci. 1997;17(1):391–400.
230. Achard S, Bullmore E. Efficiency and cost of economical brain functional networks. PLoS Comput Biol. 2007;3(2):e17.
231. Grady CL, McIntosh AR, Craik FI. Age-related differences in the functional connectivity of the hippocampus during memory encoding. Hippocampus. 2003;13(5):572–86.
232. Wang L, Laviolette P, O'Keefe K, Putcha D, Bakkour A, Van Dijk KR, et al. Intrinsic connectivity between the hippocampus and posteromedial cortex predicts memory performance in cognitively intact older individuals. NeuroImage. 2010;51(2):910–7.
233. Maillet D, Rajah MN. Association between prefrontal activity and volume change in prefrontal and medial temporal lobes in aging and dementia: a review. Ageing Res Rev. 2013;12(2):479–89.

234. Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, et al. Disruption of large-scale brain systems in advanced aging. Neuron. 2007;56(5):924–35.
235. Damoiseaux JS, Beckmann CF, Arigita EJ, Barkhof F, Scheltens P, Stam CJ, et al. Reduced resting-state brain activity in the "default network" in normal aging. Cereb Cortex. 2008;18(8):1856–64.
236. Lustig C, Snyder AZ, Bhakta M, O'Brien KC, McAvoy M, Raichle ME, et al. Functional deactivations: change with age and dementia of the Alzheimer type. Proc Natl Acad Sci U S A. 2003;100(24):14504–9.
237. Daselaar SM, Prince SE, Cabeza R. When less means more: deactivations during encoding that predict subsequent memory. NeuroImage. 2004;23(3):921–7.
238. Li SJ, Li Z, Wu G, Zhang MJ, Franczak M, Antuono PG. Alzheimer Disease: evaluation of a functional MR imaging index as a marker. Radiology. 2002;225(1):253–9.
239. Franzmeier N, Hartmann J, Taylor ANW, Araque-Caballero MA, Simon-Vermot L, Kambeitz-Ilankovic L, et al. The left frontal cortex supports reserve in aging by enhancing functional network efficiency. Alzheimers Res Ther. 2018;10(1):28.
240. Franzmeier N, Hartmann JC, Taylor ANW, Araque Caballero MA, Simon-Vermot L, Buerger K, et al. Left frontal hub connectivity during memory performance supports reserve in aging and mild cognitive impairment. J Alzheimers Dis. 2017;59(4):1381–92.
241. Stern Y, Arenaza-Urquijo EM, Bartres-Faz D, Belleville S, Cantilon M, Chetelat G, et al. Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimers Dement. 2020;16(9):1305–11.
242. Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci U S A. 2004;101(13):4637–42.
243. Rombouts SA, Barkhof F, Goekoop R, Stam CJ, Scheltens P. Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study. Hum Brain Mapp. 2005;26(4):231–9.
244. Sorg C, Riedl V, Muhlau M, Calhoun VD, Eichele T, Laer L, et al. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. Proc Natl Acad Sci U S A. 2007;104(47):18760–5.
245. Wang L, Zang Y, He Y, Liang M, Zhang X, Tian L, et al. Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. NeuroImage. 2006;31(2):496–504.
246. Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, et al. Alzheimer's disease. Lancet. 2016;388(10043):505–17.
247. Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013;12(2):207–16.
248. Saykin AJ, Wishart HA, Rabin LA, Santulli RB, Flashman LA, West JD, et al. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. Neurology. 2006;67(5):834–42.
249. Rabin LA, Smart CM, Amariglio RE. Subjective cognitive decline in preclinical Alzheimer's disease. Annu Rev Clin Psychol. 2017;13:369–96.
250. Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chetelat G, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement. 2014;10(6):844–52.
251. Molinuevo JL, Rabin LA, Amariglio R, Buckley R, Dubois B, Ellis KA, et al. Implementation of subjective cognitive decline criteria in research studies. Alzheimers Dement. 2017;13(3):296–311.
252. Koppara A, Wagner M, Lange C, Ernst A, Wiese B, Konig HH, et al. Cognitive performance before and after the onset of subjective cognitive decline in old age. Alzheimers Dement. 2015;1(2):194–205.
253. Buckley RF, Maruff P, Ames D, Bourgeat P, Martins RN, Masters CL, et al. Subjective memory decline predicts greater rates of clinical progression in preclinical Alzheimer's disease. Alzheimers Dement. 2016;12(7):796–804.
254. Slavin MJ, Sachdev PS, Kochan NA, Woolf C, Crawford JD, Giskes K, et al. Predicting cognitive, functional, and diagnostic change over 4 years using baseline subjective cognitive complaints in the Sydney memory and ageing study. Am J Geriatr Psychiatry. 2015;23(9):906–14.
255. Gifford KA, Liu D, Lu Z, Tripodis Y, Cantwell NG, Palmisano J, et al. The source of cognitive complaints predicts diagnostic conversion differentially among nondemented older adults. Alzheimers Dement. 2014;10(3):319–27.
256. Ronnlund M, Sundstrom A, Adolfsson R, Nilsson LG. Subjective memory impairment in older adults predicts future dementia independent of baseline memory performance: evidence from the Betula prospective cohort study. Alzheimers Dement. 2015;11(11):1385–92.
257. Mitchell AJ, Beaumont H, Ferguson D, Yadegarfar M, Stubbs B. Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. Acta Psychiatr Scand. 2014;130(6):439–51.
258. Slot RER, Verfaillie SCJ, Overbeek JM, Timmers T, Wesselman LMP, Teunissen CE, et al. Subjective Cognitive Impairment Cohort (SCIENCe): study design and first results. Alzheimers Res Ther. 2018;10(1):76.
259. Cheng YW, Chen TF, Chiu MJ. From mild cognitive impairment to subjective cognitive decline: conceptual and methodological evolution. Neuropsychiatr Dis Treat. 2017;13:491–8.
260. Swinford CG, Risacher SL, Charil A, Schwarz AJ, Saykin AJ. Memory concerns in the early Alzheimer's disease prodrome: regional association with tau deposition. Alzheimers Dement. 2018;10:322–31.
261. Amariglio RE, Becker JA, Carmasin J, Wadsworth LP, Lorius N, Sullivan C, et al. Subjective cognitive complaints and amyloid burden in cognitively normal older individuals. Neuropsychologia. 2012;50(12):2880–6.
262. van Harten AC, Visser PJ, Pijnenburg YA, Teunissen CE, Blankenstein MA, Scheltens P, et al. Cerebrospinal fluid Abeta42 is the best predictor of clinical progression in patients with subjective complaints. Alzheimers Dement. 2013;9(5):481–7.
263. Verfaillie SC, Tijms B, Versteeg A, Benedictus MR, Bouwman FH, Scheltens P, et al. Thinner temporal and parietal cortex is related to incident clinical progression to dementia in patients with subjective cognitive decline. Alzheimers Dement. 2016;5:43–52.
264. Wang Y, Risacher SL, West JD, McDonald BC, Magee TR, Farlow MR, et al. Altered default mode network connectivity in older adults with cognitive complaints and amnestic mild cognitive impairment. J Alzheimers Dis. 2013;35(4):751–60.
265. Contreras JA, Goni J, Risacher SL, Amico E, Yoder K, Dzemidzic M, et al. Cognitive complaints in older adults at risk for Alzheimer's disease are associated with altered resting-state networks. Alzheimers Dement. 2017;6:40–9.
266. Zanchi D, Montandon ML, Sinanaj I, Rodriguez C, Depoorter A, Herrmann FR, et al. Decreased fronto-parietal and increased default mode network activation is associated with subtle cognitive deficits in elderly controls. Neurosignals. 2017;25(1):127–38.
267. Risacher SL, Kim S, Nho K, Foroud T, Shen L, Petersen RC, et al. APOE effect on Alzheimer's disease biomarkers in older adults with significant memory concern. Alzheimers Dement. 2015;11(12):1417–29.
268. Rodda JE, Dannhauser TM, Cutinha DJ, Shergill SS, Walker Z. Subjective cognitive impairment: increased prefrontal cortex

activation compared to controls during an encoding task. Int J Geriatr Psychiatry. 2009;24(8):865–74.
269. Erk S, Spottke A, Meisen A, Wagner M, Walter H, Jessen F. Evidence of neuronal compensation during episodic memory in subjective memory impairment. Arch Gen Psychiatry. 2011;68(8):845–52.
270. Striepens N, Scheef L, Wind A, Meiberth D, Popp J, Spottke A, et al. Interaction effects of subjective memory impairment and ApoE4 genotype on episodic memory and hippocampal volume. Psychol Med. 2011;41(9):1997–2006.
271. Hayes JM, Tang L, Viviano RP, van Rooden S, Ofen N, Damoiseaux JS. Subjective memory complaints are associated with brain activation supporting successful memory encoding. Neurobiol Aging. 2017;60:71–80.
272. Rami L, Sala-Llonch R, Sole-Padulles C, Fortea J, Olives J, Llado A, et al. Distinct functional activity of the precuneus and posterior cingulate cortex during encoding in the preclinical stage of Alzheimer's disease. J Alzheimers Dis. 2012;31(3):517–26.
273. Smith JD. Apolipoproteins and aging: emerging mechanisms. Ageing Res Rev. 2002;1(3):345–65.
274. Bookheimer SY, Strojwas MH, Cohen MS, Saunders AM, Pericak-Vance MA, Mazziotta JC, et al. Patterns of brain activation in people at risk for Alzheimer's disease. N Engl J Med. 2000;343(7):450–6.
275. Burggren AC, Small GW, Sabb FW, Bookheimer SY. Specificity of brain activation patterns in people at genetic risk for Alzheimer disease. Am J Geriatr Psychiatr. 2002;10(1):44–51.
276. Bondi MW, Houston WS, Eyler LT, Brown GG. fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. Neurology. 2005;64(3):501–8.
277. Elgh E, Larsson A, Eriksson S, Nyberg L. Altered prefrontal brain activity in persons at risk for Alzheimer's disease: an fMRI study. Int Psychogeriatr. 2003;15(2):121–33.
278. Trivedi MA, Schmitz TW, Ries ML, Torgerson BM, Sager MA, Hermann BP, et al. Reduced hippocampal activation during episodic encoding in middle-aged individuals at genetic risk of Alzheimer's disease: a cross-sectional study. BMC Med. 2006;4:1.
279. Rombouts SA, Barkhof F, Van Meel CS, Scheltens P. Alterations in brain activation during cholinergic enhancement with rivastigmine in Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2002;73(6):665–71.
280. Kircher TT, Erb M, Grodd W, Leube DT. Cortical activation during cholinesterase-inhibitor treatment in Alzheimer disease: preliminary findings from a pharmaco-fMRI study. Am J Geriatr Psychiatry. 2005;13(11):1006–13.
281. Goekoop R, Scheltens P, Barkhof F, Rombouts SA. Cholinergic challenge in Alzheimer patients and mild cognitive impairment differentially affects hippocampal activation--a pharmacological fMRI study. Brain. 2006;129(Pt 1):141–57.
282. Risacher SL, Wang Y, Wishart HA, Rabin LA, Flashman LA, McDonald BC, et al. Cholinergic enhancement of brain activation in mild cognitive impairment during episodic memory encoding. Front Psychiatry. 2013;4:105.
283. Dumas JA, McDonald BC, Saykin AJ, McAllister TW, Hynes ML, West JD, et al. Cholinergic modulation of hippocampal activity during episodic memory encoding in postmenopausal women: a pilot study. Menopause. 2010;17(4):852–9.
284. Bozzali M, MacPherson SE, Dolan RJ, Shallice T. Left prefrontal cortex control of novel occurrences during recollection: a psychopharmacological study using scopolamine and event-related fMRI. NeuroImage. 2006;33(1):286–95.
285. Budson AE. Understanding memory dysfunction. Neurologist. 2009;15(2):71–9.
286. Binder JR, Desai RH, Graves WW, Conant LL. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb Cortex. 2009;19(12):2767–96.
287. Cappa SF. Imaging studies of semantic memory. Curr Opin Neurol. 2008;21(6):669–75.
288. Vigneau M, Beaucousin V, Herve PY, Duffau H, Crivello F, Houde O, et al. Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing. NeuroImage. 2006;30(4):1414–32.
289. Ralph MA, Jefferies E, Patterson K, Rogers TT. The neural and computational bases of semantic cognition. Nat Rev Neurosci. 2017;18(1):42–55.
290. Xu Y, He Y, Bi Y. A tri-network model of human semantic processing. Front Psychol. 2017;8:1538.
291. Wingfield A, Grossman M. Language and the aging brain: patterns of neural compensation revealed by functional brain imaging. J Neurophysiol. 2006;96(6):2830–9.
292. Taler V, Monetta L, Sheppard C, Ohman A. Semantic function in mild cognitive impairment. Front Psychol. 2019;10:3041.
293. Martin A. Functional neuroimaging of semantic memory. In: Kingstone A, editor. Handbook of functional neuroimaging of cognition. Cambridge, MA: Bradford; 2001. p. 153–86.
294. Grossman M, Smith EE, Koenig P, Glosser G, DeVita C, Moore P, et al. The neural basis for categorization in semantic memory. NeuroImage. 2002;17(3):1549–61.
295. Levy DA, Bayley PJ, Squire LR. The anatomy of semantic knowledge: medial vs. lateral temporal lobe. Proc Natl Acad Sci U S A. 2004;101(17):6710–5.
296. Martin A. GRAPES-Grounding representations in action, perception, and emotion systems: how object properties and categories are represented in the human brain. Psychon Bull Rev. 2016;23(4):979–90.
297. Wallentin M, Lund TE, Ostergaard S, Ostergaard L, Roepstorff A. Motion verb sentences activate left posterior middle temporal cortex despite static context. Neuroreport. 2005;16(6):649–52.
298. Simmons WK, Ramjee V, Beauchamp MS, McRae K, Martin A, Barsalou LW. A common neural substrate for perceiving and knowing about color. Neuropsychologia. 2007;45(12):2802–10.
299. Kuchinke L, Jacobs AM, Grubich C, Vo ML, Conrad M, Herrmann M. Incidental effects of emotional valence in single word processing: an fMRI study. NeuroImage. 2005;28(4):1022–32.
300. Bechara A, Damasio H, Damasio AR. Emotion, decision making and the orbitofrontal cortex. Cereb Cortex. 2000;10(3):295–307.
301. Bechara A, Tranel D, Damasio H. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. Brain. 2000;123(Pt 11):2189–202.
302. Patterson K, Nestor PJ, Rogers TT. Where do you know what you know? The representation of semantic knowledge in the human brain. Nat Rev Neurosci. 2007;8(12):976–87.
303. Simmons WK, Martin A. The anterior temporal lobes and the functional architecture of semantic memory. J Int Neuropsychol Soc. 2009;15(5):645–9.
304. Jefferies E, Lambon Ralph MA. Semantic impairment in stroke aphasia versus semantic dementia: a case-series comparison. Brain. 2006;129(Pt 8):2132–47.
305. Warrington EK. The selective impairment of semantic memory. Q J Exp Psychol. 1975;27(4):635–57.
306. Mummery CJ, Patterson K, Wise RJ, Vandenberghe R, Price CJ, Hodges JR. Disrupted temporal lobe connections in semantic dementia. Brain. 1999;122(Pt 1):61–73.
307. Lehmann S, Murray MM. The role of multisensory memories in unisensory object discrimination. Brain Res Cogn Brain Res. 2005;24(2):326–34.
308. Robinson G, Blair J, Cipolotti L. Dynamic aphasia: an inability to select between competing verbal responses? Brain. 1998;121(Pt 1):77–89.
309. Price CJ, Mummery CJ, Moore CJ, Frakowiak RS, Friston KJ. Delineating necessary and sufficient neural systems with functional imaging studies of neuropsychological patients. J Cogn Neurosci. 1999;11(4):371–82.

310. Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M. Differential effects of early hippocampal pathology on episodic and semantic memory. Science. 1997;277(5324):376–80.
311. Manns JR, Hopkins RO, Squire LR. Semantic memory and the human hippocampus. Neuron. 2003;38(1):127–33.
312. Corkin S. Permanent present tense: the unforgettable life of the amnesic patient, H. M. New York, NY: Basic Books; 2013.
313. Sheldon S, Moscovitch M. The nature and time-course of medial temporal lobe contributions to semantic retrieval: an fMRI study on verbal fluency. Hippocampus. 2012;22(6):1451–66.
314. Sharon T, Moscovitch M, Gilboa A. Rapid neocortical acquisition of long-term arbitrary associations independent of the hippocampus. Proc Natl Acad Sci U S A. 2011;108(3):1146–51.
315. Coutanche MN, Thompson-Schill SL. Fast mapping rapidly integrates information into existing memory networks. J Exp Psychol Gen. 2014;143(6):2296–303.
316. Salthouse TA. Speed and knowledge as determinants of adult age differences in verbal tasks. J Gerontol. 1993;48(1):29–36.
317. Albert MS, Heller HS, Milberg W. Changes in naming ability with age. Psychol Aging. 1988;3(2):173–8.
318. Au R, Joung P, Nicholas M, Obler LK. Naming ability across the adult life span. Aging Cogn. 1995;2(4):300–11.
319. Rich JB, Park NW, Dopkins S, Brandt J. What do Alzheimer's disease patients know about animals? It depends on task structure and presentation format. J Int Neuropsychol Soc. 2002;8(1):83–94.
320. Cooke A, Grossman M, DeVita C, Gonzalez-Atavales J, Moore P, Chen W, et al. Large-scale neural network for sentence processing. Brain Lang. 2006;96(1):14–36.
321. Gold BT, Andersen AH, Jicha GA, Smith CD. Aging influences the neural correlates of lexical decision but not automatic semantic priming. Cereb Cortex. 2009;19(11):2671–9.
322. Johnson SC, Saykin AJ, Flashman LA, McAllister TW, O'Jile JR, Sparling MB, et al. Similarities and differences in semantic and phonological processing with age: patterns of functional MRI activation. Aging Neuropsychol Cognit. 2001;8(4):307–20.
323. Nielson KA, Douville KL, Seidenberg M, Woodard JL, Miller SK, Franczak M, et al. Age-related functional recruitment for famous name recognition: an event-related fMRI study. Neurobiol Aging. 2006;27(10):1494–504.
324. Wierenga CE, Benjamin M, Gopinath K, Perlstein WM, Leonard CM, Rothi LJ, et al. Age-related changes in word retrieval: role of bilateral frontal and subcortical networks. Neurobiol Aging. 2008;29(3):436–51.
325. Grossman M, Cooke A, DeVita C, Alsop D, Detre J, Chen W, et al. Age-related changes in working memory during sentence comprehension: an fMRI study. NeuroImage. 2002;15(2):302–17.
326. Tyler LK, Shafto MA, Randall B, Wright P, Marslen-Wilson WD, Stamatakis EA. Preserving syntactic processing across the adult life span: the modulation of the frontotemporal language system in the context of age-related atrophy. Cereb Cortex. 2010;20(2):352–64.
327. Meinzer M, Flaisch T, Wilser L, Eulitz C, Rockstroh B, Conway T, et al. Neural signatures of semantic and phonemic fluency in young and old adults. J Cogn Neurosci. 2009;21(10):2007–18.
328. Diaz MT, Johnson MA, Burke DM, Madden DJ. Age-related differences in the neural bases of phonological and semantic processes. J Cogn Neurosci. 2014;26(12):2798–811.
329. Garrard P, Patterson K, Watson PC, Hodges JR. Category specific semantic loss in dementia of Alzheimer's type. Functional-anatomical correlations from cross-sectional analyses. Brain. 1998;121(Pt 4):633–46.
330. Grossman M. Not all words are created equal. Category-specific deficits in central nervous system disease. Neurology. 1998;50(2):324–5.
331. Grossman M, Robinson K, Biassou N, White-Devine T, D'Esposito M. Semantic memory in Alzheimer's disease: representativeness, ontologic category, and material. Neuropsychology. 1998;12(1):34–42.
332. Woodard JL, Seidenberg M, Nielson KA, Antuono P, Guidotti L, Durgerian S, et al. Semantic memory activation in amnestic mild cognitive impairment. Brain. 2009;132(Pt 8):2068–78.
333. Gigi A, Babai R, Penker A, Hendler T, Korczyn AD. Prefrontal compensatory mechanism may enable normal semantic memory performance in mild cognitive impairment (MCI). J Neuroimaging. 2010;20(2):163–8.
334. Johnson SC, Saykin AJ, Baxter LC, Flashman LA, Santulli RB, McAllister TW, et al. The relationship between fMRI activation and cerebral atrophy: comparison of normal aging and Alzheimer disease. NeuroImage. 2000;11(3):179–87.
335. McGeown WJ, Shanks MF, Forbes-McKay KE, Venneri A. Patterns of brain activity during a semantic task differentiate normal aging from early Alzheimer's disease. Psychiatry Res. 2009;173(3):218–27.
336. Grossman M, Koenig P, Glosser G, DeVita C, Moore P, Rhee J, et al. Neural basis for semantic memory difficulty in Alzheimer's disease: an fMRI study. Brain. 2003;126(Pt 2):292–311.
337. Gold BT, Jiang Y, Jicha GA, Smith CD. Functional response in ventral temporal cortex differentiates mild cognitive impairment from normal aging. Hum Brain Mapp. 2010;31(8):1249–59.
338. Assaf M, Jagannathan K, Calhoun V, Kraut M, Hart J Jr, Pearlson G. Temporal sequence of hemispheric network activation during semantic processing: a functional network connectivity analysis. Brain Cogn. 2009;70(2):238–46.
339. Binder JR, Frost JA, Hammeke TA, Bellgowan PS, Rao SM, Cox RW. Conceptual processing during the conscious resting state. A functional MRI study. J Cogn Neurosci. 1999;11(1):80–95.
340. Vitali P, Abutalebi J, Tettamanti M, Rowe J, Scifo P, Fazio F, et al. Generating animal and tool names: an fMRI study of effective connectivity. Brain Lang. 2005;93(1):32–45.
341. Adlam AL, Bozeat S, Arnold R, Watson P, Hodges JR. Semantic knowledge in mild cognitive impairment and mild Alzheimer's disease. Cortex. 2006;42(5):675–84.
342. Duong A, Whitehead V, Hanratty K, Chertkow H. The nature of lexico-semantic processing deficits in mild cognitive impairment. Neuropsychologia. 2006;44(10):1928–35.
343. Mickes L, Wixted JT, Fennema-Notestine C, Galasko D, Bondi MW, Thal LJ, et al. Progressive impairment on neuropsychological tasks in a longitudinal study of preclinical Alzheimer's disease. Neuropsychology. 2007;21(6):696–705.
344. Smith JA, Knight RG. Memory processing in Alzheimer's disease. Neuropsychologia. 2002;40(6):666–82.
345. Lind J, Persson J, Ingvar M, Larsson A, Cruts M, Van Broeckhoven C, et al. Reduced functional brain activity response in cognitively intact apolipoprotein E epsilon4 carriers. Brain. 2006;129(Pt 5):1240–8.
346. Seidenberg M, Guidotti L, Nielson KA, Woodard JL, Durgerian S, Antuono P, et al. Semantic memory activation in individuals at risk for developing Alzheimer disease. Neurology. 2009;73(8):612–20.
347. McGeown WJ, Shanks MF, Venneri A. Prolonged cholinergic enrichment influences regional cortical activation in early Alzheimer's disease. Neuropsychiatr Dis Treat. 2008;4(2):465–76.
348. D'Esposito M, Postle BR, Jonides J, Smith EE. The neural substrate and temporal dynamics of interference effects in working memory as revealed by event-related functional MRI. Proc Natl Acad Sci U S A. 1999;96(13):7514–9.
349. Smith EE, Jonides J. Storage and executive processes in the frontal lobes. Science. 1999;283(5408):1657–61.
350. Diamond A. Executive functions. Annu Rev Psychol. 2013;64:135–68.

351. Baddeley AD. Is working memory still working? Am Psychol. 2001;56(11):851–64.
352. Becker JT, Morris RG. Working memory(s). Brain Cogn. 1999;41:1–8.
353. Curtis CE, D'Esposito M. Persistent activity in the prefrontal cortex during working memory. Trends Cogn Sci. 2003;7(9):415–23.
354. Baddeley A. Working memory. Curr Biol. 2010;20(4):R136–40.
355. D'Esposito M. From cognitive to neural models of working memory. Philos Trans R Soc Lond Ser B Biol Sci. 2007;362(1481):761–72.
356. Smith EE, Jonides J. Neuroimaging analyses of human working memory. Proc Natl Acad Sci U S A. 1998;95(20):12061–8.
357. Smith EE, Jonides J, Marshuetz C, Koeppe RA. Components of verbal working memory: evidence from neuroimaging. Proc Natl Acad Sci U S A. 1998;95(3):876–82.
358. Wager TD, Smith EE. Neuroimaging studies of working memory: a meta-analysis. Cogn Affect Behav Neurosci. 2003;3(4):255–74.
359. D'Esposito M, Postle BR. The cognitive neuroscience of working memory. Annu Rev Psychol. 2015;66(1):115–42.
360. Lara AH, Wallis JD. The role of prefrontal cortex in working memory: a mini review. Front Syst Neurosci. 2015;9:173.
361. Chai WJ, Abd Hamid AI, Abdullah JM. Working memory from the psychological and neurosciences perspectives: a review. Front Psychol. 2018;9:401.
362. Turner GR, Spreng RN. Executive functions and neurocognitive aging: dissociable patterns of brain activity. Neurobiol Aging. 2012;33(4):826.e1–13.
363. Farras-Permanyer L, Guardia-Olmos J, Pero-Cebollero M. Mild cognitive impairment and fMRI studies of brain functional connectivity: the state of the art. Front Psychol. 2015;6:1095.
364. Kirova AM, Bays RB, Lagalwar S. Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. Biomed Res Int. 2015;2015:748212.
365. Baddeley A. Working memory. C R Acad Sci III. 1998;321(2–3):167–73.
366. Baddeley A. Working memory. Science. 1992;255(5044):556–9.
367. Cowan N. Evolving conceptions of memory storage, selective attention, and their mutual constraints within the human information-processing system. Psychol Bull. 1988;104(2):163–91.
368. Cowan N, Nugent LD, Elliott EM, Ponomarev I, Saults JS. The role of attention in the development of short-term memory: age differences in the verbal span of apprehension. Child Dev. 1999;70(5):1082–97.
369. D'Esposito M, Deouell LY, Gazzaley A. Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. Nat Rev Neurosci. 2003;4(11):863–72.
370. Dickerson BC. Functional magnetic resonance imaging of cholinergic modulation in mild cognitive impairment. Curr Opin Psychiatry. 2006;19(3):299–306.
371. Greicius M. Resting-state functional connectivity in neuropsychiatric disorders. Curr Opin Neurol. 2008;21(4):424–30.
372. Rasch B, Papassotiropoulos A, de Quervain DF. Imaging genetics of cognitive functions: focus on episodic memory. NeuroImage. 2010;53(3):870–7.
373. Loewenstein DA, Curiel RE, Duara R, Buschke H. Novel cognitive paradigms for the detection of memory impairment in preclinical Alzheimer's disease. Assessment. 2018;25(3):348–59.
374. Courtney SM, Petit L, Maisog JM, Ungerleider LG, Haxby JV. An area specialized for spatial working memory in human frontal cortex. Science. 1998;279(5355):1347–51.
375. Awh E, Jonides J. Overlapping mechanisms of attention and spatial working memory. Trends Cogn Sci. 2001;5(3):119–26.
376. Curtis CE, Rao VY, D'Esposito M. Maintenance of spatial and motor codes during oculomotor delayed response tasks. J Neurosci. 2004;24(16):3944–52.
377. Klein C, Fischer B, Hartnegg K, Heiss WH, Roth M. Optomotor and neuropsychological performance in old age. Exp Brain Res. 2000;135(2):141–54.
378. Chein JM, Fiez JA. Dissociation of verbal working memory system components using a delayed serial recall task. Cereb Cortex. 2001;11(11):1003–14.
379. Davachi L, Maril A, Wagner AD. When keeping in mind supports later bringing to mind: neural markers of phonological rehearsal predict subsequent remembering. J Cogn Neurosci. 2001;13(8):1059–70.
380. Jonides J, Schumacher EH, Smith EE, Koeppe RA, Awh E, Reuter-Lorenz PA, et al. The role of parietal cortex in verbal working memory. J Neurosci. 1998;18(13):5026–34.
381. Druzgal TJ, D'Esposito M. Dissecting contributions of prefrontal cortex and fusiform face area to face working memory. J Cogn Neurosci. 2003;15(6):771–84.
382. Linden DE, Bittner RA, Muckli L, Waltz JA, Kriegeskorte N, Goebel R, et al. Cortical capacity constraints for visual working memory: dissociation of fMRI load effects in a fronto-parietal network. NeuroImage. 2003;20(3):1518–30.
383. Ranganath C, DeGutis J, D'Esposito M. Category-specific modulation of inferior temporal activity during working memory encoding and maintenance. Brain Res Cogn Brain Res. 2004;20(1):37–45.
384. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci. 2001;24:167–202.
385. Gazzaley A, Cooney JW, McEvoy K, Knight RT, D'Esposito M. Top-down enhancement and suppression of the magnitude and speed of neural activity. J Cogn Neurosci. 2005;17(3):507–17.
386. Li HJ, Hou XH, Liu HH, Yue CL, He Y, Zuo XN. Toward systems neuroscience in mild cognitive impairment and Alzheimer's disease: a meta-analysis of 75 fMRI studies. Hum Brain Mapp. 2015;36(3):1217–32.
387. D'Esposito M, Aguirre GK, Zarahn E, Ballard D, Shin RK, Lease J. Functional MRI studies of spatial and nonspatial working memory. Brain Res Cogn Brain Res. 1998;7(1):1–13.
388. Levy R, Goldman-Rakic PS. Segregation of working memory functions within the dorsolateral prefrontal cortex. Exp Brain Res. 2000;133(1):23–32.
389. Sala JB, Rama P, Courtney SM. Functional topography of a distributed neural system for spatial and nonspatial information maintenance in working memory. Neuropsychologia. 2003;41(3):341–56.
390. Fuster JM, Alexander GE. Neuron activity related to short-term memory. Science. 1971;173(3997):652–4.
391. Riggall AC, Postle BR. The relationship between working memory storage and elevated activity as measured with functional magnetic resonance imaging. J Neurosci. 2012;32(38):12990–8.
392. Emrich SM, Riggall AC, Larocque JJ, Postle BR. Distributed patterns of activity in sensory cortex reflect the precision of multiple items maintained in visual short-term memory. J Neurosci. 2013;33(15):6516–23.
393. Anders TR, Fozard JL, Lillyquist TD. Effects of age upon retrieval from short-term memory. Dev Psychol. 1972;6:214–7.
394. Van der Linden M, Bredart S, Beerten A. Age-related differences in updating working memory. Br J Psychol. 1994;85(Pt 1):145–52.
395. Grady CL. Brain imaging and age-related changes in cognition. Exp Gerontol. 1998;33(7–8):661–73.

396. Mattay VS, Fera F, Tessitore A, Hariri AR, Berman KF, Das S, et al. Neurophysiological correlates of age-related changes in working memory capacity. Neurosci Lett. 2006;392(1–2):32–7.
397. Cappell KA, Gmeindl L, Reuter-Lorenz PA. Age differences in prefontal recruitment during verbal working memory maintenance depend on memory load. Cortex. 2010;46(4):462–73.
398. Fischer H, Nyberg L, Karlsson S, Karlsson P, Brehmer Y, Rieckmann A, et al. Simulating neurocognitive aging: effects of a dopaminergic antagonist on brain activity during working memory. Biol Psychiatry. 2010;67(6):575–80.
399. Mitchell KJ, Johnson MK, Raye CL, D'Esposito M. fMRI evidence of age-related hippocampal dysfunction in feature binding in working memory. Brain Res Cogn Brain Res. 2000;10(1–2):197–206.
400. Park DC, Welsh RC, Marshuetz C, Gutchess AH, Mikels J, Polk TA, et al. Working memory for complex scenes: age differences in frontal and hippocampal activations. J Cogn Neurosci. 2003;15(8):1122–34.
401. Grady CL, Yu H, Alain C. Age-related differences in brain activity underlying working memory for spatial and nonspatial auditory information. Cereb Cortex. 2008;18(1):189–99.
402. Baddeley AD, Baddeley HA, Bucks RS, Wilcock GK. Attentional control in Alzheimer's disease. Brain. 2001;124(Pt 8):1492–508.
403. Lim HK, Juh R, Pae CU, Lee BT, Yoo SS, Ryu SH, et al. Altered verbal working memory process in patients with Alzheimer's disease: an fMRI investigation. Neuropsychobiology. 2008;57(4):181–7.
404. Peters JC, Goebel R, Roelfsema PR. Remembered but unused: the accessory items in working memory that do not guide attention. J Cogn Neurosci. 2009;21(6):1081–91.
405. Yetkin FZ, Rosenberg RN, Weiner MF, Purdy PD, Cullum CM. fMRI of working memory in patients with mild cognitive impairment and probable Alzheimer's disease. Eur Radiol. 2006;16(1):193–206.
406. Firbank M, Kobeleva X, Cherry G, Killen A, Gallagher P, Burn DJ, et al. Neural correlates of attention-executive dysfunction in Lewy body dementia and Alzheimer's disease. Hum Brain Mapp. 2016;37(3):1254–70.
407. Melrose RJ, Jimenez AM, Riskin-Jones H, Weissberger G, Veliz J, Hasratian AS, et al. Alterations to task positive and task negative networks during executive functioning in Mild Cognitive Impairment. Neuroimage Clin. 2018;19:970–81.
408. Clement F, Gauthier S, Belleville S. Executive functions in mild cognitive impairment: emergence and breakdown of neural plasticity. Cortex. 2013;49(5):1268–79.
409. Bokde AL, Karmann M, Born C, Teipel SJ, Omerovic M, Ewers M, et al. Altered brain activation during a verbal working memory task in subjects with amnestic mild cognitive impairment. J Alzheimers Dis. 2010;21(1):103–18.
410. Saykin AJ, Wishart HA, Rabin LA, Flashman LA, McHugh TL, Mamourian AC, et al. Cholinergic enhancement of frontal lobe activity in mild cognitive impairment. Brain. 2004;127(Pt 7):1574–83.
411. Migo EM, Mitterschiffthaler M, O'Daly O, Dawson GR, Dourish CT, Craig KJ, et al. Alterations in working memory networks in amnestic mild cognitive impairment. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2015;22(1):106–27.
412. Kochan NA, Breakspear M, Slavin MJ, Valenzuela M, McCraw S, Brodaty H, et al. Functional alterations in brain activation and deactivation in mild cognitive impairment in response to a graded working memory challenge. Dement Geriatr Cogn Disord. 2010;30(6):553–68.
413. Nho K, Risacher SL, Crane PK, DeCarli C, Glymour MM, Habeck C, et al. Voxel and surface-based topography of memory and executive deficits in mild cognitive impairment and Alzheimer's disease. Brain Imaging Behav. 2012;6(4):551–67.
414. Rombouts SA, van Swieten JC, Pijnenburg YA, Goekoop R, Barkhof F, Scheltens P. Loss of frontal fMRI activation in early frontotemporal dementia compared to early AD. Neurology. 2003;60(12):1904–8.
415. Berlingeri M, Bottini G, Basilico S, Silani G, Zanardi G, Sberna M, et al. Anatomy of the episodic buffer: a voxel-based morphometry study in patients with dementia. Behav Neurol. 2008;19(1–2):29–34.
416. Luck D, Danion JM, Marrer C, Pham BT, Gounot D, Foucher J. The right parahippocampal gyrus contributes to the formation and maintenance of bound information in working memory. Brain Cogn. 2010;72(2):255–63.
417. Hampson M, Driesen NR, Skudlarski P, Gore JC, Constable RT. Brain connectivity related to working memory performance. J Neurosci. 2006;26(51):13338–43.
418. Protzner AB, Cortese F, Alain C, McIntosh AR. The temporal interaction of modality specific and process specific neural networks supporting simple working memory tasks. Neuropsychologia. 2009;47(8–9):1954–63.
419. Rissman J, Gazzaley A, D'Esposito M. Dynamic adjustments in prefrontal, hippocampal, and inferior temporal interactions with increasing visual working memory load. Cereb Cortex. 2008;18(7):1618–29.
420. Anticevic A, Repovs G, Shulman GL, Barch DM. When less is more: TPJ and default network deactivation during encoding predicts working memory performance. NeuroImage. 2010;49(3):2638–48.
421. Esposito F, Aragri A, Latorre V, Popolizio T, Scarabino T, Cirillo S, et al. Does the default-mode functional connectivity of the brain correlate with working-memory performances? Arch Ital Biol. 2009;147(1–2):11–20.
422. Grady CL, Protzner AB, Kovacevic N, Strother SC, Afshin-Pour B, Wojtowicz M, et al. A multivariate analysis of age-related differences in default mode and task-positive networks across multiple cognitive domains. Cereb Cortex. 2010;20(6):1432–47.
423. Li Z, Moore AB, Tyner C, Hu X. Asymmetric connectivity reduction and its relationship to "HAROLD" in aging brain. Brain Res. 2009;1295:149–58.
424. Lou W, Shi L, Wang D, Tam CW, Chu WC, Mok VC, et al. Decreased activity with increased background network efficiency in amnestic MCI during a visuospatial working memory task. Hum Brain Mapp. 2015;36(9):3387–403.
425. Wang P, Li R, Yu J, Huang Z, Yan Z, Zhao K, et al. Altered distant synchronization of background network in mild cognitive impairment during an executive function task. Front Behav Neurosci. 2017;11:174.
426. Wang P, Li R, Yu J, Huang Z, Li J. Frequency-dependent brain regional homogeneity alterations in patients with mild cognitive impairment during working memory state relative to resting state. Front Aging Neurosci. 2016;8:60.
427. Sambataro F, Murty VP, Callicott JH, Tan HY, Das S, Weinberger DR, et al. Age-related alterations in default mode network: impact on working memory performance. Neurobiol Aging. 2010;31(5):839–52.
428. Saunders NL, Summers MJ. Attention and working memory deficits in mild cognitive impairment. J Clin Exp Neuropsychol. 2010;32(4):350–7.
429. Binnewijzend MA, Adriaanse SM, Van der Flier WM, Teunissen CE, de Munck JC, Stam CJ, et al. Brain network alterations in Alzheimer's disease measured by eigenvector centrality in fMRI are related to cognition and CSF biomarkers. Hum Brain Mapp. 2014;35(5):2383–93.

430. Kobeleva X, Firbank M, Peraza L, Gallagher P, Thomas A, Burn DJ, et al. Divergent functional connectivity during attentional processing in Lewy body dementia and Alzheimer's disease. Cortex. 2017;92:8–18.
431. Teipel S, Ehlers I, Erbe A, Holzmann C, Lau E, Hauenstein K, et al. Structural connectivity changes underlying altered working memory networks in mild cognitive impairment: a three-way image fusion analysis. J Neuroimaging. 2015;25(4):634–42.
432. Seo EH, Kim H, Lee KH, Choo IH. Altered executive function in pre-mild cognitive impairment. J Alzheimers Dis. 2016;54(3):933–40.
433. Viviano RP, Hayes JM, Pruitt PJ, Fernandez ZJ, van Rooden S, van der Grond J, et al. Aberrant memory system connectivity and working memory performance in subjective cognitive decline. NeuroImage. 2019;185:556–64.
434. Dumas JA, Kutz AM, McDonald BC, Naylor MR, Pfaff AC, Saykin AJ, et al. Increased working memory-related brain activity in middle-aged women with cognitive complaints. Neurobiol Aging. 2013;34(4):1145–7.
435. Rodda J, Dannhauser T, Cutinha DJ, Shergill SS, Walker Z. Subjective cognitive impairment: functional MRI during a divided attention task. Eur Psychiatry. 2011;26(7):457–62.
436. Filbey FM, Slack KJ, Sunderland TP, Cohen RM. Functional magnetic resonance imaging and magnetoencephalography differences associated with APOEepsilon4 in young healthy adults. Neuroreport. 2006;17(15):1585–90.
437. Craig MC, Brammer M, Maki PM, Fletcher PC, Daly EM, Rymer J, et al. The interactive effect of acute ovarian suppression and the cholinergic system on visuospatial working memory in young women. Psychoneuroendocrinology. 2010;35(7):987–1000.
438. Dumas JA, Saykin AJ, McDonald BC, McAllister TW, Hynes ML, Newhouse PA. Nicotinic versus muscarinic blockade alters verbal working memory-related brain activity in older women. Am J Geriatr Psychiatry. 2008;16(4):272–82.
439. Goekoop R, Rombouts SA, Jonker C, Hibbel A, Knol DL, Truyen L, et al. Challenging the cholinergic system in mild cognitive impairment: a pharmacological fMRI study. NeuroImage. 2004;23(4):1450–9.
440. Tekes A, Mohamed MA, Browner NM, Calhoun VD, Yousem DM. Effect of age on visuomotor functional MR imaging. Acad Radiol. 2005;12(6):739–45.
441. D'Esposito M, Zarahn E, Aguirre GK, Rypma B. The effect of normal aging on the coupling of neural activity to the bold hemodynamic response. NeuroImage. 1999;10(1):6–14.
442. Huettel SA, Singerman JD, McCarthy G. The effects of aging upon the hemodynamic response measured by functional MRI. NeuroImage. 2001;13(1):161–75.
443. Taoka T, Iwasaki S, Uchida H, Fukusumi A, Nakagawa H, Kichikawa K, et al. Age correlation of the time lag in signal change on EPI-fMRI. J Comput Assist Tomogr. 1998;22(4):514–7.
444. Mehagnoul-Schipper DJ, van der Kallen BF, Colier WN, van der Sluijs MC, van Erning LJ, Thijssen HO, et al. Simultaneous measurements of cerebral oxygenation changes during brain activation by near-infrared spectroscopy and functional magnetic resonance imaging in healthy young and elderly subjects. Hum Brain Mapp. 2002;16(1):14–23.
445. Ross MH, Yurgelun-Todd DA, Renshaw PF, Maas LC, Mendelson JH, Mello NK, et al. Age-related reduction in functional MRI response to photic stimulation. Neurology. 1997;48(1):173–6.
446. Ward NS, Frackowiak RS. Age-related changes in the neural correlates of motor performance. Brain. 2003;126(Pt 4):873–88.
447. Buckner RL, Snyder AZ, Sanders AL, Raichle ME, Morris JC. Functional brain imaging of young, nondemented, and demented older adults. J Cogn Neurosci. 2000;12(Suppl 2):24–34.
448. Kannurpatti SS, Motes MA, Rypma B, Biswal BB. Neural and vascular variability and the fMRI-BOLD response in normal aging. Magn Reson Imaging. 2010;28(4):466–76.
449. Price CJ, Friston KJ. Cognitive conjunction: a new approach to brain activation experiments. NeuroImage. 1997;5(4 Pt 1):261–70.
450. Price CJ, Moore CJ, Friston KJ. Subtractions, conjunctions, and interactions in experimental design of activation studies. Hum Brain Mapp. 1997;5(4):264–72.
451. Morcom AM, Henson RNA. Increased prefrontal activity with aging reflects nonspecific neural responses rather than compensation. J Neurosci. 2018;38(33):7303–13.
452. Stephan KE, Penny WD, Moran RJ, den Ouden HE, Daunizeau J, Friston KJ. Ten simple rules for dynamic causal modeling. NeuroImage. 2010;49(4):3099–109.
453. Limongi R, Sutherland SC, Zhu J, Young ME, Habib R. Temporal prediction errors modulate cingulate-insular coupling. NeuroImage. 2013;71:147–57.
454. Hedden T, Van Dijk KR, Becker JA, Mehta A, Sperling RA, Johnson KA, et al. Disruption of functional connectivity in clinically normal older adults harboring amyloid burden. J Neurosci. 2009;29(40):12686–94.
455. Restom K, Bangen KJ, Bondi MW, Perthen JE, Liu TT. Cerebral blood flow and BOLD responses to a memory encoding task: a comparison between healthy young and elderly adults. NeuroImage. 2007;37(2):430–9.
456. Sheline YI, Raichle ME, Snyder AZ, Morris JC, Head D, Wang S, et al. Amyloid plaques disrupt resting state default mode network connectivity in cognitively normal elderly. Biol Psychiatry. 2010;67(6):584–7.
457. Sperling RA, Laviolette PS, O'Keefe K, O'Brien J, Rentz DM, Pihlajamaki M, et al. Amyloid deposition is associated with impaired default network function in older persons without dementia. Neuron. 2009;63(2):178–88.
458. Zhang K, Johnson B, Pennell D, Ray W, Sebastianelli W, Slobounov S. Are functional deficits in concussed individuals consistent with white matter structural alterations: combined fMRI & DTI study. Exp Brain Res. 2010;204(1):57–70.
459. Jeong J. EEG dynamics in patients with Alzheimer's disease. Clin Neurophysiol. 2004;115(7):1490–505.
460. Zhu J, Coppens RP, Rabinovich NE, Gilbert DG. Effects of bupropion sustained release on task-related EEG alpha activity in smokers: individual differences in drug response. Exp Clin Psychopharmacol. 2017;25(1):41–9.
461. Chien DT, Bahri S, Szardenings AK, Walsh JC, Mu F, Su MY, et al. Early clinical PET imaging results with the novel PHF-tau radioligand [F-18]-T807. J Alzheimers Dis. 2013;34(2):457–68.
462. Xia CF, Arteaga J, Chen G, Gangadharmath U, Gomez LF, Kasi D, et al. [(18)F]T807, a novel tau positron emission tomography imaging agent for Alzheimer's disease. Alzheimers Dement. 2013;9(6):666–76.
463. Marquie M, Normandin MD, Vanderburg CR, Costantino IM, Bien EA, Rycyna LG, et al. Validating novel tau positron emission tomography tracer [F-18]-AV-1451 (T807) on postmortem brain tissue. Ann Neurol. 2015;78(5):787–800.
464. Buckner RL, Snyder AZ, Shannon BJ, LaRossa G, Sachs R, Fotenos AF, et al. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J Neurosci. 2005;25(34):7709–17.
465. Huijbers W, Mormino EC, Wigman SE, Ward AM, Vannini P, McLaren DG, et al. Amyloid deposition is linked to aberrant entorhinal activity among cognitively normal older adults. J Neurosci. 2014;34(15):5200–10.

466. Huijbers W, Mormino EC, Schultz AP, Wigman S, Ward AM, Larvie M, et al. Amyloid-beta deposition in mild cognitive impairment is associated with increased hippocampal activity, atrophy and clinical progression. Brain. 2015;138(Pt 4):1023–35.
467. Koch K, Myers NE, Gottler J, Pasquini L, Grimmer T, Forster S, et al. Disrupted intrinsic networks link amyloid-beta pathology and impaired cognition in prodromal Alzheimer's disease. Cereb Cortex. 2015;25(12):4678–88.
468. Adamczuk K, De Weer AS, Nelissen N, Dupont P, Sunaert S, Bettens K, et al. Functional changes in the language network in response to increased amyloid beta deposition in cognitively intact older adults. Cereb Cortex. 2016;26(1):358–73.
469. Edelman K, Tudorascu D, Agudelo C, Snitz B, Karim H, Cohen A, et al. Amyloid-beta deposition is associated with increased medial temporal lobe activation during memory encoding in the cognitively normal elderly. Am J Geriatr Psychiatry. 2017;25(5):551–60.
470. Busche MA, Konnerth A. Impairments of neural circuit function in Alzheimer's disease. Philos Trans R Soc Lond Ser B Biol Sci. 2016;371(1700):20150429.
471. Leal SL, Landau SM, Bell RK, Jagust WJ. Hippocampal activation is associated with longitudinal amyloid accumulation and cognitive decline. elife. 2017;6:e22978.
472. Ossenkoppele R, Schonhaut DR, Scholl M, Lockhart SN, Ayakta N, Baker SL, et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain. 2016;139(Pt 5):1551–67.
473. Marks SM, Lockhart SN, Baker SL, Jagust WJ. Tau and beta-amyloid are associated with medial temporal lobe structure, function, and memory encoding in normal aging. J Neurosci. 2017;37(12):3192–201.
474. Maass A, Lockhart SN, Harrison TM, Bell RK, Mellinger T, Swinnerton K, et al. Entorhinal tau pathology, episodic memory decline, and neurodegeneration in aging. J Neurosci. 2018;38(3):530–43.
475. Sepulcre J, Sabuncu MR, Li Q, El Fakhri G, Sperling R, Johnson KA. Tau and amyloid beta proteins distinctively associate to functional network changes in the aging brain. Alzheimers Dement. 2017;13(11):1261–9.
476. Schultz AP, Chhatwal JP, Hedden T, Mormino EC, Hanseeuw BJ, Sepulcre J, et al. Phases of hyperconnectivity and hypoconnectivity in the default mode and salience networks track with amyloid and tau in clinically normal individuals. J Neurosci. 2017;37(16):4323–31.
477. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Feldman HH, Frisoni GB, et al. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology. 2016;87(5):539–47.
478. Leal SL, Yassa MA. Integrating new findings and examining clinical applications of pattern separation. Nat Neurosci. 2018;21(2):163–73.
479. Yassa MA, Stark CE. Pattern separation in the hippocampus. Trends Neurosci. 2011;34(10):515–25.
480. Reagh ZM, Noche JA, Tustison NJ, Delisle D, Murray EA, Yassa MA. Functional imbalance of anterolateral entorhinal cortex and hippocampal dentate/CA3 underlies age-related object pattern separation deficits. Neuron. 2018;97(5):1187–98.e4.
481. Boccia M, Silveri MC, Sabatini U, Guariglia C, Nemmi F. Neural Underpinnings of the decline of topographical memory in mild cognitive impairment. Am J Alzheimers Dis Other Dement. 2016;31(8):618–30.
482. Phillips JS, McMillan CT, Smith EE, Grossman M. Category learning in Alzheimer's disease and normal cognitive aging depends on initial experience of feature variability. Neuropsychologia. 2017;98:98–110.
483. Dermody N, Hornberger M, Piguet O, Hodges JR, Irish M. Prospective memory impairments in Alzheimer's disease and behavioral variant frontotemporal dementia: clinical and neural correlates. J Alzheimers Dis. 2016;50(2):425–41.
484. Gaubert M, Villain N, Landeau B, Mezenge F, Egret S, Perrotin A, et al. Neural correlates of self-reference effect in early Alzheimer's disease. J Alzheimers Dis. 2017;56(2):717–31.
485. Genon S, Bahri MA, Collette F, Angel L, d'Argembeau A, Clarys D, et al. Cognitive and neuroimaging evidence of impaired interaction between self and memory in Alzheimer's disease. Cortex. 2014;51:11–24.
486. Souchay C. Metamemory in Alzheimer's disease. Cortex. 2007;43(7):987–1003.
487. Zamboni G, Drazich E, McCulloch E, Filippini N, Mackay CE, Jenkinson M, et al. Neuroanatomy of impaired self-awareness in Alzheimer's disease and mild cognitive impairment. Cortex. 2013;49(3):668–78.
488. Ries ML, McLaren DG, Bendlin BB, Guofanxu, Rowley HA, Birn R, et al. Medial prefrontal functional connectivity--relation to memory self-appraisal accuracy in older adults with and without memory disorders. Neuropsychologia. 2012;50(5):603–11.
489. Lustig C, Buckner RL. Preserved neural correlates of priming in old age and dementia. Neuron. 2004;42(5):865–75.
490. Jacobsen JH, Stelzer J, Fritz TH, Chetelat G, La Joie R, Turner R. Why musical memory can be preserved in advanced Alzheimer's disease. Brain. 2015;138(Pt 8):2438–50.
491. Bondi MW. Genetic and brain imaging contributions to neuropsychological functioning in preclinical dementia. J Int Neuropsychol Soc. 2002;8(7):915–7.
492. Shoghi-Jadid K, Small GW, Agdeppa ED, Kepe V, Ercoli LM, Siddarth P, et al. Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer disease. Am J Geriatr Psychiatry. 2002;10(1):24–35.
493. Burggren AC, Bookheimer SY. Structural and functional neuroimaging in Alzheimer's disease: an update. Curr Top Med Chem. 2002;2(4):385–93.
494. Klunk WE, Lopresti BJ, Ikonomovic MD, Lefterov IM, Koldamova RP, Abrahamson EE, et al. Binding of the positron emission tomography tracer Pittsburgh compound-B reflects the amount of amyloid-beta in Alzheimer's disease brain but not in transgenic mouse brain. J Neurosci. 2005;25(46):10598–606.
495. Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol. 2004;55(3):306–19.
496. Risacher SL, Saykin AJ. Neuroimaging and other biomarkers for Alzheimer's disease: the changing landscape of early detection. Annu Rev Clin Psychol. 2013;9:621–48.
497. Cummings J, Lee G, Nahed P, Kambar M, Zhong K, Fonseca J, et al. Alzheimer's disease drug development pipeline: 2022. Alzheimers Dement. 2022;8(1):e12295.
498. Day GS, Scarmeas N, Dubinsky R, Coerver K, Mostacero A, West B, et al. Aducanumab use in symptomatic Alzheimer disease evidence in focus: a report of the AAN Guidelines Subcommittee. Neurology. 2022;98(15):619–31.