3.13 Short-Term and Working Memory Systems

B. R. Buchsbaum and M. D'Esposito, University of California, Berkeley, CA, USA

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3.13.1 Introduction

Humans and other animals with elaborately evolved sensory systems are prodigious consumers of information: each successive moment in an ever-changing environment nets a vast informational catch – a rich and teeming mélange of sights, sounds, smells, and sensations. Everything that is caught by the senses, however, is not kept; and that which is kept may not be kept for long. Indeed, the portion of experience that survives the immediate moment is but a small part of the overall sensory input. With regard to memory storage, then, the brain is not a pack rat, but a judicious and discerning collector of the most important pieces of experience. A good collector of experience, however, is also a good speculator: The most important information to store in memory is that which is most likely to be relevant at some time in the future. Of course, a large amount of information that might be important in the next few seconds is very unlikely to be of any importance in a day, a month, or a year. It might be stated more generally that to a large degree the relevance of information is time-bounded – sense-data collected and registered in the present is far more likely to be useful in a few seconds than it is to be in a few minutes. It would seem, then, that the temporary relevance of information demands the existence of a temporary storage system – a kind of memory that is capable of holding onto the sense-data of the 'just past' in an easily accessible form, while allowing older information to discreetly expire.

The existence of this kind of 'short-term memory' has been well established over the past century through the detailed study of human performance on tasks designed to examine the limits, properties, and underlying structure of human memory. Moreover, in recent years, much has been learned about the neurobiological basis of short-term memory through the study of brain-damaged patients, the effect of cortical ablations on animal behavior, electrophysiological recordings from single cells in the nonhuman primate, and regional brain activity as measured by modern functional neuroimaging tools such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). In this chapter, we examine how the psychological concept of short-term memory (STM) has, through a variety of neuroscientific investigations, been validated as a biological reality.

3.13.2 Evidence for the Existence of Short-Term Memory

An important scientific tenet, often referred to as the principle of parsimony, dictates that when two competing theories are put forth to explain a phenomenon,

and neither one is clearly superior to the other in its explanatory power, then the simpler of the two is to be preferred. The simplest conceivable theory of memory is that it is a unitary mental faculty; that all memories, no matter how recent or how remote, are made possible by a single functional system. This idea also appears to be the way in which people naturally conceive of memory, inasmuch as the single term 'memory' has been sufficiently expressive and precise to refer to the act of remembering in all its everyday variety. But soon after psychologists began to characterize memory in terms of human performance, a strong case emerged for the existence of different kinds of memory involving separate systems for the storage of old and new experiences.

In the mid-1960s, evidence began to accumulate in support of the view that separate functional systems underlie memory for recent and memory for more distant events. A particularly robust finding came from studies of free recall in which it was demonstrated that when subjects are presented a list of words and asked to repeat as many as possible in any order, performance is best for the first few items (the primacy effect) and for the last few items (the recency effect) – a pattern of accuracy that when plotted as a function of serial position (see **Figure 1**) appears U-shaped (Waugh and Norman, 1965; Glanzer and Cunitz, 1966). When a brief filled retention period is interposed between stimulus presentation and recall, however, performance on early items is relatively unaffected, but the recency effect disappears (Postman and Phillips, 1965; Glanzer and Cunitz, 1966). These findings suggest that in the immediate recall condition the last few items of a list are recalled best because they remain accessible in a short-term store, whereas early items are more permanently represented (and thus unaffected by the insertion of a filled delay) in a long-term store. This idea that memory, as a functional system, contains both short- and long-term stores is exemplified by the two-store memory model of Atkinson and Shiffrin (1968). In this prototype psychological memory model, comprising a short-term store (STS) and long-term store (LTS), information enters the system through the STS, where it is encoded and enriched, before being passed on to the LTS for permanent storage (**Figure 2**). Although the idea that short-term storage is a necessary prerequisite for entry into the LTS has not held up, the two-store model of Atkinson and Shiffrin crystallized the very idea of memory as a divisible, dichotomous system and provided the conceptual framework for the interpretation of patterns of memory deficits observed in patients with brain damage.

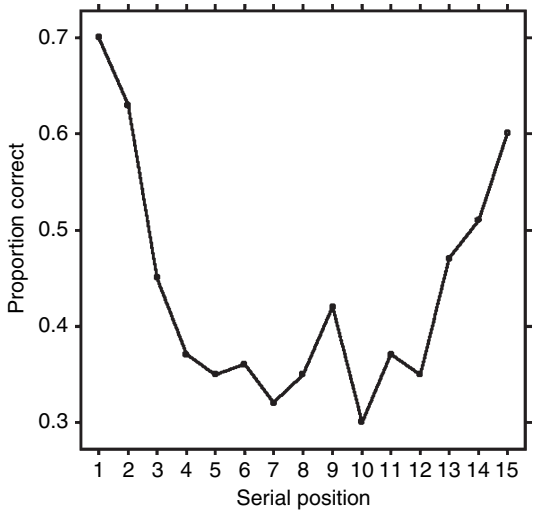


Figure 1 Plot of recall accuracy as a function of serial position in a test of free recall. Primacy and recency effects are evident in the U-shaped pattern of the curve. Adapted from Glanzer M and Cunitz A-R (1966) Two storage mechanisms in free recall. *J. Verbal Learn. Verbal Behav.* 5: 351–360; used with permission.

3.13.2.1 Evidence from Neurology and Neuropsychology

Perhaps the most compelling evidence for the existence of two memory stores comes from case studies of persons with focal brain lesions. In the early 1950s an astonishing, if tragic, discovery was made. A surgical procedure for the treatment of intractable epilepsy that involved bilateral removal of the medial temporal lobe in patient H. M. resulted in a catastrophic impairment in his ability to form new long-term memories, though, remarkably, his STM was left intact (Scoville and Milner, 1957). Thus, H. M., although perfectly capable of repeating back a string of digits – the classic test of STM – was unable to permanently store new facts and events. In the following decade, when Warrington and Shallice (Warrington and Shallice, 1969; Shallice and Warrington, 1970) reported a number of case studies of patients with temporoparietal lesions who had dramatically impaired STM for numbers and words coupled with a preserved ability to learn supra-span (e.g., greater than 10 items) word lists with repeated study, the case for a separation between STM and long-term memory (LTM) was immeasurably strengthened. It is important to emphasize that

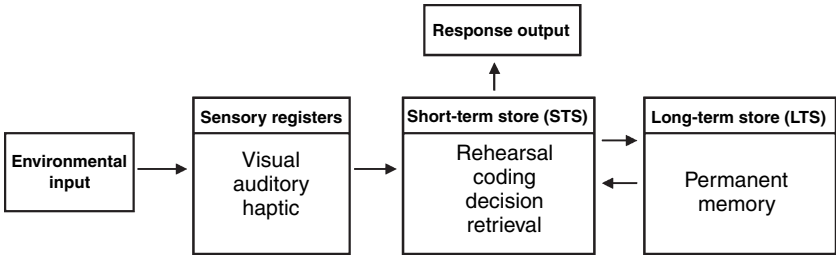


Figure 2 An information-flow diagram of Atkinson and Shiffrin's (1968) memory model. Information arriving to senses enters a short-term store (STS), where it can be maintained temporarily before entering a long-term store (LTS).

the STM deficits exhibited by such patients were, in the purest cases (Shallice and Warrington, 1977), not accompanied by any obvious deficits in ordinary language comprehension and production. Thus, for instance, patient J. B. was able to carry on conversations normally and to speak fluently without abnormal pauses, errors, or other symptoms of aphasia; in short, the 'language faculty,' considered to encompass the processes necessary for the online comprehension and production of meaningful speech, need not be disturbed even in the presence of a nearly complete eradication of verbal STM (Shallice and Butterworth, 1977). This established an important dissociation between the STM syndrome and the aphasic syndromes – a class of neurological disorders that specifically affect language ability – and argued, again, for a dedicated system in the brain for the temporary storage of information.

In summary, the discovery of 'short-term memory patients,' as they were to be called in the neuropsychological investigations of Warrington, Shallice, and others, provided a kind of evidential death blow to extant single-store hypotheses of memory (e.g., Melton, 1963), insofar as it established a double dissociation both in brain localization (LTM – medial temporal lobe, verbal STM – temporoparietal cortex) and patterns of performance, between short- and long-term memory systems. In addition, the STM disorder could be clearly distinguished, at the behavioral level at least, from the major language disorders such as Broca's and Wernicke's aphasia.

3.13.2.2 From Short-Term Memory to Working Memory

STM had, until the landmark work of Baddeley and colleagues (Baddeley and Hitch, 1974; Baddeley, 1986), typically been viewed as a more or less passive and amorphous medium for the brief storage of information derived from the senses. Questions tended to focus on the principles governing the mnemonic 'life cycle' of an item in memory – that is, why and at what rate are items forgotten? What is the role of passive decay? What is the role of interference, both proactive and retroactive, in forgetting? What is the route from STM to LTM, and what are the factors that influence this process? These questions, though of fundamental importance to understanding how memory works, tended to emphasize the general mechanisms – the procedures and principles of memory – rather than the underlying functional architecture of the system. What was missing from this line of research was the recognition that the contents of STM are not physical elements governed by certain lawful and inexorable processes of decay and interference, but rather dynamic representations of a fluid cognition, capable of being maintained, transformed, and manipulated by active, executive processes of higher control. Thus, for instance, two of the most important variables in studies of STM before the emergence of the Working Memory model were time (e.g., between stimulus presentation and recall) and serial order (e.g., of a list of items), both of which variables are defined by the inherent structure of the environmental input. (The term working memory has taken on the general meaning in much of psychology and neuroscience as active maintenance or manipulation of information held in memory, independent of the specific model of Baddeley and colleagues to which we refer with initial capital letters as 'Working Memory' or 'the Working Memory model.') In more recent years, at least as great an emphasis has been placed on variables that reflect an ability or attribute of the subject, for instance, his or her rate of articulation (Hulme et al., 1999), memory capacity (Cowan, 2001), or degree of inhibitory control (Hasher et al., 1999). Interest in these 'internal variables' is a recognition of the fact that what is 'in memory' at a moment in time is defined to various degrees by the structure of the input (e.g., time, serial order), the passive properties

of the storage medium (e.g., rate of decay, interference susceptibility), and the active processes of control that continually monitor and operate on the contents of memory. It is this last ingredient that puts the 'work' into working memory; it makes explicit the active and transformative character of mental processes and acknowledges that the content of memory need not mirror the structure and arrangement of environmental input, but rather may reflect the intentions, plans, and goals of the conscious organism.

With that introduction in mind, let us now give a brief overview of the Working Memory model of Baddeley and colleagues (Baddeley and Hitch, 1974; Baddeley, 1986). Whereas contemporary models of STM tended to emphasize storage buffers as the receptacles for information arriving from the senses, Baddeley and Hitch (1974) focused on rehearsal processes, that is, strategic mechanisms for the maintenance of items in memory. Thus, for example, when one is trying to keep a telephone or license plate number 'in mind,' a common strategy is to repeatedly rehearse, either subvocally or out loud, the contents of the numeric or alphanumeric sequence. Research had shown that in tests of serial recall, when subjects are prevented from engaging in covert rehearsal during a delay period that is inserted between stimulus presentation and recall, overall performance is dramatically impaired (Baddeley et al., 1975). In the case of verbal material, then, it was clear that in many ways the ability to keep words in memory depended in large part on articulatory processes. This insight was central to the development of the verbal component of Working Memory, the 'phonological loop' (see the section titled 'The phonological loop'), and led to a broader conceptualization of STM that seeks not only to explain how and why information enters and exits awareness, but rather how resources are marshaled in a strategic effort to capture and maintain the objects of memory in the focus of attention.

The central tenets of the Working Memory model are as follows: (1) It is a limited capacity system; at any moment in time, there is only a finite amount of information directly available for processing in memory. (2) The specialized subsystems devoted to the representation of information of a particular type, for instance, verbal or visuospatial, are structurally independent of one another; the integrity of information represented in one domain is protected from the interfering effects of information that may be arriving to another domain. (3) Storage of information in memory is distinct from the processes that underlie stimulus perception; rather, there is a two-stage process whereby

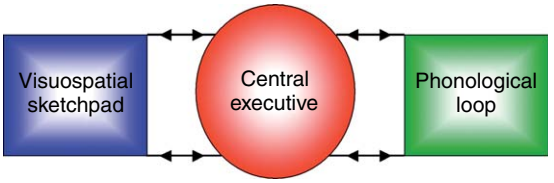


Figure 3 The Working Memory model comprises a control system, the central executive, and two storage systems, the visuospatial sketchpad and the phonological loop.

sensory information is first analyzed by perceptual modules and then transferred into specialized storage buffers that have no other role but to temporarily 'hold' preprocessed units of information. Moreover, the pieces of information that reside in such specialized buffers are subject to passive, time-based decay as well as interitem interference (e.g., similar sounding words such as 'man, mad, map, cap, mad' can lead to interference within a specialized phonological storage structure); finally, such storage buffers have no built-in or internal mechanism for maintaining or otherwise refreshing their contents – rather, this must occur from without, through the process of rehearsal, which might be a motor or top-down control mechanism that can sequentially access and refresh the contents that remain active within the store.

The initial Working Memory model proposed by Baddeley and Hitch (1974), but later refined somewhat (Salame and Baddeley, 1982; Baddeley, 1986), argued for the existence of three functional components of working memory (**Figure 3**). The 'central executive' was envisioned as a control system of limited attentional capacity responsible for coordinating and controlling two subsidiary slave systems, a phonological loop and a visuospatial sketchpad. The phonological loop was responsible for the storage and maintenance of information in a verbal form, and the visuospatial sketchpad was dedicated to the storage maintenance of visuospatial information.

3.13.2.3 The Central Executive

As has already been mentioned, working memory is viewed as a limited capacity system. There are a number of reasons for this capacity limitation, but an important one relates to what one might call the allocation of attention. Although many people are perfectly capable of walking and chewing gum at the same time, it is far more difficult to simultaneously perform more attention-demanding tasks, such as, to choose an unlikely example, monitoring the price of a stock for a quick trade while cogitating about one's next move in a highly competitive game

of chess. Thus, quite apart from the structural limitations inherent to memory storage systems (e.g., the natural inclination of memory traces to fade with time and interference), there also appear to be certain fundamental constraints on 'how much' attention can be allocated to the set of active tasks at any one time (Kahneman, 1973). The central executive component of working memory sits, as it were, at the helm of the cognitive apparatus and is responsible for the dispensation of attentional resources to the subsidiary components (e.g., the phonological loop) in working memory (Baddeley, 1986). Because total attentional capacity is finite, there must be a mechanism that intervenes to determine how the pool of attention is to be divided among the many possible actions, with their different levels of priority and reward contingencies, that are afforded by the environment. Thus, in dual-task paradigms, the central executive plays a crucial role in the scheduling and shifting of resources between tasks, and it can be used to explain the decline in performance that may be observed even when the two tasks in question involve different memory subsystems (Baddeley, 1992). Finally, it has often been pointed out that the central executive concept is too vague to act as anything other than a kind of placeholder for what is undoubtedly a much more complex system than is implied by the positing of a unitary and homunculus-like central cognitive operator (for a model of executive cognition, see Shallice, 1982). Provided, however, that the concept is not taken too literally, it can serve as a convenient way to refer to the complex and variegated set of processes that constitute the brain's executive system.

3.13.2.4 The Phonological Loop

Built into the architecture of the Working Memory model is a separation between domain-specific mechanisms of memory maintenance and domain-general mechanisms of executive control. Thus, the verbal component of working memory, or the phonological loop, is viewed as a 'slave' system that can be mobilized by the central executive when verbal material has to be retained in memory over some uncertain delay. Within the phonological loop it is the interplay of two components – the phonological store and the articulatory rehearsal process – that enables representations of verbal material to be kept in an active state. The phonological store is a passive buffer in which speech-based information can be stored for brief (approximately 2-s) periods. The articulatory control process serves to refresh and revivify the contents of the store, thus allowing the system to maintain short sequences of verbal items in memory for an extended interval. This division of labor between two interlocking components, one an active process and the other a passive store, is crucial to the model's explanatory power. For instance, when the articulatory control process is interfered with through the method of articulatory suppression (e.g., by requiring subjects to say 'hiya' over and over again), items in the store rapidly decay, and recall performance suffers greatly. The store, then, lacks a mechanism of reactivating its own contents but possesses memory capacity, whereas, conversely, the articulatory rehearsal process lacks an intrinsic memory capacity of its own, but can exert its effect indirectly by refreshing the contents of the store.

3.13.2.5 The Visuospatial Sketchpad

The other slave system in the Working Memory model is the visuospatial sketchpad, which is critical for the online retention of object and spatial information. Again, as is suggested by the term 'sketchpad,' the maintenance of visuospatial imagery in an active state requires top-down, or strategic, processing. As with the phonological loop, where articulatory suppression interferes with the maintenance of verbal information, a concurrent processing demand in the visuospatial domain, such as tracking a spot of light moving on a screen, random eye movements, or the presentation of irrelevant visual information during learning, likewise impairs memory performance. Although the symmetry between sensory and motor representations of visuospatial information is less obvious than it is in the case of speech, it has been demonstrated that saccadic rehearsal is important for the maintenance of spatial information (Postle et al., 2005). Baddeley (1986) initially proposed that in the context of spatial memory, covert eye movements can act as a way of revisiting locations in memory and thus operate very much like the articulatory rehearsal process known to be important for the maintenance of verbal information. Moreover, requiring subjects to perform a spatial interference task that disrupts or otherwise occupies this rehearsal component significantly impairs the performance of tests of spatial working memory, but has no effect on nonspatial visual memory tasks (Cocchini et al., 2002). In contrast, retention of visual shape or color information is interfered with by visual perceptual input, but not by a concurrent demand in the spatial domain (Klauer and Zhao, 2004). Thus, the principles that underlie the operation of the

phonological loop are qualitatively similar to those that underlie the operation of the visuospatial sketchpad; in both cases, maintenance processes consist of covert motor performance that serves to reactivate the memory traces residing in sensory stores. This mechanism might be most simply described as 'remembering by doing,' a strategy that is most effective when a motor code, which can be infinitely regenerated and which is under the subject's voluntary control, can be substituted for a fragile and less easily maintained perceptual memory code.

3.13.2.6 Summary

Working Memory is a system for the maintenance and manipulation of information that is stored in domain-specific memory buffers. Separate cognitive components are dedicated to the functions of storage, rehearsal, and executive control. Informational encapsulation and domain segregation dictate that auditory-verbal and visual information is kept in separate storage subsystems – the phonological loop and the visuospatial sketchpad, respectively. These storage subsystems themselves comprise specialized components for the passive storage of memory traces, which are subject to time and interference-based decay, and for the reactivation of these memory traces by way of simulation or rehearsal. Thus, storage components represent memory traces, but have no internal means of refreshing them, whereas rehearsal processes (e.g., articulatory, saccadic) have no mnemonic capacity of their own, but can reactivate the decaying traces held in temporary stores.

3.13.3 The Emergence of Working Memory as a Neuroscientific Concept

In the writings of the great neurologist Carl Wernicke, the idea that discrete pieces of cerebral cortex function as storehouses for 'memory images' is ubiquitous. For instance, the speech-perception deficit that accompanies lesions to the posterior superior temporal gyrus (STG), and that is one of the most characteristic symptoms of what is now referred to as Wernicke's aphasia, arises because this region of the auditory pathway, according to Wernicke, constitutes a location wherein 'auditory word images' are stored (Eggert and Wernicke, 1977). Indeed, Wernicke had a view of memory that shares much with some more modern formulations (Damasio, 1989; Wheeler et al., 2000; Cowan, 2001; Ruchkin et al., 2003) insofar as he viewed 'memories' as a reactivation of percepts originally formed during the sensory processing of an external stimulus:

> The sense impressions projected onto the cerebral cortex from the outside world last longer than the external stimulus affecting the sense organ; they can reappear in the form of memory images independently of the stimulus that produced them, although in less vivid form. (Eggert and Wernicke, 1977: 35)

Wernicke's ideas on memory, of course, predated the modern distinction between STM and LTM and were not intended to address the phenomenon that is today referred to as 'working memory.' Indeed, to Wernicke, perception and memory were part and parcel of the same functional–anatomical unit, whereby memory is perception evoked in the absence of direct external stimulation. The modern concept of working memory, however, distinguishes between stimulus recognition and discrimination, and the systems required to keep the products or residue of such sensory processes in the focus of attention during the temporal delays that often naturally intervene between stimulus perception and a contingent action. That is, unlike the memory images of Wernicke, which are punctate events, singular episodes, working memory entails sustained and persisting attention to an object or set of objects that exist in some upper register of the individual's consciousness. In this sense, then, the first insights into the neurobiological underpinnings of a memory whose purpose is to bridge cross-temporal contingencies (Fuster, 1997) comes from the work of Jacobsen, who studied nonhuman primate behavior after ablation to the prefrontal cortices. In comparing normal chimpanzees to those that had suffered extensive injury to the prefrontal cortex (PFC), Jacobsen (1936) noted:

> The normal chimpanzee has considerable facility in using sticks or other objects to manipulate its environment, e.g., to reach a piece of food beyond its unaided reach. It can solve such problems when it must utilize several sticks, some of which may not be immediately available in the visual field. After ablation of the prefrontal areas, the chimpanzee continues to use sticks as tools but it may have difficulty solving the problem if the necessary sticks and the food are not simultaneously present in the visual field. It exhibits also a characteristic 'memory' defect. Given an opportunity to observe a piece of food being concealed under one

> of two similar cups, it fails to recall after a few seconds under which cup the lure has been hidden. . . . (Jacobsen, 1936: 317)

In his pioneering experimental work, Jacobsen (1936) discovered that damage to the PFC of the monkey produces selective deficits in a task requiring a delayed response to the presentation of a sensory stimulus. The delayed-response tasks were initially devised by Hunter (1913) as a way of differentiating between animals on the basis of their ability to use information not currently available in the sensory environment to guide an imminent response. In the classic version of this test, a monkey is shown the location of a food morsel that is then hidden from view and placed in one of two wells. After a delay period of a few seconds, the monkey chooses one of the two locations and is rewarded if the choice corresponds to the location of the food. Variations on this test include the delayed alternation task, the delayed match-to-sample task, and the delayed nonmatch-to-sample task. The family of delayed-response tasks measures a complex cognitive ability that requires at least three clearly identifiable subprocesses: to recognize and properly encode the to-be-remembered item, to hold an internal representation of the item 'online' across an interval of time, and finally, to initiate the appropriate motor command when a response is prompted. Jacobsen showed that lesions to the PFC impair only the second of these three functions, suggesting a fundamental role for the region in immediate or short-term memory. Thus, monkeys with lesions to PFC perform in the normal range on a variety of tests requiring sensorimotor behavior, such as visual pattern discrimination and motor learning and control (i.e., tasks without a short-term mnemonic component). Although the impairments in the performance of delayed-response tasks in Jacobsen's studies were caused by large prefrontal lesions that often extended into the frontal pole and orbital surface, later studies showed that lesions confined to the region of the principal sulcus produced deficits equally as severe (Blum, 1952; Butters et al., 1972).

Fuster and Alexander (1971) reported the first direct physiological measures of PFC involvement in STM. With microelectrodes placed in the PFC, they measured the firing patterns of neurons during a spatial delayed-response task and showed that many cells showed increased firing, relative to an intertrial baseline period, during both cue presentation and the later retention period. Importantly, some cells fired exclusively during the delay period and therefore could be considered pure 'memory cells.' The results were interpreted as providing evidence for PFC involvement in the focusing of attention "on information that is being or that has been placed in temporary memory storage for prospective utilization" (p. 654). Many subsequent electrophysiological studies have demonstrated memory-related activity in the PFC of the monkey during delayed-response tasks of various kinds (e.g., Niki, 1974; Niki and Watanabe, 1976; Joseph and Barone, 1987; Quintana et al., 1988), although it was Patricia Goldman-Rakic who first drew a parallel (but see Passingham, 1985) and then firmly linked the phenomenon of persistent activity in PFC to the cognitive psychological concept of 'working memory.' In a monumental review of the existing literature on the role of the PFC in STM, Goldman-Rakic (1987), citing lesion and electrophysiological studies in the monkey, human neuropsychology, and the cytoarchitectonics and corticocortical connections of the PFC, argued that the dorsolateral PFC (the principal sulcus of the monkey) plays an essential role in holding visuospatial information in memory before the initiation of a response and in the absence of guiding sensory stimulation. In this and later work (especially that of Wilson et al., 1993), Goldman-Rakic developed a model of PFC in which visuospatial and (visual) object working memory were topographically segregated, with the former localized to the principal sulcus and the latter localized to a more ventral region along the inferior convexity of the lateral PFC (**Figure 4**).

This domain-specific view of the prefrontal organization, which was supported by observed dissociations in the responsivity of neurons in dorsal and ventral areas of the PFC during delayed-response tasks, could be viewed as an anterior expansion of the dorsal ('where') and ventral ('what') streams that had been discovered in the visual system in posterior neocortex (Ungerleider and Mishkin, 1982). In addition, the parallel and modular nature of the proposed functional and neuroanatomical architecture of PFC was in keeping with the tenet of domain independence in the Working Memory model of Baddeley and colleagues.

The connection between persistent activation in the PFC of the monkey and a model of memory developed in the field of cognitive psychology might seem tenuous, especially in light of the fact that the Working Memory model was originally formulated on the basis of evidence derived from behavioral

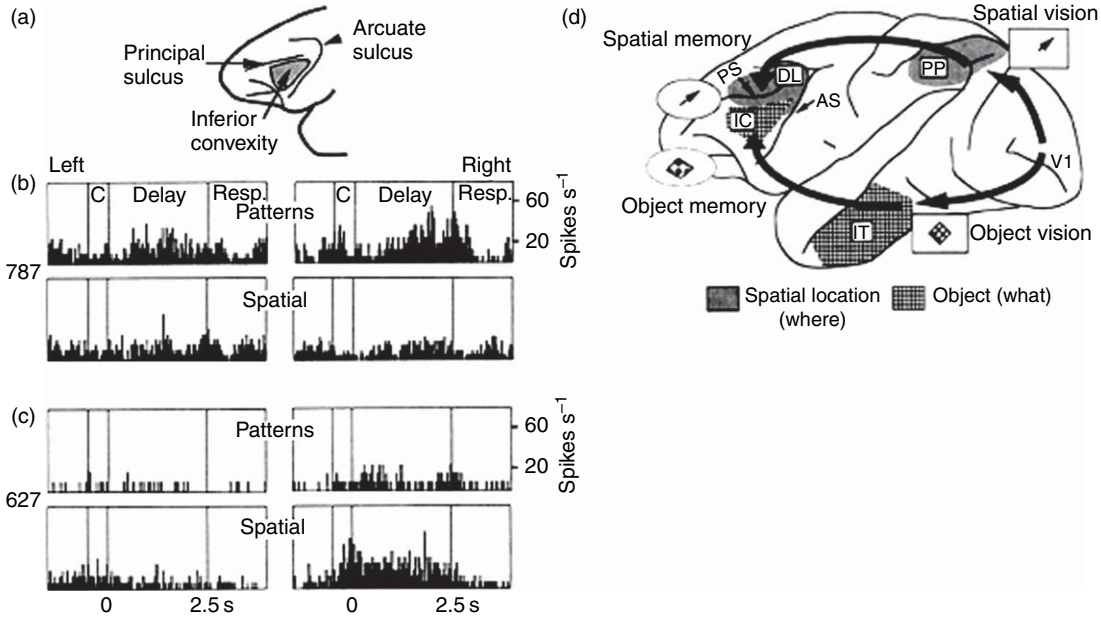


Figure 4 (a) Diagram of the frontal lobe and location of principal sulcus and inferior convexity. (b) Responses of inferior convexity neuron with visual object-specific activity in the delayed-response task. Upper panels show delay-period activity for object memory trials; lower panels show lack of response on spatial memory trials. (c) Responses of dorsolateral prefrontal neuron with spatial memory selectivity. Upper panels show lack of responsivity on object memory trials; lower panels show delay-period activity on spatial memory trials. (d) Schematic diagram illustrating the dorsal and ventral streams in the visual system and their connections with PFC. The posterior parietal (PP) is concerned with spatial perception, and the inferior temporal (IT) cortex with object recognition. These regions are connected with the dorsolateral (DL) and inferior convexity (IC) prefrontal cortices where, according to the Goldman-Rakic model, memory for spatial location and object identity are encoded in working memory. PS, principal sulcus; AS, arcuate sulcus. Adapted from Wilson FA, Scalaidhe SP, and Goldman-Rakic PS (1993) Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science* 260: 1955–1958, with permission.

studies using linguistic material – an informational medium clearly unavailable to monkeys. For Goldman-Rakic, though, the use of the term 'working memory' in the context of nonhuman primate electrophysiology was not intended as an offhand or otherwise desultory nod to psychology (Goldman-Rakic 1990), but rather as a reasoned and deliberate effort to unify both our understanding of, and manner of referencing, a common neurobiological mechanism underlying an aspect of higher cognition that is well developed in primate species. Certainly, in retrospect, the decision to label the phenomenon of persistent activity in PFC with the term 'working memory' has had an immeasurable impact on memory research and indeed may be thought of as one of the two or three most important events contributing to the emergence of an integrated and unified approach to the study of neurobiology and psychology. Nowhere was this fusion between psychology and neurobiology more apparent, and nowhere were the ideas of Goldman-Rakic on visuospatial working memory more energetically tested and challenged, than in the realm of functional brain imaging.

3.13.3.1 Functional Neuroimaging Studies of Working Memory

At about the same time at which Fuster and Alexander (1971) recorded neural activity in the monkey PFC during a working memory task, Ingvar and colleagues (Ingvar, 1977; Ingvar and Risberg, 1965) examined variation in regional cerebral blood flow (rCBF) during tasks requiring complex mental activity. Indeed, Risberg and Ingvar (1973), in the first functional neuroimaging study of STM, showed that during a backward digit span task, the largest increases in rCBF, compared with a resting baseline, were observed in prerolandic and anterior frontal cortex. It was not, however, until the emergence of PET and the development of the O-15 tracer that the mapping of brain activity during the exercise of higher mental functions would become genuinely

amenable to the evaluation of complex hypotheses about the neural basis of cognition. In the middle and late 1980s, technological advances in the PET technique, with its relatively high spatial resolution (approximately 1 cm^3), were accompanied by a critical conceptual innovation known as 'cognitive subtraction' that provided the inferential machinery needed to link regional variation in brain activity to experimental manipulations at the task or psychological level (Posner et al., 1988). Thus, for any set of hypothesized mental processes (*a,b,c*), if a task can be devised in which one condition recruits all of the processing components (Task $1_{a,b,c}$) and another condition recruits only a subset of the components (Task $2_{a,b}$), subtraction of the observed regional activity during Task 2 from that observed during Task 1 should reveal the excess neural activity due to the performance of Task 1, and thus is associated with the cognitive component *c*. The Working Memory model of Baddeley, with its discrete cognitive components (e.g., central executive, phonological loop, and visuospatial scratchpad) was an ideal model with which to test the power of cognitive subtraction using modern neuroimaging tools. Indeed, in the span of only 2 years, the landmark studies of Paulesu et al. (1993), Jonides et al. (1993), and D'Esposito (1995), had mapped all of the cognitive components of the Working Memory model onto specific regions of the cerebral cortex. The challenge in successive years was to go beyond this sort of 'psychoneural transcription' – which is necessarily a unidirectional mapping between the cognitive box and the cerebral convolution – and begin to develop models that generate hypotheses that refer directly to the brain regions and mechanisms that underlie working memory. In the following sections, we review how neuroimaging studies of STM and executive control used the Working Memory model to gain an initial neural foothold on which later studies were buttressed and that would lead to insights and advances in our understanding of working memory as it is implemented in the brain.

3.13.3.2 Visuospatial Working Memory

The first study of visuospatial working memory in PET was carried out by Jonides and colleagues in 1993, using the logic of cognitive subtraction to isolate mnemonic processes associated with the maintenance of visuospatial information, in a task very similar to those used by Goldman-Rakic and her colleagues with monkeys (Goldman-Rakic 1987; Funahashi et al., 1989). During 'memory' scans, subjects were shown an array of three dots appearing for 200 ms on the circumference of a 14-mm imaginary circle and instructed to maintain the items in memory during a 3-s retention interval. This was followed by a probe for location-memory consisting of a circular outline that either did or did not (with equal probability) enclose one of the previously memorized dots, and to which subjects responded with a yes/no decision. In 'perception' scans, the three dots and the probe outline were presented simultaneously, so that subjects did not have to retain the location of the items in memory during a delay, but instead simply had to decide whether the outline encircled one of the three displayed dots (see **Figure 5**).

Subtraction of the 'perception' scans from the 'memory' scans revealed a right-lateralized network of cortical regions that would become a hallmark of neuroimaging studies of visuospatial working memory: the posterior parietal lobe, dorsal premotor cortex, occipital cortex (Brodmann area 19), and PFC. In their interpretation of the findings, the

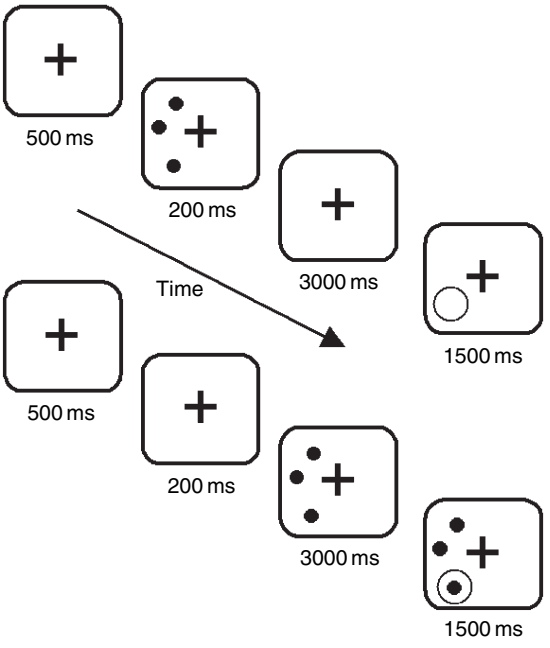


Figure 5 Schematic presentation of spatial memory task from Jonides J, Smith EE, Koeppe RA, Awh E, Minoshima S, and Mintun MA (1993) Spatial working memory in humans as revealed by PET. *Nature* 363: 623–625 and Smith EE, Jonides J, Koeppe RA, Awh E, Schumacher EH, and Minoshima S (1995) Spatial versus object working-memory – PET investigations. *J. Cogn. Neurosci.* 7: 337–356. Top panel shows example memory trial; bottom panel shows example perception trial.

authors suggested that the occipital activity reflected a role in the creation, but not necessarily the maintenance, of an internal visual image of the dot pattern, and that activity in the PFC might reflect one of two things: (1) the literal storage of a representation of the image in memory during the delay, or (2) the representation of a pointer or link to other brain circuitry, perhaps in the occipital or parietal lobe, that is actually responsible for maintaining the memory engram. These two explanations for the observation of prefrontal activity during working memory tasks, which in later years would often be pitted against each other, nicely frame the emerging debate on the division of labor among the cortical regions involved in the maintenance of information in working memory.

A major aim of many of the early neuroimaging studies of visuospatial working memory was to duplicate the canonical finding of Goldman-Rakic and colleagues of a dorsal-ventral dissociation in monkey PFC for spatial and object working memory. Studies by Petrides et al. (1993) and McCarthy et al. (1994) demonstrated with PET and functional MRI (fMRI), respectively, that middorsolateral PFC (Brodmann areas 9 and 46) shows increased activity during spatial working memory when compared with a control condition. An attempt to show a neuroanatomical double dissociation between spatial and object working memory was undertaken by Smith et al. (1995) in a PET study that used carefully controlled nonverbalizable object stimuli that were presented in both object and spatial task contexts. This study found distinct brain circuits for the storage of spatial and object information, with spatial working memory relying primarily on right-hemisphere regions in the prefrontal (BA 46) and parietal (BA 40) cortices, and object working memory involving only a left inferotemporal area. These results, however, only partially replicated the monkey study of Wilson et al. (1993), who had found distinct regions in PFC for spatial and object working memory. A similar pattern was found a year later in work by McCarthy et al. (1996), in which regional differences between object and spatial working memory were most pronounced across hemispheres rather than between dorsal and ventral divisions of the PFC. In a contemporaneous review and meta-analysis of all human neuroimaging studies of working memory, D'Esposito et al. (1998) showed that there was virtually no evidence for a neuroanatomical dissociation between spatial and object working memory. Indeed, establishing a correspondence between the functional neuroanatomy of visuospatial working memory in the monkey and human brains would prove remarkably difficult, leading to a protracted debate among and between monkey neurophysiologists and human neuroimaging researchers about the proper way to conceptualize the functional topography of working memory in the PFC (Goldman-Rakic, 2000; Miller, 2000). Increasingly, efforts were made to adapt human neuroimaging studies to resemble as closely as possible the kinds of tasks used in animal electrophysiology, such as the delayed match-to-sample procedure. The emergence of event-related fMRI, with its superior spatial and temporal resolution to O-15 PET, was critical to this new effort at cross-disciplinary synthesis and reconciliation and led to a number of fundamental insights on the brain basis of working memory, to the discussion of which we now turn.

Early PET studies of working memory relied exclusively on the logic of cognitive subtraction to isolate hypothesized components of a complex cognitive task. Thus, even for working memory tasks that consisted of a number of temporal phases within a given trial (e.g., stimulus presentation → memory maintenance → recognition decision), the low temporal resolution of PET prohibited separate statistical assessment of activity within a single task phase. Event-related fMRI, on the other hand, with its temporal resolution on the order of 2 to 4 s, could be used to examine functional activity in different portions of a multiphase trial, provided that each of the sequential task components was separated by approximately 4 s (Zarahn et al., 1997). This methodology permits the isolation of maintenance-related activity during the delay period of a match-to-sample procedure without relying on a complex cognitive subtraction (**Figure 6**).

Using event-related fMRI, Courtney et al. (1998) demonstrated a neuroanatomical dissociation between delay period activity during working memory maintenance for either the identity (object memory) or location (spatial memory) of a set of three face stimuli. Greater activity during the delay period on face identity trials was observed in the left inferior frontal gyrus, whereas greater activity during the delay period of the location task was observed in dorsal frontal cortex, a finding consistent with the spatial/object domain segregation thesis of Goldman-Rakic (1987). Unlike previous studies that had implicated human BA 46 – the presumed homologue to the monkey principal sulcus – in spatial working memory, Courtney observed enhanced delay-period activity for the location task, bilaterally, in the superior frontal sulcus, a region just anterior to the frontal eye fields.

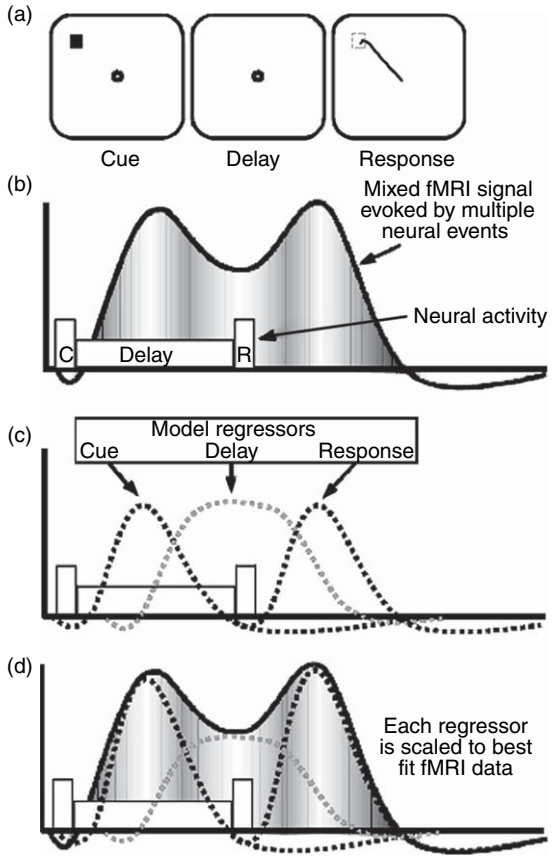
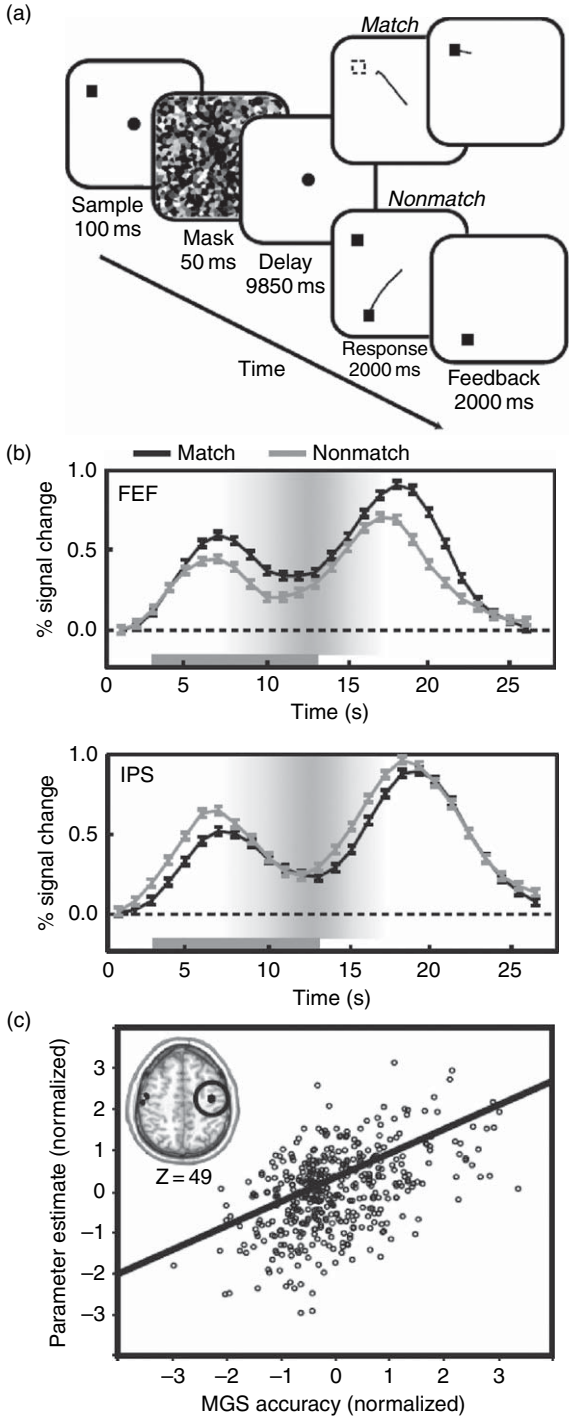


Figure 6 Delayed-response task and modeling with trial components of event-related fMRI data. (a) A prototypic spatial delayed-response task, like all delayed-response tasks, has three main epochs: a sample cue period where stimuli-to-be-remembered are presented, an unfilled delay period where stimuli are retained in memory, and finally a response period where a memory-guided response is required. (b) When multiple sequential neural events occur within a trial, the resulting fMRI response (R) is a mixture of signals arising from more than one time and more than one trial component. The gradient under the curve schematically represents the mixing or temporal overlap of the various signal components. For example, the white region at the peak of the first hump is evoked almost exclusively from neural processing during the cue phase of the task. However, just a few seconds later, in the darker portion just to the right, the signal is a mixture of processing at the cue phase and the beginning of the delay period. (c) In order to resolve the individual components of the mixed fMRI signal, separate regressors can be used to independently model the cue, delay, and response phases of the trial. (d) The magnitudes of the regressors scale with the degree to which they account for variance in the observed time series data. The magnitude of the delay regressor can be used as an index for maintenance-related activity.

A control task requiring sensory guided eye movements was used to functionally delineate the frontal eye fields and thus distinguish them from regions with a specifically mnemonic function. They concluded that the localization of spatial working memory in the superior frontal sulcus (posterior and superior to BA 46) indicated an evolutionary displacement in the functional anatomy of the PFC, possibly due to the emergence of new cognitive abilities such as abstract reasoning, complex problem solving, and planning for the future. In short, then, this study was the first functional neuroimaging study to fully replicate the object versus spatial working memory dissociation shown by Goldman-Rakic and colleagues, insofar as one accepts their proposal that the human homologue to the monkey principal sulcus is located not in the middle frontal gyrus or BA 46, but rather in the superior frontal sulcus.

The study by Courtney represented a high water mark in the level of agreement between human neuroimaging and monkey electrophysiological studies of visuospatial working memory and their mutual correspondence to the Goldman-Rakic conception of a domain-segregated topography of prefrontal cortical function. Although several subsequent studies of spatial working memory offered support (Munk et al., 2002; Sala et al., 2003; Walter et al., 2003; Leung et al., 2004) for a specifically mnemonic role of the superior frontal sulcus in tasks of spatial working memory, other studies failed to replicate the finding (Postle and D'Esposito, 1999; Postle et al., 2000; Postle, 2006). The primary disagreement concerns not whether delay-period activity is found in the superior frontal sulcus during spatial working memory – it is – but rather whether such activity subserves an exclusively mnemonic or storage function. For instance, although Postle et al. (2000) observed delay-period activity in this region during a spatial working memory task, they also found it to be equally active during the generation of two-dimensional saccades, a task that required visuospatial attention and motor control but placed no demands on memory storage. In addition, the neural circuitry underlying spatial selective attention largely overlaps with that of spatial working memory (Corbetta et al., 2002), including the superior frontal sulcus, the frontal eye fields, and the intraparietal sulcus (IPS). Curtis et al. (2004) scanned subjects while they performed an oculomotor delayed-response task that required maintenance of the spatial position of a single dot of light over a delay period after which a memory-guided saccade was generated. Both frontal eye fields (FEF) and IPS delay-period activity showed activity that spanned the entire delay period (**Figure 7**). In addition, the magnitude of FEF and IPS delay-period activity predicted the accuracy of the memory-guided saccade generated after the

delay. This relationship suggests that the fidelity of the stored location is reflected in the delay-period activity. One interpretation of this result is that the persistent activity observed in the PFC reflects the operations of control processes that do not store information *per se*, but rather act to focus attention via top-down signals to posterior parietal cortex, toward particular locations in space.



3.13.3.3 Visual Object Working Memory

A number of studies have investigated the maintenance of objects, mostly visually presented faces, houses, and line drawings that are not easily verbalizable (e.g., Smith et al., 1995; Courtney et al., 1996, 1997; McCarthy et al., 1996; Belger et al., 1998; Postle and D'Esposito, 1999; Druzgal and D'Esposito, 2001, 2003; Rama et al., 2001; Mecklinger et al., 2002; Linden et al., 2003; Postle et al., 2003; Sala et al., 2003). Consistently, posterior cortical areas within the inferior temporal lobe that normally respond to the visual presentation of select objects also tend to activate during object working memory tasks. Therefore, the temporal lobe appears to play an important role in short-term storage of object features. For example, the fusiform gyrus, the ventral convexity surface of the temporal lobe, shows greater activation when a subject is shown pictures of faces than when other types of complex visual stimuli such as pictures of houses or scenes or household objects are presented (Kanwisher et al., 1997). Indeed, given its selective response properties, the fusiform gyrus has been termed the fusiform face area or FFA.

Four important findings indicate that posterior extrastriate cortical regions like the FFA play an important role in the mnemonic storage of object features. First, the FFA shows persistent delay-period activity (Druzgal and D'Esposito, 2001, 2003; Rama et al., 2001; Postle et al., 2003) during working memory tasks. Second, the activity in the FFA is somewhat selective for faces; it is greater during delays in which subjects are maintaining faces compared to with other objects (Sala et al., 2003). Third, as the number of faces that are being maintained increases, the magnitude of the delay-period activity increases in the FFA (Jha and McCarthy, 2000; Druzgal and D'Esposito, 2001, 2003). Such load effects strongly suggest a role in STS because, as the number of items that must be represented increases, so should the storage demands. Fourth, using a delayed paired associates task, Ranganath et al. (2004) have shown that the FFA responds during an unfilled delay interval following the presentation of a house that the subject has learned is associated with a certain face. Therefore, the delay-period FFA activity likely reflects the reactivated image of the associated face that was retrieved from LTM despite the fact that no face was actually presented before the delay. Together, these studies suggest that posterior regions of visual association cortex, like the FFA, participate in the internal storage of specific classes of visual object features. Most likely, the mechanisms used to create internal representations of objects that are no longer in our environment are similar to the mechanisms used to represent objects that exist in our external environment.

There have been several reports of delay-period-specific activations in the PFC during object working memory tasks as well (e.g., Courtney et al., 1998; Postle et al., 1999; Jha and McCarthy, 2000; Nystrom et al., 2000; Stern et al., 2000; Rama et al., 2001; Munk et al., 2002; Pessoa et al., 2002; Druzgal and D'Esposito, 2003; Ranganath et al., 2003; Sala et al., 2003). However, the localization of the delay-period activity appears varied across the dorsal, ventral, and medial portions of the PFC. The most consistent

Figure 7 Event-related study of spatial working memory by Curtis et al. (2004). (a) Schematic depiction of the oculomotor delayed-response tasks where subjects used the cue's location to make a memory-guided saccade. Both the matching-to-sample (top) and nonmatching-to-sample (bottom) tasks began with the brief presentation of a small. During matching trials, the subject made a memory-guided saccade (depicted by the thin black line) after the disappearance of the fixation cue marking the end of the delay. Feedback was provided by the representation of the cue. At this point, the subject corrected any errors by shifting gaze to the cue. The difference between the endpoint fixation after the memory-guided saccade and the fixation to acquire the feedback cue was used as an index of memory accuracy. During nonmatching trials, the subject made a saccade to the square that did not match the location of the sample cue. (b) Average (± S.E. bars) bold time series data for matching (black) and nonmatching-to-sample (gray) oculomotor delayed-response tasks. The solid gray bar represents the delay interval. The gray gradient in the background depicts the probability that the bold signal is emanating from the delay period, where darker indicates more probable. The frontal eye fields (FEF) show greater delay period activity during the matching task where an oculomotor strategy is efficient. The right intraparietal sulcus (IPS) shows greater delay period activity during the nonmatching task when subjects are biased from using such a strategy. (c) Scatter plot showing the correlation between memory-guided saccade (MGS) accuracy and the magnitude of the delay period parameter estimates in the right FEF. More accurate MGS were associated with greater delay period activity. From Curtis CE, Rao VY, and D'Esposito M (2004) Maintenance of spatial and motor codes during oculomotor delayed response tasks. *J. Neurosci.* 24: 3944–3952; used with permission.

finding in that regard may be a greater bias toward right hemisphere activation for object working memory compared with verbal working memory.

3.13.3.4 Verbal Working Memory

Research on the neural basis of verbal working memory has, for a number of reasons, taken a rather different course from corresponding work in the visuospatial domain. First, whereas in visual working memory many of the most influential ideas and concepts have derived from work in the monkey, verbal working memory is a uniquely human phenomenon and has therefore benefited from animal research only indirectly or by analogy with the visual system. Even research on the primary modality relevant to verbal working memory, that of audition, is surprisingly scarce in the monkey literature, owing to the difficulty in training nonhuman primates to perform delayed-response tasks with auditory stimuli, which can take upwards of 15 000 learning trials (see Fritz et al., 2005). On the other hand, an entirely different state of affairs prevails in the field of human cognitive psychology, where verbal short-term and working memory has over the last 40 years been studied extensively, almost to the exclusion of other modalities, resulting in thousands of published articles, a host of highly reliable and replicated behavioral phenomena, and dozens of sophisticated computational models. Finally, the study of aphasic patients has provided a wealth of information about the neural circuitry underlying language, and systematic neurological and neuropsychological inquiries into the impairments that accompany damage to the language system have yielded detailed neuroanatomical models. The aphasia literature notwithstanding, the study of the neural basis of verbal working memory has depended, to a much greater extent than has been the case in the visuospatial domain, on pure cognitive models of memory, in particular the phonological loop of Baddeley and colleagues. Not surprisingly as it turns out, there are notable similarities between working memory for visual and linguistic material, despite the absence of an exactly analogous capacity in nonhuman primates.

Early neurological investigations of patients with language disturbances or aphasia revealed that lesions to specific parts of the cerebral cortex could cause extremely selective deficits in language abilities. Thus, lesions to the inferior frontal gyrus are associated with Broca's aphasia, a disorder that causes severe impairments in speech production. Broca's aphasia is not, however, a disorder of peripheral motor coordination, such as the ability to move and control the tongue and mouth, but rather is a disorder of the ability to plan, program, and access the motor codes required for the production of speech (Goodglass, 1993). The functions of speech perception and comprehension in Broca's aphasia are generally preserved, however. Lesions to the posterior superior temporal gyrus and surrounding cortex, on the other hand, are associated with Wernicke's aphasia, a complex syndrome that is characterized by fluent, but error-filled, production and poor comprehension and perception of speech. A third, less-studied syndrome called conduction aphasia, typically caused by lesions in the posterior sylvian region (generally less extensive and relatively superior to lesions causing Wernicke's aphasia), is associated with preserved speech perception and comprehension, occasional errors in otherwise fluent spontaneous speech (e.g., phoneme substitutions), and severe difficulties with verbatim repetition of words and sentences (Damasio and Damasio, 1980). From the standpoint of verbal STM, a number of important points can be drawn from these three classic aphasic syndromes. First, the neural structures that underlie the perception and production of speech are partly dissociable. Thus, it appears that the brain retains at least two codes for the representation of speech: a sensory, or acoustic, code and an articulatory, or motor, code; the former is necessary for the perception of speech, and the latter is required for the production of speech. It is tempting to postulate that posterior temporal lesions primarily affect receptive language functions, whereas anterior lesions affect productive language functions – but this is not quite true; both Wernicke's aphasia and conduction aphasia are caused by posterior lesions, yet only the former is associated with a receptive language disturbance (Hickok and Poeppel, 2000). Second, all the aforementioned disorders affect basic aspects of language processing, such as the comprehension, production, and perception of speech. Even conduction aphasia, for which a deficit in repetition of speech is often emphasized, is characterized by speech errors that occur in the course of natural language production. Finally, the classical Wernicke-Lichteim-Geschwind (Geschwind, 1965) model of language explains each of these three syndromes as disruptions to components of a neuroanatomical network of areas, in the inferior frontal and superior temporal cortices, that subserve language function.

In the 1960s a handful of patients were described that did not fit nicely into the classic aphasiological rubric. Both Luria et al. (1967) and Warrington and

Shallice (1969) described patients with damage to the temporoparietal cortex who were severely impaired at repeating sequences of words or digits spoken aloud by the experimenter. Luria referred to the deficit as an acoustic-amnestic aphasia, whereas Warrington and Shallice (1969), who were perhaps more attuned to extant information-processing models in cognitive psychology, referred to the deficit as a "selective impairment of auditory-verbal short-term memory" (p. 885) In both of these cases, however, the memory impairment was accompanied by a deficit in ordinary speech production (i.e., word-finding difficulties, errors of speech, and reading difficulty), which was, in fact, consistent with the rather routine diagnosis of conduction aphasia, and therefore complicated the argument in favor of a pure memory impairment. Several years later, however, a patient (J. B.) (Shallice and Butterworth 1977), also with a temporoparietal lesion, was described who had a severely reduced auditory–verbal immediate memory span (one or two items) and yet was otherwise unimpaired in ordinary language use, including speech production and even long-term learning of supraspan lists of words. Several other such patients have since been described (for a review, see Shallice and Vallar, 1990), thus strengthening the case for the existence of an auditory–verbal storage component located in temporoparietal cortex.

The puzzle, of course, with respect to the classic neurological model of language discussed earlier, is how a lesion in the middle of the perisylvian speech center could produce a deficit in auditory–verbal immediate memory without any collateral deficit in basic language functioning. One possibility is that the precise location of the brain injury is determinative, so that a particularly focal and well-placed lesion in temporoparietal cortex might spare cortex critical for speech perception and production, while damaging a region dedicated to the storage of auditory–verbal information. However, the number of patients that have been described with a selective impairment to auditory–verbal STM is small, and the lesion locations that have been reported are comparable to those that might, in another patient, have led to conduction or Wernicke's aphasia (Damasio, 1992; Goodglass, 1993; Dronkers et al., 2004). This would seem, then, to be a question particularly well suited to high-resolution functional neuroimaging.

Systematic investigations of STM patients on tests of verbal working memory were essential to the logical development of the phonological loop (Vallar and Baddeley, 1984). For instance, the phonological store component – a passive buffer capable of storing approximately 2 s worth of speech-based information – is a descendant of the auditory–verbal store of Warrington and Shallice. Although Baddeley and colleagues considered neuropsychological investigations to be an extremely useful source of evidence for the development of an information-processing model of verbal working memory, they did not explicitly link the hypothesized components of the loop to regions of the brain. Thus, when the first functional neuroimaging studies of the neural correlates of the phonological loop were carried out, they were done without strong *a priori* neuroanatomical predictions – unlike the early PET studies of visuospatial working memory, which were guided by a large body of monkey literature.

Before we discuss these neuroimaging efforts, it is important to review in slightly more detail certain key aspects of the phonological loop. As has already been discussed in this chapter, the concept of a buffer or a memory store implies an independence from perceptual or motor processing. Thus, the storage component in the phonological loop – the phonological store – plays no direct role in the sensory analysis and processing of acoustic input. How, then, does information arrive to the phonological store? It turns out that information can enter the store in various ways. Verbal information that is presented visually must first be subvocalized, before it enters the store. Subvocalization (or silent speech) is necessary to recode a visual-orthographic stimulus into a phonological form. In contrast, acoustic information has direct and obligatory access to the phonological store. Despite this asymmetry in the manner in which auditory- and visual-verbal information enters the store, the representational code of the store is not modality specific, in the sense that it is not strictly tied to an acoustic input source. Once verbal material has entered the phonological store, it begins to decay rapidly. Phonological traces within the store can be refreshed, however, through the operation of the articulatory rehearsal process, which can cycle or loop through the contents of the store, serially reviving each of the decaying memory traces.

Faced with this more or less abstract model of the cognitive architecture of verbal working memory, the functional neuroimager must formulate some simple heuristics that can help constrain the neuroanatomical space in which to search for the various components of the phonological loop. For instance, the articulatory rehearsal process is wholly dependent on the brain circuit that underlies speech production, and

therefore one would expect that the operation of this component would rely to a large extent on the contribution of the inferior frontal gyrus, or Broca's area. Clearly, because acoustic information has obligatory access to the phonological store, one should expect to find its neural correlate in a region that activates during passive auditory stimulation (Becker et al., 1999; Chein and Fiez, 2001). In addition, because visual–verbal information enters the phonological store only by way of the articulatory rehearsal process, one should expect both silent reading (accompanied by subvocalization) and subvocal rehearsal to activate the phonological store. On the other hand, one should not expect to find the neural correlate of the phonological store in a region that is known to be critical for speech perception proper because of the model's explicit separation of perceptual and storage modules. The last heuristic is probably the most important and probably the most philosophically problematic: It has to be assumed that the modular organization of the phonological loop is reflected by a similarly modular organization in the brain – which is to say that one must stipulate that the same brain region cannot simultaneously fulfill the role of more than one component of the model. Thus, one must assume that the articulatory rehearsal process and the phonological store are not both located in the same brain region or set of regions. In fact, though, there is ample evidence from neuropsychological investigations that the articulatory rehearsal and phonological store components do not share a common neuroanatomical substrate (e.g., Vallar et al., 1997).

The first study that attempted to localize the components of phonological loop in the brain was that of Paulesu and colleagues (1993). In one task, English letters were visually presented on a monitor, and subjects were asked to remember them. In a second task, letters were presented, and rhyming judgments were made about them (press a button if letter rhymes with 'B'). In a baseline condition, Korean letters were visually presented, and subjects were asked to remember them using a visual code. According to the authors' logic, the first task would require the contribution of all the components of the phonological loop – subvocal rehearsal, phonological storage, and executive processes – whereas the second (rhyming) task would only require subvocal rehearsal and executive processes. This reasoning was based on previous research showing that when letters are presented visually (Vallar and Baddeley, 1984), rhyming decisions engage the subvocal rehearsal system, but not the phonological store. Thus, a subtraction of the rhyming condition from the letter-rehearsal condition should isolate the neural locus of the phonological store. First, results were presented for the two tasks requiring phonological processing with the baseline tasks (viewing Korean letters) that did not. Several areas were shown to be significantly more active in the phonological tasks, including (in all cases, bilaterally) Broca's area (BA44/45), the supplementary motor cortex (SMA), the insula, the cerebellum, Brodmann area 22/42, and Brodmann area 40. Subtracting the rhyming condition from the phonological STM condition left a single brain area: Brodmann area 40 (BA 40) – the neural correlate of the phonological store.

Not surprisingly the articulatory rehearsal process recruited a distributed neural circuit that included the inferior frontal gyrus. The implication of multiple brain regions during articulatory rehearsal is not surprising, given the complexity of the process and the variety of lesion sites associated with a speech-production deficit. On the other hand, the localization of the phonological store in a single brain region, BA 40 (or the supramarginal gyrus), comports with the idea of a solitary receptacle where phonological information is temporarily stored. A number of follow-up PET studies, using various tasks and design logic, generally replicated the basic finding of the Paulesu study, namely, a fronto-insular-cerebellar network associated with rehearsal processes and a parietal locus for the phonological store (Awh et al., 1996; Salmon et al., 1996; Schumacher et al., 1996; Jonides et al., 1998; Smith and Jonides, 1999).

In a perspicacious review of these premillennial PET studies of verbal working memory, Becker et al. (1999) questioned whether the localization of the phonological store in BA 40 of the parietal cortex could be reconciled with the logical architecture of the phonological loop. They noted that because auditory material has obligatory access to the store, its neural correlate ought to show robust activation during simple auditory perception. Functional neuroimaging studies of passive auditory listening, however, do not show activity in the parietal lobe, but are typically circumscribed to the superior temporal lobe (e.g., Binder et al., 2000). In addition, efforts to show verbal mnemonic specificity to the parietal lobe activation were uniformly unsuccessful, showing instead that working memory for words, visual objects, and spatial locations all activated the area (Nystrom et al., 2000; Zurowski et al., 2002). Thus, it would appear that if there were a true neural correlate to the phonological store, it must reside within the confines of the auditory cortical zone of the superior temporal cortex.

As was the case in the visuospatial domain, the emergence of event-related fMRI, with its ability to isolate delay-period activity during working memory, was an inferential boon to the study of verbal working memory. Postle et al. (1999) showed, with visual–verbal presentation of letter stimuli, that delay-period activity in single subjects was often localized in the posterior superior temporal cortex rather than in the parietal lobe. Buchsbaum et al. (2001) also used an event-related fMRI paradigm, in which, on each trial, subjects were presented with acoustic speech information that they then rehearsed subvocally for 27 s, followed by a rest period.

Analysis focused on identifying regions that were responsive both during the perceptual phase and the rehearsal phase of the trial. Activation occurred in two regions in the posterior superior temporal cortex, one in the posterior superior temporal sulcus (STS) bilaterally and one along the dorsal surface of the left posterior planum temporale, that is, in the Sylvian fissure at the parietal-temporal boundary (area Spt). Notably, although the parietal lobe did show delay-period activity, it was unresponsive during auditory stimulus presentation. In a follow-up study, Hickok (2003) showed that the same superior temporal regions (posterior STS and Spt) were active both during the perception and delay-period maintenance of short (5 s) musical melodies, suggesting that these posterior temporal storage sites are not restricted to speech-based, or phonological, information (**Figure 8**).

In addition, Stevens (2004) and Rama et al. (2004) have shown that memory for voice identity, independent of phonological content (i.e., matching speaker identity as opposed to word identity), selectively activates the mid-STS and the anterior STG of the superior temporal region, but not the more posterior and dorsally situated Spt region. Buchsbaum et al. (2005) have further shown that the mid-STS is more active when subjects recall verbal information that is acoustically presented than when the information is visually presented, whereas area Spt shows equally strong delay-period activity for both auditory and

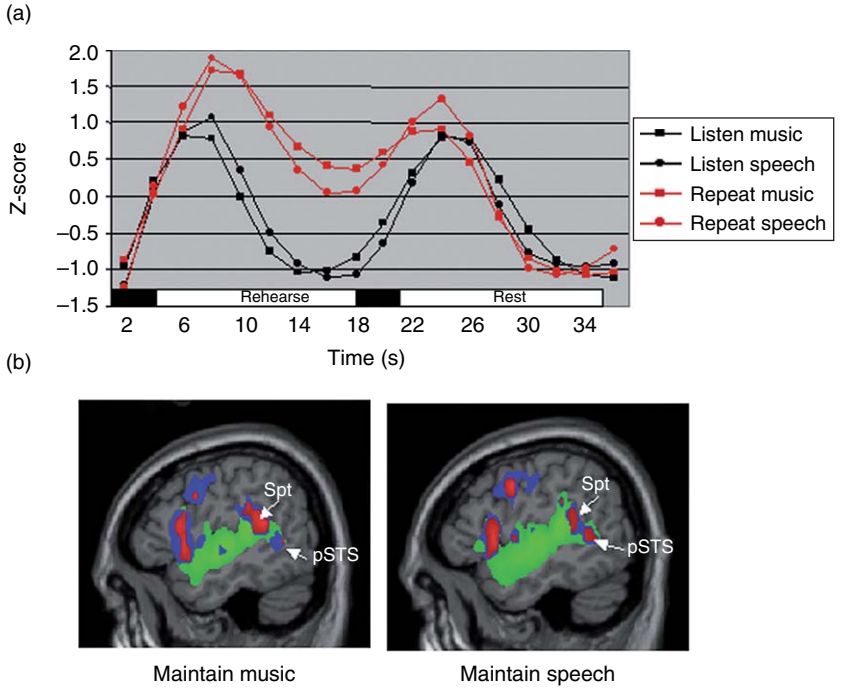


Figure 8 Main results from Hickok et al. (2003) study of verbal and musical working memory maintenance. (a) Averaged time course of activation over the course of a trial in area Spt for speech and music conditions. Timeline at bottom shows structure of each trial; black bars indicate auditory stimulus presentation. Red traces indicate activation during rehearsal trials, black traces indicate activity during listen-only trials in which subjects did not rehearse stimuli at all. (b) Activation maps of in the left hemisphere (sagittal slices) showing three response patterns for both music rehearsal (left) and speech rehearsal trials (right): auditory-only responses shown in green; delay-period responses shown in blue; and auditory + rehearsal responses shown in red. Arrows indicate the location of area Spt. pSTS, posterior superior temporal sulcus. From Hickok G, Buchsbaum B, Humphries C, and Muftuler T (2003) Auditory-motor interaction revealed by fMRI: Speech, music, and working memory in area Spt. *J. Cogn. Neurosci.* 15: 673–682; used with permission.

visual forms of input. Thus, it appears that different regions in the auditory association cortex of the superior temporal cortex are attuned to different qualities or features of a verbal stimulus, such as voice information, input modality, phonological content, and lexical status (e.g., Martin and Freedman, 2001) – and all these codes may play a role in the short-term maintenance of verbal information.

Additional support for a feature-based topography of auditory association cortex comes from neuroanatomical tract-tracing studies in the monkey that have revealed separate temporo-prefrontal pathways arising along the anterior–posterior axis of the superior temporal region (Romanski et al., 1999; Romanski, 2004). The posterior part of the STG projects to dorsolateral PFC (BA 46, 8), whereas neurons in the anterior STG are more strongly connected to the ventral PFC, including BA 12 and 47. Several authors have suggested, similar to the visual system, a dichotomy between ventral-going auditory-object and a dorsal-going auditory-spatial processing streams (Rauschecker and Tian, 2000; Tian et al., 2001). Thus, studies have shown that the neurons in the rostral STG show more selective responses to classes of complex sounds, such as vocalizations, whereas more caudally located regions show more spatial selectivity (Rauschecker and Tian, 2000; Tian et al., 2001). Hickok and Poeppel (2004, 2000) have proposed that human speech processing also proceeds along diverging auditory dorsal and ventral streams, although they emphasize the distinction between perception for action, or auditory-motor integration, in the dorsal stream and perception for comprehension in the ventral stream. Buchsbaum et al. (2005) have shown with fMRI time series data that, consistent with the monkey connectivity patterns, the most posterior and dorsal part of the superior temporal cortex, area Spt, shows the strongest functional connectivity with dorsolateral and posterior (premotor) parts of the PFC, whereas the midportion of the STS is most tightly coupled with BA 12 and 47 of the ventrolateral PFC (see **Figure 9**). Moreover, in a gross distinction between anterior (BA 47) and posterior (BA 44/6), parts of the PFC have been associated with conceptual-semantic and phonological-articulatory aspects of verbal processing (Poldrack et al., 1999; Wagner et al., 2001).

Earlier we posed the question of how a lesion in posterior sylvian cortex, an area of known importance for online language processing, could occasionally produce an impairment restricted to phonological STM. One solution to this puzzle is that subjects

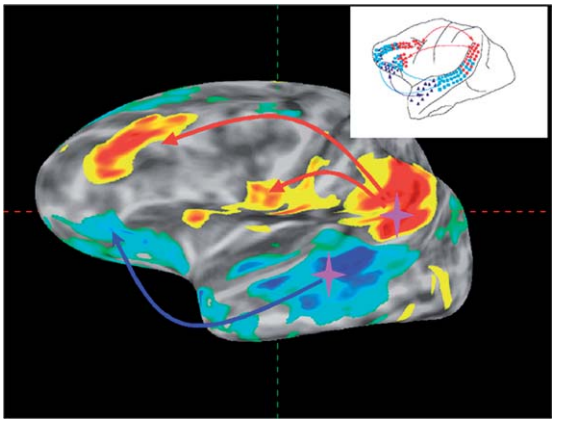


Figure 9 Map of functional connectivity delay-period maintenance of verbal stimuli from Buchsbaum et al. (2005). Seed regions for correlation analysis are denoted by stars located in area Spt and the middle part of the STS. Warm colors show areas more strongly correlated with Spt than with STS; cold colors show areas more strongly correlated with STS than Spt. Inset shows temporal-prefrontal connectivity in the monkey. From Buchsbaum BR, Olsen RK, Koch P, and Berman KF (2005) Human dorsal and ventral auditory streams subserve rehearsal-based and echoic processes during verbal working memory. *Neuron* 48: 687–697; used with permission. Inset from Scott SK and Johnsrude IS (2003) The neuroanatomical and functional organization of speech perception. *Trends Neurosci.* Feb; 26(2): 100–107; used with permission.

with selective verbal STM deficits from posterior temporal lesions retain their perceptual and comprehension abilities due to the sparing of the ventral stream pathways, whereas the preservation of speech production is due to an unusual capacity in these subjects for right-hemisphere control of speech. The STM deficit arises, then, from a selective deficit in auditory-motor integration – or the ability to translate between acoustic and articulatory speech codes – a function that is especially taxed during tests of repetition and STM (Hickok et al., 2003; Hickok and Poeppel, 2004).

The study of the neural basis of verbal working memory has proceeded from a large body of human neurological evidence pointing to the critical role of anterior regions (e.g., Broca's area) in speech production and posterior regions (e.g., temporoparietal cortex) in perceptual and mnemonic aspects of speech processing. This contrasts rather sharply with neurobiological investigations of spatial working memory, which was initially driven almost entirely by studies in the monkey and, in addition, posited a direct role for lateral PFC in mnemonic storage (Goldman-Rakic, 1987). Thus, for instance,

although there has been a great deal of debate as to whether the dorsolateral PFC stores information or whether it simply maintains pointers or links to posterior cortices where mnemonic representations are held (see Postle, 2006), there has, on the contrary, been little if any debate as to whether Broca's area is involved in verbal mnemonic storage *per se*, as it has generally been assumed that the inferior frontal region plays a specific role in motor-speech planning. Indeed, however, if we expand our conception of memory to include not just the percepts of the past, but the goals, plans, and intentions of the future – the "memory of the future" in David Ingvar's (1985) phrase – then the role of both dorsal and inferior frontal regions in spatial and verbal memory might relate to prospective operations that relate to objects held in working memory.

3.13.3.5 Models of Prefrontal Organization of Working Memory

Although there is strong support that the lateral PFC is critical for working memory maintenance processes, its precise role is still unclear. Goldman-Rakic and colleagues first proposed that different PFC regions are critical for active maintenance of different types of information. Based on monkey electrophysiological and lesion studies (Funahashi et al., 1989; Wilson et al., 1993), they theorized that persistent activity within the ventrolateral PFC would reflect the temporary maintenance of nonspatial codes (such as an object's color and shape), whereas dorsolateral PFC activity would reflect the maintenance of spatial codes (such as the location of an object in space). This hypothesis had the appeal of parsimony, as a similar organization exists in the visual system, which is segregated into what and where pathways (Ungerleider and Mishkin, 1982). Also, anatomical studies in monkeys have demonstrated that the parietal cortex (i.e., spatial vision regions) predominantly projects to a dorsal region of the lateral PFC (Cavada and Goldman-Rakic, 1989; Petrides and Pandya, 1984), whereas the temporal cortex (i.e., object vision regions) projects more ventrally within lateral PFC (Barbas, 1988).

Another possible axis along which the human lateral PFC may be organized is according to the type of operations performed on information being actively maintained, rather than the type of information being maintained. For example, Petrides proposed that there are two processing systems, one dorsal and the other ventral, within lateral PFC (Petrides and Pandya, 1994). It was proposed that ventral PFC (Brodmann's areas 45, 47) is the site where information is initially received from posterior association areas and where active comparisons of maintained information are made. In contrast, the dorsal PFC (areas 9, 46, 9/46) is recruited only when monitoring and manipulation of this information are required.

This model received initial support from an empirical PET study performed by Owen, Petrides, and colleagues (Owen et al., 1996) in which dorsal PFC activation was found during three spatial working memory tasks thought to require greater monitoring of remembered information than two other memory tasks that activated only the ventral PFC. We also tested this model of process-specific PFC organization using event-related fMRI (D'Esposito et al., 1999). In our study, subjects were presented two types of trials in random order in which they were required to either (1) maintain a sequence of letters across a delay period or (2) manipulate (alphabetize) this sequence during the delay to respond correctly to a probe. In every subject, delay-period activity was found in both dorsal and ventral PFC in both types of trials. However, dorsal PFC activity was greater in trials during which actively maintained information was manipulated. These findings suggest that the dorsal PFC may exhibit greater recruitment during conditions that require additional processing of actively maintained information, supporting a process-specific PFC organization.

On the surface, these two models of PFC organization seem incompatible, and to this day papers continue to be published pitting one against the other. However, a closer look at the empirical data from human functional imaging and monkey physiology studies over the past 10 years leads to the conclusion that both models accurately describe PFC organization. The persistence of the notion that these models are orthogonal to each other may result in part from a lack in precision of the anatomical definitions of the dorsal and ventral PFC that were being used. For example, as reviewed earlier, the principal evidence cited to support domain-specific PFC organization in humans (Leung et al., 2002) derives from studies by Courtney and colleagues, who found that the superior frontal sulcus (area 6/8) appears specific to spatial working memory, whereas regions within the inferior frontal gyrus (areas 45, 47) appear specific to nonspatial information (e.g., faces). Unquestionably, the superior frontal sulcus is anatomically dorsal to the inferior frontal gyrus. Thus, on the surface these data provide strong support for a dorsal-what versus a ventral-where,

domain-specific PFC organization. However, other data from monkey physiological and human functional imaging studies seem inconsistent with the domain-specific hypothesis because they provide evidence that certain dorsal and ventral PFC regions do not appear specific to one domain of information. For example, several single-unit recording studies during delayed-response tasks have found a mixed population of neurons throughout dorsal and ventral regions of lateral PFC that are not clearly segregated by the type of information (i.e., spatial vs. nonspatial) that is being stored (Rosenkilde et al., 1981; Fuster et al., 1982; Quintana et al., 1988; Rao et al., 1997). Also, cooling of PFC (Fuster and Bauer, 1974; Bauer and Fuster, 1976; Quintana and Fuster, 1993) and dorsal PFC lesions causes impairments on nonspatial working memory tasks (Mishkin et al., 1969; Petrides, 1995), and ventral PFC lesions cause spatial impairments (Iversen and Mishkin, 1970; Butters et al., 1973). Finally, another study found that ventral PFC lesions in monkeys did not lead to delay-dependent defects on a visual pattern-association task and color-matching task (Rushworth et al., 1997). Also, numerous human functional imaging studies have failed to find different patterns of PFC activation during spatial versus nonspatial working memory tasks (e.g., Owen et al., 1998; Postle and D'Esposito, 1999; Nystrom et al., 2000).

How can we reconcile all these findings? The answer emerges from a close examination of the particular PFC regions that do or do not exhibit persistent activity that is specific to a particular type of information. Thus, domain specificity may exist within the superior frontal sulcus (area 6/8) and portions of the inferior frontal gyrus (areas 44, 45, 47), but other lateral PFC regions such as middle frontal gyrus (areas 9, 46, 9/46) may not show domain specificity. A coarse subdivision of the PFC into dorsal and ventral regions fails to account for the possibility that both domain-specific and process-specific organization may exist. A hybrid model of PFC organization could accommodate the empirical findings (Postle et al., 2000). But a hybrid model may not be able to capture, in cognitive or neural terms, the specific type of processes that are being attributed to the middle frontal gyrus (areas 9, 46, 9/46). Are the processes attributed to this region (e.g., monitoring and manipulation) distinct from active maintenance processes? For example, one possibility is that monitoring and manipulation tasks recruit the middle frontal gyrus because they require active maintenance of more abstract relations (e.g., semantic, temporal) between items. In this view, the PFC is not organized by different types of processing modules, but by the abstractness of the representations being actively maintained. This organization could be hierarchic, ranging from features of an object (e.g., red), to more abstract dimensions (e.g., color), to superordinate representations such as goals or task context (e.g., color-naming task). Evidence from functional neuroimaging studies has begun to provide support for this idea.

A recent neuroimaging study has tested this model of hierarchical PFC organization, all within one set of experiments (Koechlin et al., 2003). In this fMRI study, the frequency of to-be-selected representations was manipulated in an effort to affect levels of PFC processing. Manipulation of the number of responses within a block primarily affected premotor cortex. Manipulation of the number of relevant stimulus dimensions within a block affected dorsolateral PFC. Finally, manipulation of the across-block frequency of cue-to-response or cue-to-dimension mappings affected PFC responses. Interestingly, structural equation modeling of the fMRI data revealed path coefficients from the PFC to the dorsal PFC to premotor cortex but not in the opposite direction, broadly consistent with a hierarchic organization. An important contribution from this study is that it considers the entire frontal cortex, from premotor regions to the most anterior portion of PFC (area 10), an area that has been relatively ignored in working memory research. This type of PFC organization is also consistent with data (O'Reilly et al., 2002), which demonstrated that a connectionist model possessing a concrete feature level and an abstract dimension level in its PFC could produce the double dissociations reported in the monkey data.

Miller and Cohen (2001) have presented a synthesis of empirical findings with a theoretical model regarding how basic maintenance processes subserved by the PFC can exert cognitive control. They propose that PFC delay activity is specific to those representations that are behaviorally relevant, enabling an animal or human to prospectively integrate across time when selecting an action. Automatic behaviors can be mediated by computations in posterior neocortices with little influence from internal goals maintained by the PFC. When bottom-up processes are insufficient for or in conflict with current goals, available cues may be insufficient to uniquely specify a response. Under such circumstances, the active maintenance of behaviorally relevant representations permits the appropriate selection for action.

The PFC has extensive reciprocal connections with most of the brain and is situated at the apex of mnemonic, affective, perceptual, and motor pathways arising from posterior and subcortical processors. Thus, it is in a privileged position to store behaviorally relevant representations and exert cognitive control. The frontal cortex appears hierarchically organized, not simply in a dorsal/ventral fashion, but in a posterior/anterior direction from premotor regions to frontopolar cortex. Future research must continue to determine the regional distinctions that define the functional topography of the frontal cortex and the principles by which these regions interact to produce controlled behavior.

In summary, goal-directed behavior, which is both intentional and flexible, requires the active maintenance of a broad range of perceptual, mnemonic, and motor representations. For example, imagine hitting a golf ball. If your ball is in the woods, you may need to maintain the location of the flag in the distance as you keep your eye on the ball. As you prepare to hit your ball, you also have to maintain the rules of the game because any movement of the ball as you address it may result in a penalty stroke. And finally, if you are playing poorly, it is important to maintain the original goal for taking up the game – to exercise and enjoy yourself.

3.13.4 Summary and Conclusions

Elucidation of the cognitive and neural architectures underlying STM has been an important focus of neuroscience research for much of the past two decades. The emergence of the concept of working memory, with its emphasis on the utilization of the objects stored in memory in the service of behavioral goals, has enlarged our understanding and broadened the scope of neuroscience research of STM. Data from numerous studies have been reviewed and have demonstrated that a network of brain regions, including the PFC, is critical for the active maintenance of internal representations. Moreover, it appears that the PFC has functional subdivisions that are organized according to the domain (verbal, spatial, object, etc.) of the topographical inputs arriving from posterior cortices. In addition, however, a level of representational abstractness is achieved through the integration of information converging in the PFC. Finally, working memory function is not localized to a single brain region but is rather an emergent property of the functional interactions between the PFC and other posterior neocortical regions. Numerous questions remain about the neural basis of this complex cognitive system, but studies such as those reviewed in this chapter should continue to provide converging evidence that may provide answers to the many residual questions.

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