

From cognitive to neural models of working memory

Mark D'Esposito*

*Helen Wills Neuroscience Institute and Department of Psychology, University of California,
132 Barker Hall, Berkeley, CA 94720-3190, USA*

Working memory refers to the temporary retention of information that was just experienced or just retrieved from long-term memory but no longer exists in the external environment. These internal representations are short-lived, but can be stored for longer periods of time through active maintenance or rehearsal strategies, and can be subjected to various operations that manipulate the information in such a way that makes it useful for goal-directed behaviour. Empirical studies of working memory using neuroscientific techniques, such as neuronal recordings in monkeys or functional neuroimaging in humans, have advanced our knowledge of the underlying neural mechanisms of working memory. This rich dataset can be reconciled with behavioural findings derived from investigating the cognitive mechanisms underlying working memory. In this paper, I review the progress that has been made towards this effort by illustrating how investigations of the neural mechanisms underlying working memory can be influenced by cognitive models and, in turn, how cognitive models can be shaped and modified by neuroscientific data. One conclusion that arises from this research is that working memory can be viewed as neither a unitary nor a dedicated system. A network of brain regions, including the prefrontal cortex (PFC), is critical for the active maintenance of internal representations that are necessary for goal-directed behaviour. Thus, working memory is not localized to a single brain region but probably is an emergent property of the functional interactions between the PFC and the rest of the brain.

Keywords: working memory; short-term memory; executive function; cognitive control; prefrontal cortex; functional magnetic resonance imaging

1. INTRODUCTION

What is the neural basis of working memory? To answer this question, one must begin with a proper definition of the term 'working memory'. To me, working memory refers to the temporary retention of information that was just experienced but no longer exists in the external environment, or was just retrieved from long-term memory. These internal representations are short-lived, but can be stored for longer periods of time through active maintenance or rehearsal strategies, and can be subjected to various operations that manipulate the information in ways that make it useful for goal-directed behaviour. Thus, working memory is critically important in cognition and seems necessary for many cognitive abilities, such as reasoning, language comprehension, planning and spatial processing. However, it is clear from the numerous empirical studies of working memory that are published each year that it is an evolving construct, one that has come a long way over the past 30 years, since [Baddeley & Hitch \(1974\)](#) introduced their highly influential cognitive model of working memory.

Within a cognitive framework, [Baddeley](#) conceptualized working memory as a cognitive system comprising multiple components that support executive control (see also [Burgess *et al.* 2007](#); [Robbins 2007](#); [Stuss & Alexander 2007](#)) as well as active maintenance of

temporarily maintained information ([Baddeley 1986](#)). Thus, a 'central executive system' was proposed as a system that could actively regulate the distribution of limited attentional resources and coordinate information within limited capacity verbal and spatial memory storage buffers. The central executive system, based on the analogous supervisory attentional system introduced by [Norman & Shallice \(1986\)](#), was proposed to take control over cognitive processing when novel tasks are engaged and/or when existing behavioural routines have to be overridden. Empirical studies of working memory using neuroscientific techniques, such as neuronal recordings in monkeys (e.g. [Funahashi *et al.* 1989](#)) and functional neuroimaging in humans (e.g. [Curtis *et al.* 2004](#)), have provided a rich dataset that can be reconciled with behavioural findings derived by testing cognitive models of working memory such as the one proposed by [Baddeley](#). In this paper, I review the progress that has been made towards this effort by illustrating how investigations of the neural mechanisms underlying working memory can be influenced by cognitive models and, in turn, how cognitive models can be shaped and modified by neuroscientific data.

2. TRADITIONAL COGNITIVE MODELS OF WORKING MEMORY

A critical component of [Baddeley's](#) working memory model is the existence of verbal and spatial storage buffers. The cognitive concept of a buffer translated into neural terms would propose that temporary

*despo@berkeley.edu

One contribution of 14 to a Discussion Meeting Issue 'Mental processes in the human brain'.

retention of task-relevant information requires transfer of that information to a part of the brain that is dedicated to the storage of information. Presumably, such buffers are analogous to a computer's RAM, which serves as a cache for information transferred from the hard drive that is processed by a CPU. Consistent with this interpretation of a working memory 'buffer', many descriptions of cognitive models of working memory refer to the information being 'in' or 'out' of working memory. For example, in a recent review of working memory, [Repovs & Baddeley \(2006\)](#) state that 'the function of the articulatory rehearsal process is to retrieve and re-articulate the contents held *in* this phonological store and in this way to refresh the memory trace. Further, while speech input *enters* the phonological store automatically, information from other modalities enters the phonological store only through recoding into phonological form, a process performed by articulatory rehearsal'. Later, the authors refer to 'focal shifts of attention to memorized locations that provide a rehearsal-like function of maintaining information active *in* spatial working memory'. Thus, one question that neuroscientific data can address regarding how the brain implements working memory processes is whether such buffers or storage sites exist in distinct parts of the brain to support the active maintenance of task-relevant information.

Another cognitive model of working memory, put forth by [Cowan \(1988, 1999\)](#), proposes that the 'contents of working memory' are not maintained within dedicated storage buffers, but rather are simply the subset of information that is within the focus of attention at a given time. He describes an embedded-processes model where working memory comes from hierarchically arranged faculties comprising long-term memory, the subset of working long-term memory that is currently activated and the subset of activated memory that is the focus of attention. These ideas are similar to that put forth by [Anderson \(1983\)](#) who referred to working memory as those representations currently at a high level of activation. Thus, task-relevant representations are not in working memory, but they do have levels of activation that can be higher or lower. After use, for example, representations may be temporarily more active or 'primed'. In this formulation, working memory does not have a size, or maximum number of items, as a structural feature. Instead, performance on working memory tasks is determined by the level of activation of relevant representations, and the discriminability of activation levels between relevant and irrelevant representations ([Kimberg *et al.* 1997](#)).

Again, in neural terms, Cowan or Anderson's cognitive model of working memory would predict that information that is represented throughout the brain is not transferred to an independent buffer or storage site, but rather that temporary retention of task-relevant information is mediated by the activation of the neural structures that represent the information being maintained or stored (for a further discussion of these and related ideas see [Ruchkin *et al.* \(2003\)](#) and the commentary that followed). In other words, the temporary retention of a face, for example, would

require activation of cortical areas that are involved in the perceptual processing of faces.

It is not possible in this paper to consider all cognitive models of working memory (for an excellent starting point, the reader is referred to [Miyake & Shah 1999](#)). However, based on the models put forth by [Baddeley and Cowan](#) as prototypes, one can begin to consider how the cognitive mechanisms proposed by such models are implemented in the brain. Thus, with these cognitive models in mind, I review evidence that begins to provide some insight into the neural mechanisms regarding how relevant information is temporarily stored in the service of goal-directed behaviour.

From a neuroscience perspective, it is counter-intuitive that all temporarily stored information during goal-directed behaviour requires specialized dedicated buffers. Clearly, there could not be a sufficient number of independent buffers to accommodate the infinite types of information that need to be actively maintained to accommodate all potential or intended actions. In a system with only two buffers, such as verbal and visuospatial, how would the retention of odours or tactile sensations, which cannot always be recoded into verbal or visuospatial representations, be accomplished? More recently, an additional episodic buffer has been proposed to be a store capable of multidimensional coding that allows the binding of information to create an integrated episode ([Baddeley 2000](#)). However, even with the addition of this buffer, [Baddeley's](#) working memory model cannot accommodate storage of all possible types of information processed by the human brain (it is important to note, however, that this was not probably the original intent of this model). Alternatively, in [Cowan's](#) proposal, which does not rely on the concept of specialized dedicated storage buffers, active maintenance or storage of task-relevant representations could be implemented with a neural system where memory storage occurs in the very same brain circuitry that supports the perceptual representation of information. Such a neural system presumably would be more flexible and efficient than one that transfers information back and forth between dedicated storage buffers. Can studies of brain function, either in animal or man, test these competing hypotheses?

3. NEURAL MODELS OF WORKING MEMORY

For over 30 years, the results of experiments in behaving monkeys using recordings from single neurons within the lateral prefrontal cortex (PFC, [figure 1a](#)) have consistently found persistent, sustained levels of neuronal firing during the retention interval in tasks that require a monkey to retain information over a brief period of time (e.g. [Fuster & Alexander 1971](#); [Kubota & Niki 1971](#); [Funahashi *et al.* 1989](#)). This sustained activity is thought to provide a bridge between the stimulus cue (e.g. the location of a flash of light) and its contingent response (e.g. a later delayed saccade to the remembered location). These results have been supported by the functional neuroimaging studies in humans, and there is now a critical mass of studies that find lateral PFC activity in humans during delay tasks (for review, see [Curtis & D'Esposito 2003](#)).

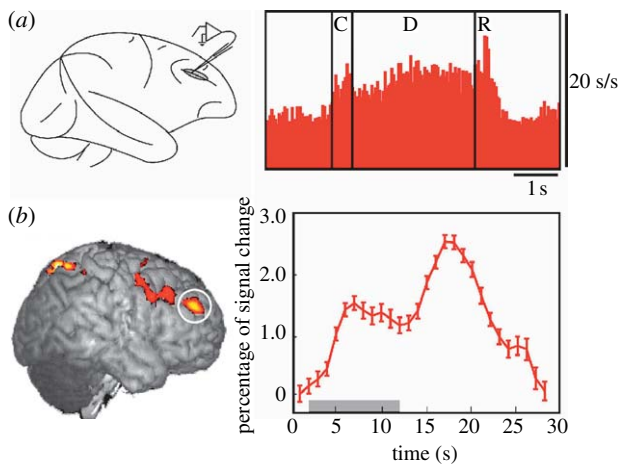


Figure 1. Neural activity in the monkey and the human lateral PFC during the retention interval of a spatial oculomotor delayed response (ODR) task. (a) Macaque: average of single-unit recordings from 46 neurons with delay-period activity from the monkey lateral PFC (brain area (BA) area 46; adapted from Funahashi *et al.* 1989). C, cue; D, delay; R, response. (b) Human: significant delay-period activity (left) and average (\pm s.e.) fMRI signal (right) from right lateral PFC (BA area 46; circled) in a human performing an ODR task (unpublished data from my laboratory). The grey bar represents the length of the delay interval. Note that how in both cases the level of PFC activity persists throughout the delay, seconds after the stimulus cue has disappeared.

For example, in a functional magnetic resonance imaging (fMRI) study using an oculomotor delay task identical to that used in monkey studies, we observed not only the frontal cortex activity during the retention interval (figure 1b), but also the magnitude of the activity correlated positively with the accuracy of the memory-guided saccade that followed later. This relationship suggests that the fidelity of the actively maintained location is reflected in the delay-period activity (Curtis *et al.* 2004). Thus, the existence of persistent neural activity during blank memory intervals of delay tasks is a powerful empirical finding, which lends strong support for the hypothesis that such activity represents a neural mechanism for the active maintenance or storage of task-relevant representations. The necessity of the PFC for the active maintenance of task-relevant representations has been demonstrated by studies that have found impaired performance on delay tasks in monkeys with selective lesions of the lateral PFC (Bauer & Fuster 1976; Funahashi *et al.* 1993).

However, monkey physiology studies recording from other brain areas and human fMRI studies of working memory have also found that the PFC is not the only region that is active during the temporary retention of task-relevant information. For example, we also observed in the previously mentioned fMRI study (Curtis *et al.* 2004) that different brain regions were involved during the performance of the oculomotor delayed response task. Specifically, different brain regions were active depending on whether the task required the temporary maintenance of retrospective (e.g. past sensory events) or prospective (e.g. representations of anticipated action and preparatory set) codes. During the performance of this task, participants in the

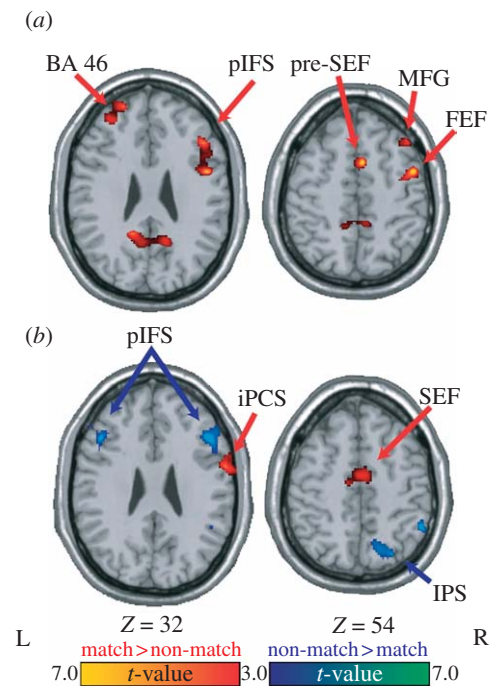


Figure 2. Statistical parametric t -maps contrasting oculomotor delayed matching-to-sample versus non-matching-to-sample delay period-specific activity (Curtis *et al.* 2004). Activity during the (a) early and (b) late delay periods is shown. Warm colours depict regions with greater delay-period activity on matching than non-matching trials. Cool colours depict regions with greater delay-period activity on non-matching than matching trials. BA, brain area; FEF, frontal eye fields; SEF, supplementary eye fields; MFG, middle frontal gyrus; pIFS, posterior inferior frontal sulcus; iPCS, inferior precentral sulcus; IPS, intraparietal sulcus.

study were biased towards or against the use of a prospective motor code. In one condition (match trials), the participants were able to plan a saccade to the target as soon as the cue appeared and then they could simply postpone the initiation of the saccade until after the delay. During these trials, delay-period activity should reflect this strategy, i.e. the maintenance of a prospective motor code. In a comparison condition (non-match trials), a saccade was made after the retention interval to an unpredictable location that did not match the location of the sample. The participants still had to remember the location of the sample so that they could discern between the matching and non-matching targets. Since a saccade was never made to the sample location and the non-matching location was unpredictable, we expected that, during these trials, the participants were biased away from maintaining a motor code during the delay. Instead, the nature of these trials encouraged the maintenance of a retrospective sensory code. We found that delay-period activity was greater for the match when compared with non-match trials within oculomotor regions; whereas delay-period activity for non-match trials was greater in frontal and parietal regions (figure 2). Thus, this study demonstrated not only that many different brain regions exhibit persistent neural activity during active maintenance of task-relevant information, but also that a unique network of brain regions are recruited depending on the type of information being actively maintained. Our fMRI data also support the notion that even within the

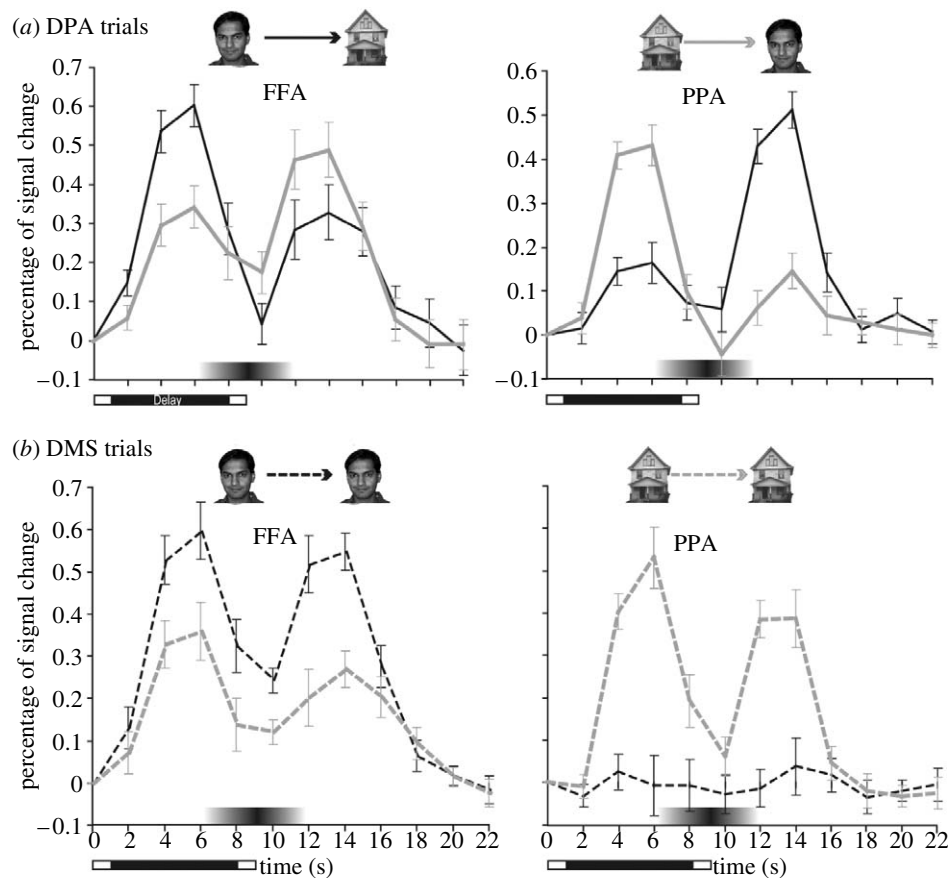


Figure 3. Human inferior temporal cortex activity during visual working memory maintenance and associative memory retrieval (Ranganath *et al.* 2004). (a) DPA trials: on DPA trials, activity during the cue phase in the FFA (left) and PPA (right) was enhanced when each region's preferred stimulus was presented (black line, face stimuli; grey line, house stimuli). However, during the delay period, activity in these regions reflected the type of information that was active in memory, rather than the previously presented cue stimulus, i.e. delay activity in the FFA was greater when a face was recalled in response to a house cue and delay activity in the PPA was greater when a house was recalled in response to a face cue. (b) DMS trials: on DMS trials, cue and delay-period activity in the FFA and PPA was enhanced when subjects maintained each region's preferred stimulus type (black dashed line, face stimuli; grey dashed line, house stimuli).

domain of spatial information, separable neural mechanisms are engaged for the active maintenance of 'motor' plans versus 'spatial' codes. Moreover, given that our task only required the oculomotor system, it is probable that distinct neural circuitry will be recruited when the motor act involves other modalities, such as speech or limb output (e.g. Hickok *et al.* 2003). Thus, this is the first piece of evidence presented in this review that the concept of specialized buffers (for, say, verbal versus spatial information) may not map adequately onto neural architecture. Rather, the findings appear more consistent with a system in which active maintenance involves the recruitment of the same circuitry that represents the information itself, with different circuits for different types of spatial information (e.g. visual versus oculomotor).

Similar findings exist when the 'visual' component of working memory is investigated with neuroscientific methods. For example, in another fMRI study (Ranganath *et al.* 2004), we asked the participants to learn a series of faces, houses and face-house associations and they were scanned while performing a delayed match-to-sample (DMS) and delayed paired-associate (DPA) task with these stimuli. Results showed that delay-period activity within category-selective inferior temporal subregions reflected the type of

information that was being actively maintained—the fusiform gyrus showed enhanced activity when participants maintained previously shown faces on DMS trials, and when subjects recalled faces in response to a house cue on DPA trials. Likewise, the parahippocampal gyrus showed enhanced activity when participants maintained previously shown houses on DMS trials and when they recalled houses in response to a face cue on DPA trials (figure 3). These fMRI findings are consistent with several monkey neurophysiological studies which have also shown that temporal lobe neurons exhibit persistent stimulus-selective activity in tasks requiring the active maintenance of visual object information across short delays (Miyashita & Chang 1988; Miller *et al.* 1993; Nakamura & Kubota 1995). Again, like spatial and motor codes, active maintenance of visual stimuli is mediated by the activation of cortical regions that also support processing of that information, perceptual in this case.

4. IS PHONOLOGICAL WORKING MEMORY SPECIAL?

Neuroscientific studies of verbal working memory, which has been most extensively studied by behavioural methods (Vallar & Shallice 1990), provide a similar

view regarding the neural mechanisms underlying working memory. Consistently, performance on tasks that tap the 'phonological loop', as conceptualized by Baddeley, engage a set of brain regions that are thought to be involved in phonological processing. For example, using functional neuroimaging techniques during verbal working memory tasks, the left inferior parietal lobe, posterior inferior frontal gyrus (Broca's area), premotor cortex and the cerebellum are typically activated (e.g. Paulesu *et al.* 1993; Awh *et al.* 1996).

However, is this network of brain regions also responsible for the active maintenance of non-phonological language representations (e.g. lexical-semantic)? For visual word recognition, a functionally specialized processing stream is thought to exist within inferior temporal cortex, representing visual words at increasingly higher levels of abstraction along a posterior-to-anterior axis (Cohen & Dehaene 2004). Intracranial electrophysiological recordings (Nobre *et al.* 1994), for example, show that posterior inferior temporal cortex differentiates letter strings from non-linguistic complex visual objects. Brain activity in more anterior inferior temporal cortical regions, in contrast, distinguishes words from non-words and is affected by the semantic context of words, indicating that anterior inferior temporal cortex holds more elaborate linguistic representations (see also Marslen-Wilson & Tyler 2007; Patterson 2007). To demonstrate that there is distinct neural circuitry supporting the active maintenance of non-phonological language representations, we explored the role of language regions within the left inferotemporal cortex (ITC) that are involved in visual word recognition and word-related semantics. Using fMRI, we first localized a visual 'word form' area within inferior temporal cortex area and then demonstrated that this area was involved in the active maintenance of visually presented words during a delay task (Fiebach *et al.* 2006). Specifically, we found that this area was recruited more for the active maintenance of words than pseudowords (i.e. orthographically legal and pronounceable non-words). Maintenance of pseudowords should not elicit strong sustained activation in such brain regions, as no stored representations pre-exist for these items. These results suggest that verbal working memory may be conceptualized as involving sustained activation of all relevant pre-existing cortical language (phonological, lexical or semantic) representations.

If working memory maintenance processes reflect the prolonged activation of the same brain regions that support online processing, evidence for cortical activity in the absence of stimuli should be evident not only in association cortex (as discussed thus far) but also within primary cortical regions. This indeed is the case as such effects have been observed in primary olfactory (Zelano *et al.* 2005), visual (Klein *et al.* 2000; Silver *et al.* 2006) and auditory cortex (Calvert *et al.* 1997; Kraemer *et al.* 2005). Thus, the neuroscientific data presented in this paper are consistent with most or all neural populations being able to retain information that can be accessed and kept active over several seconds, via persistent neural activity in the service of goal-directed behaviour.

5. NEURAL MECHANISMS OF ACTIVE MAINTENANCE OF TASK-RELEVANT REPRESENTATIONS

The observed persistent neural activity during delay tasks may reflect active rehearsal mechanisms. Active rehearsal is hypothesized to consist of the repetitive selection of relevant representations or recurrent direction of attention to those items. Subvocal articulations probably mediate the rehearsal of verbalizable memoranda (Baddeley 1986) since articulatory suppression (e.g. uttering 'the...the...the' during a retention interval), which interferes with rehearsal, degrades memory performance (Murray 1968). In addition, the ventrolateral frontal cortex (i.e. Broca's area) is often activated in working memory tasks where subvocal rehearsal is the main strategy for maintenance (Bench *et al.* 1993; Awh *et al.* 1996). Similar mechanisms may be involved in the active maintenance of visual information such as objects, which may be represented by their visual features (e.g. size, colour, texture, shape) as well as verbal information associated by an individual with a visual stimulus (Postle *et al.* 2005). The mechanisms underlying rehearsal of non-verbalizable material like spatial locations have been more difficult to resolve, but are likely to involve related motor and/or attentional processes (Awh *et al.* 1999; Awh & Jonides 2001). Positional information might be represented in oculomotor coordinates, where the memorized location might be maintained in terms of a saccade vector that acquires the target. Therefore, rehearsal of locations could simply be the reactivations of oculomotor programmes without actually making overt eye movements and can account for consistent activation of the frontal eye fields during spatial working memory tasks (Courtney *et al.* 1998). Thus, the rehearsal may be one mechanism by which transiently activated representations can be reactivated and refreshed.

Active maintenance (or rehearsal) of task-relevant representations clearly requires interactions between brain regions (Goldman-Rakic 1988; Fuster 1995, 2003). Such interactions could support working memory maintenance processes via synaptic reverberations in recurrent circuits (Durstewitz *et al.* 2000b; Wang 2001) or synchronous oscillations between neuronal populations (Singer & Gray 1995; Engel *et al.* 2001). Owing to the limitations in available methodology, only a few studies to date have been able to assess if and how neurons and brain regions interact to facilitate active maintenance processes (Fuster *et al.* 1985; Chafee & Goldman-Rakic 1998; Tomita *et al.* 1999; Funahashi & Inoue 2000; Constantinidis *et al.* 2001; Tallon-Baudry *et al.* 2001), although this is a critical issue for the future (see also Vuilleumier & Driver 2007). In other words, neither single neuron recordings nor standard univariate analysis of fMRI data, in which each neuron or voxel or brain region is analysed independently of all others, reveal more than the nature of isolated activity within these regions. Thus, only indirect evidence exists to support the assertion that working memory maintenance processes are implemented by the interaction of nodes within a neural network. Human functional neuroimaging, however, is ideally and uniquely suited to explore network interactions, since this method

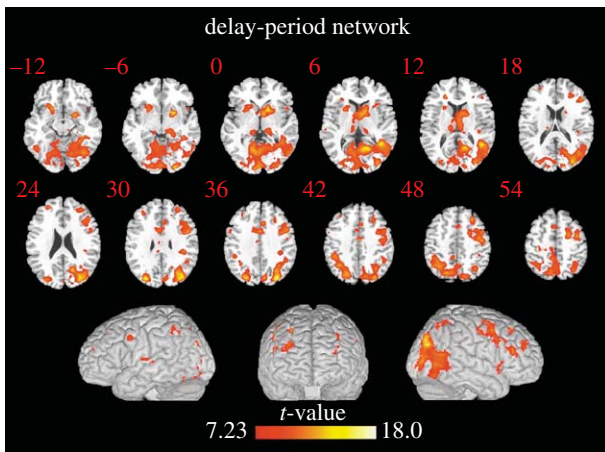


Figure 4. Delay-period correlation map with right FFA seed ($N=17$; Gazzaley *et al.* 2004). Activations are thresholded at $p < 0.05$ (corrected) and shown overlaid on both axial slices and a three-dimensionally rendered MNI template brain. The colour scale indicates the magnitude of the t -values.

simultaneously records correlates of neural activity throughout the entire functioning brain with high spatial resolution. Thus, multivariate analyses have been developed to analyse neuroimaging data (Friston *et al.* 1993; McIntosh 1998), which thus far have been used to investigate functional connectivity in many cognitive domains, such as learning (Buchel *et al.* 1999; Toni *et al.* 2002), attention (Friston & Buchel 2000; Rowe *et al.* 2002) and long-term memory (Maguire *et al.* 2000).

Recently, we developed a new multivariate method designed specifically to characterize functional connectivity in an event-related fMRI dataset and measure interregional correlations during the individual stages of a delay task (Rissman *et al.* 2004). Using this method, we specifically sought to characterize the network of brain regions associated with the maintenance of the representation of a visual stimulus over a short-delay interval. To accomplish this, we re-analysed two previously published event-related fMRI datasets (Ranganath & D'Esposito 2001; Druzgal & D'Esposito 2003) that employed similar delayed recognition paradigms on different groups of subjects and used a functionally defined region of visual association cortex as the exploratory seed. Since both tasks required the maintenance of face stimuli, the fusiform face area (FFA), a visual region that is selective for viewing faces (Kanwisher *et al.* 1997), was used as the seed. By pooling the correlation data from these two datasets into a single group-level analysis, we identified the network of brain regions that was most consistently correlated with the FFA seed during the delay period and hence associated with the active maintenance of the represented stimulus (figure 4). The presence of significant delay-period correlations between the FFA and regions of the prefrontal and parietal cortex regions supports models of working memory which suggest that higher-order association cortices interact with posterior sensory regions to facilitate the active maintenance of a sensory percept. The correlation between the FFA and these high-order regions appears to be initially established during the encoding of the cue stimulus, and these correlations are largely sustained during the delay

period, despite a dramatic decrease in the level of univariate activity. Similarly, we have also found that language-related visual association areas involved in the maintenance of words (as described earlier), in the absence of visual input, also exhibit increased functional connectivity with the PFC (Fiebach *et al.* 2006). In summary, all of these empirical findings extend neural mechanisms of maintenance processes from the finding of persistent isolated neural activity within functionally specialized brain regions to encompass the concept of persistent functional connectivity between brain regions.

As discussed earlier, physiological and behavioural data suggest that each brain region, although forming part of a functional network, may contribute different elements to active maintenance by the nature of the representations that are coded within each region. However, different brain regions within a functional network probably differ only in their degree of participation in a manner that is dependent on the context of the operation being actively performed (Fuster 1995, 2003; McIntosh 2000). This is immediately evident by noting, for example, that the same regions which are involved in temporarily maintaining a representation are often also engaged during the encoding and retrieval of that information (e.g. Funahashi *et al.* 1989). Further understanding of such neural interactions will require investigating the influence of hypothesis-driven task design manipulations on the functional connectivity between brain regions. For example, we have investigated functional connectivity during a delay task with distracting stimuli aimed at increasing active maintenance demands (Yoon *et al.* 2006). During the performance of a delayed face recognition task, selective interference was evident behaviourally when face stimuli were presented as distractors during the delay period, relative to a condition in which scene stimuli were presented as distractors. Event-related fMRI data showed that maintenance-related functional connectivity between the lateral PFC and FFAs was perturbed during these face distraction trials. These data provide additional support for the notion that a plausible mechanism for the active maintenance is the coupling of abstracted, higher-order information in the PFC and stimulus-specific sensory information in the visual association cortex through reverberant activity between these areas. Finally, it is important to note that correlational data such as these need to be complemented with techniques to establish the functional necessity of network nodes, through methods such as lesions studies in animals and man (e.g. Fuster *et al.* 1985; Mottaghy *et al.* 2002; D'Esposito *et al.* 2006; see also Vuilleumier & Driver 2007).

6. IS THERE A CENTRAL EXECUTIVE IN THE BRAIN?

Further understanding of the neural mechanisms underlying the active maintenance of task-relevant information may hinge on our ability to resolve the nature of stored representations in addition to the types of operations performed on such representations (Wood & Grafman 2003). 'Representations' are

symbolic codes for information activated either transiently or permanently within neuronal networks. 'Operations' are processes or computations performed on representations. As we have reviewed thus far, models of working memory (e.g. Fuster 1985; Goldman-Rakic 1987; Petrides 1994; Kieras *et al.* 1999; D'Esposito & Postle 2000; Miller & Cohen 2001) vary substantially in the relative importance given to representations and operations. Baddeley's original advance was to move us from the concept of short-term memory that accounted only for the storage of representations, to the concept of working memory as a multi-component system that allows for both storage and processing of temporarily active representations. Likewise, Logie (1995) considered working memory as a 'mental workspace' that cannot only hold but is also able to manipulate activated representations. In a recent peer review of an empirical paper we submitted to a journal, the following comment was offered: 'one concern is conceptual in that the authors describe their tasks as involving working memory when it is basically a letter memory task that primarily emphasizes storage with little or no processing. If working memory is defined as simultaneous storage and processing, then these tasks would probably be considered to assess short-term memory rather than working memory'. Thus, it is probably fair to say that the concept of working memory as a non-unitary system that allows for both storage and processing has gained popular acceptance in our field. However, in my opinion, less progress has been made regarding the neural mechanisms underlying the 'processing' component of working memory as compared with the 'storage' component (although see Petrides 2005).

Based on the data we have reviewed thus far, we propose that any population of neurons within primary or unimodal association cortex can exhibit persistent neuronal activity, which serves to actively maintain the representations coded by those neuronal populations. Areas of multimodal cortex, such as PFC and parietal cortex, which are in a position to integrate representations through connectivity to unimodal association cortex, are also critically involved in the active maintenance of task-relevant information (see also Burgess *et al.* 2007; Stuss & Alexander 2007). Miller & Cohen (2001) have proposed that in addition to the recent sensory information, integrated representations of task contingencies and even abstract rules (e.g. if this object then this later response) are also maintained in the PFC. This is similar to what Fuster (1997) has long emphasized, namely that the PFC is critically responsible for temporal integration and the mediation of events that are separated in time but contingent on one another. In this way, the PFC may exert 'control' in that the information it represents can bias posterior unimodal association cortex in order to keep neural representations of behaviourally relevant sensory information activated when they are no longer present in the external environment (Fuster 2000; Ranganath *et al.* 2004; Miller & D'Esposito 2005; Postle 2005). In a real world example, when a person is looking at a crowd of people, the visual scene presented to the retina may include a myriad of angles, shapes, people and objects. However, if that person is a police officer looking for an

armed robber escaping through the crowd, some mechanism of suppressing irrelevant visual information while enhancing task-relevant information is necessary for an efficient and effective search. Thus, neural activity throughout the brain that is generated by input from the outside world may be differentially enhanced or suppressed, presumably from top-down signals emanating from integrative brain regions such as PFC, based on the context of the situation. Thus, in this formulation, the processing component of working memory is that the control of actively maintained representations within primary and unimodal association cortex stems from the representational power of multimodal association cortex, such as the PFC, parietal cortex and/or hippocampus. If the PFC, for example, stores the rules and goals, then the activation of such PFC representations will be necessary when behaviour must be guided by internal states or intentions. As Miller & Cohen (2001) elegantly state, putative top-down signals originating in PFC may permit 'the active maintenance of patterns of activity that represent goals and the means to achieve them. They provide bias signals throughout much of the rest of the brain, affecting visual processes and other sensory modalities, as well as systems responsible for response execution, memory retrieval, emotional evaluation, etc. The aggregate effect of these bias signals is to guide the flow of neural activity along pathways that establish the proper mappings between inputs, internal states and outputs needed to perform a given task'. Computational models of this type of system have created a PFC module (e.g. O'Reilly *et al.* 2002) that consists of 'rule' units whose activation leads to the production of a response other than the one most strongly associated with a given input. Thus, 'this module is not responsible for carrying out input-output mappings needed for performance. Rather, this module influences the activity of other units whose responsibility is making the needed mappings' (e.g. Cohen *et al.* 1990). Thus, there is no need to propose the existence of a homunculus (e.g. central executive) in the brain that can perform a wide range of cognitive operations which are necessary for the task at hand (for a further discussion of this issue, see Shallice 1988; see also Hazy *et al.* 2006).

We have used a delay task to directly study the neural mechanisms underlying top-down modulation by investigating the processes involved when participants were required to enhance relevant and suppress irrelevant information (Gazzaley *et al.* 2005b). During each trial, participants observed sequences of two faces and two natural scenes presented in a randomized order. The tasks differed in the instructions informing the participants how to process the stimuli: (i) remember faces and ignore scenes, (ii) remember scenes and ignore faces, or (iii) passively view faces and scenes without attempting to remember them. In each task, the period in which the cue stimuli were presented was balanced for bottom-up visual information, thus allowing us to probe the influence of goal-directed behaviour on neural activity (top-down modulation). In the two memory tasks, the encoding of the task-relevant stimuli requires selective attention and thus permits the dissociation

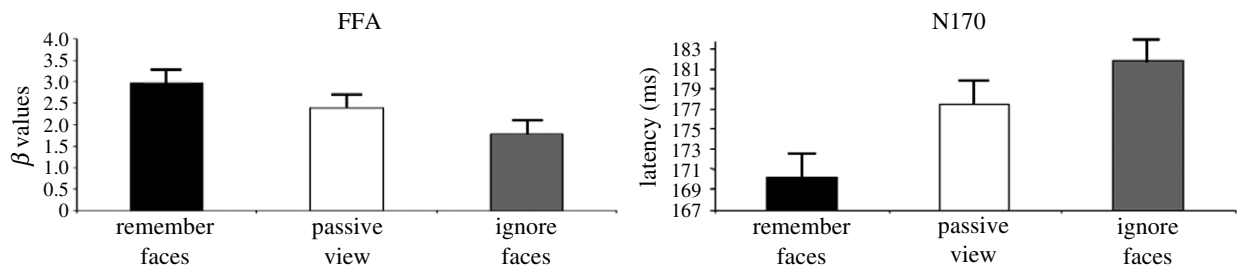


Figure 5. (a) fMRI and (b) ERP data during the performance of a face/scene delay task in healthy human individuals (Gazzaley *et al.* 2005a). The left-hand graph shows fMRI signal from the right FFA during the three behavioural conditions. fMRI signal is greatest during the 'remember faces' condition and least during the 'ignore faces' condition. The right-hand graphs show the average N170 peak latency values during the three behavioural conditions. N170 latency is earliest during the 'remember faces' condition and latest during the 'ignore faces' condition.

of physiological measures of enhancement and suppression relative to the passive baseline. Also in the memory tasks, after a short-delay period, the participants were tested on their ability to recognize a probe stimulus as being one of the task-relevant cues, yielding a behavioural measure of memory performance. These experiments were performed using both event-related fMRI and electroencephalography (event-related potentials (ERP)) to record correlates of neural activity while the participants performed the task. This allowed us to capitalize on the high spatial resolution of fMRI and the high temporal resolution of ERP.

We investigated activity measures of enhancement and suppression obtained from the visual association cortex of young healthy participants. For fMRI, we used an independent functional localizer to identify both the stimulus-selective face and scene regions in the FFA and the parahippocampal/lingual gyrus, respectively. For ERP, we used a face-selective ERP component, the N170, which is localized to posterior occipital electrodes and is thought to reflect visual association cortex activity with some face specificity (Bentin *et al.* 1996). Our fMRI and ERP data revealed top-down modulation of both activity magnitude and processing speed that occurred above or below the perceptual baseline depending on task instruction (figure 5). In other words, during the encoding period of the delay task, FFA activity was enhanced, and the N170 occurred earlier, when faces had to be remembered as compared with a condition where they were passively viewed. Likewise, FFA activity was suppressed, and the N170 occurred later, when faces had to be ignored (with scenes now being retained instead across the delay interval) compared with a condition where they were passively viewed.

Thus, there appears to be at least two types of top-down signal, one that serves to enhance task-relevant information and another that serves to suppress task-relevant information. It is well documented that the nervous system uses interleaved inhibitory and excitatory mechanisms throughout the neuroaxis (e.g. spinal reflexes, cerebellar outputs and basal ganglia movement control networks). Thus, it may not be surprising that enhancement and suppression mechanisms may exist to control cognition (Knight *et al.* 1999; Shimamura 2000). By generating contrast via both enhancements and suppressions of activity magnitude and processing speed, top-down signals bias

the likelihood of successful representation of relevant information in a competitive system.

Though it has been proposed that the PFC provides a major source of the types of top-down signals that we have described, this hypothesis largely originates from suggestive findings rather than direct empirical evidence. However, a few studies lend direct causal support to this hypothesis (see also Vuilleumier & Driver 2007). For example, Fuster *et al.* (1985) investigated the effect of cooling inactivation of specific parts of the PFC upon spiking activity in ITC neurons, during a DMS colour task. During the delay interval in this task—when persistent stimulus-specific activity in ITC neurons is observed—inactivation caused attenuated spiking profiles and a loss of stimulus specificity of ITC neurons. These two alterations of ITC signalling strongly implicate the PFC as a source of top-down signals necessary for maintaining robust sensory representations in the absence of bottom-up sensory activity. Tomita *et al.* (1999) isolated top-down signals during the retrieval of paired associates in a visual memory task. Spiking activity was recorded from stimulus-specific ITC neurons as cue stimuli were presented to the ipsilateral hemifield. This experiment's unique feature was the ability to separate bottom-up sensory signals from a top-down mnemonic reactivation, using a posterior split-brain procedure that limited hemispheric crosstalk to the anterior corpus callosum connecting each PFC. When a probe stimulus was presented ipsilaterally to the recording site, thus restricting bottom-up visual input to the contralateral hemisphere, stimulus-specific neurons became activated at the recording site approximately 170 ms later. Since these neurons received no bottom-up visual signals of the probe stimulus, with the only route between the two hemispheres being via the PFC, this experiment showed that PFC neurons were sufficient to trigger the reactivation of object-selective representations in ITC regions in a top-down manner. The combined lesion/electrophysiological approach in humans has rarely been implemented (though see Vuilleumier & Driver 2007). However, Chao & Knight (1998) studied patients with lateral PFC lesions during DMS tasks. It was found that when distracting stimuli are presented during the delay period, the amplitude of the recorded ERP from posterior electrodes was markedly increased in patients compared with controls. These results were interpreted to show disinhibition of sensory processing and support a role of the PFC in

suppressing the representation of stimuli that are irrelevant for current behaviour.

Clearly, there are other areas of multimodal cortex such as posterior parietal cortex, and the hippocampus, that can also be the source of top-down signals. For example, the hippocampus has been proposed to be specialized for 'rapid learning of arbitrary information which can be recalled in the service of controlled processing' (O'Reilly *et al.* 1999). Moreover, input from brainstem neuromodulatory systems probably plays a critical role in modulating goal-directed behaviour (see also Robbins 2007). For example, the dopaminergic system probably plays a critical role in cognitive control processes (for a review, see Cools & Robbins 2004). Specifically, it is proposed that phasic bursts of dopaminergic neurons may be critical for updating currently activated task-relevant representations whereas tonic dopaminergic activity serves to stabilize such representations (e.g. Durstewitz *et al.* 2000a; Cohen *et al.* 2002). Empirical studies in animals and man have provided support for a role of dopamine in working memory (e.g. Sawaguchi 2001; Gibbs & D'Esposito 2005).

7. CONCLUSIONS

The overall goal of cognitive neuroscience as a discipline is to determine the biological basis of the mind. As an interdisciplinary discipline that has evolved from both neuroscience and psychology, cognitive neuroscientists consume data derived from each of these disciplines in their attempt to advance cognitive theory as well as determine how the brain implements cognitive function. Advances made in understanding the cognitive and neural basis of working memory provide examples of this synergy. In my opinion, future studies must continue to consider both cognitive and neural data in the way that has been briefly illustrated in this review. Research thus far suggests that working memory can be viewed as neither a unitary nor a dedicated system. A network of brain regions, including the PFC, is critical for the active maintenance of internal representations that are necessary for goal-directed behaviour. Thus, working memory is not localized to a single brain region but probably is an emergent property of the functional interactions between the PFC and the rest of the brain.

I would like to express my sincere appreciation to all of my former and current students and postdocs for their invaluable contributions to the formulation of the ideas presented in this paper.

REFERENCES

- Anderson, J. R. 1983 *The architecture of cognition*. Cambridge, MA: Harvard University Press.
- Awh, E. & Jonides, J. 2001 Overlapping mechanisms of attention and spatial working memory. *Trends Cogn. Sci.* **5**, 119–126. (doi:10.1016/S1364-6613(00)01593-X)
- Awh, E., Jonides, J., Smith, E. E., Schumacher, E. H., Koeppel, R. A. & Katz, S. 1996 Dissociation of storage and rehearsal in verbal working memory: evidence from PET. *Psychol. Sci.* **7**, 25–31. (doi:10.1111/j.1467-9280.1996.tb00662.x)
- Awh, E., Jonides, J., Smith, E. E., Buxton, R. B., Frank, L. R., Love, T., Wong, E. C. & Gmeindl, L. 1999 Rehearsal in spatial working memory: evidence from neuroimaging. *Psychol. Sci.* **10**, 433–437. (doi:10.1111/1467-9280.00182)
- Baddeley, A. 1986 *Working memory*. New York, NY: Oxford University Press.
- Baddeley, A. 2000 The episodic buffer: a new component of working memory? *Trends Cogn. Sci.* **4**, 417–423. (doi:10.1016/S1364-6613(00)01538-2)
- Baddeley, A. & Hitch, G. J. 1974 Working memory. In *Recent advances in learning and motivation*, vol. 8 (ed. G. Bower), pp. 47–89. New York, NY: Academic Press.
- Bauer, R. H. & Fuster, J. M. 1976 Delayed-matching and delayed-response deficit from cooling dorsolateral prefrontal cortex in monkeys. *Q. J. Exp. Psychol. B* **90**, 293–302.
- Bench, C. J., Frith, C. D., Grasby, P. M., Friston, K. J., Pauls, E., Frackowiak, R. S. J. & Dolan, R. J. 1993 Investigations of the functional anatomy of attention using the Stroop test. *Neuropsychologia* **31**, 907–922. (doi:10.1016/0028-3932(93)90147-R)
- Bentin, S., Allison, T., Puce, A., Perez, E. & McCarthy, G. 1996 Electrophysiological studies of face perception in humans. *J. Cogn. Neurosci.* **8**, 551–565.
- Buchel, C., Coull, J. T. & Friston, K. J. 1999 The predictive value of changes in effective connectivity for human learning. *Science* **283**, 1538–1541. (doi:10.1126/science.283.5407.1538)
- Burgess, P. W., Gilbert, S. J. & Dumontheil, I. 2007 Function and localization within rostral prefrontal cortex (area 10). *Phil. Trans. R. Soc. B* **362**, 887–899. (doi:10.1098/rstb.2007.2095)
- Calvert, G. A., Bullmore, E. T., Brammer, M. J., Campbell, R., Williams, S. C., McGuire, P. K., Woodruff, P. W., Iversen, S. D. & David, A. S. 1997 Activation of auditory cortex during silent lipreading. *Science* **276**, 593–596. (doi:10.1126/science.276.5312.593)
- Chafee, M. V. & Goldman-Rakic, P. S. 1998 Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. *J. Neurophysiol.* **79**, 2919–2940.
- Chao, L. & Knight, R. 1998 Contribution of human prefrontal cortex to delay performance. *J. Cogn. Neurosci.* **10**, 167–177. (doi:10.1162/08992998562636)
- Cohen, L. & Dehaene, S. 2004 Specialization within the ventral stream: the case for the visual word form area. *Neuroimage* **22**, 466–476. (doi:10.1016/j.neuroimage.2003.12.049)
- Cohen, J. D., Braver, T. S. & Brown, J. W. 2002 Computational perspectives on dopamine function in prefrontal cortex. *Curr. Opin. Neurobiol.* **12**, 223–229. (doi:10.1016/S0959-4388(02)00314-8)
- Constantinidis, C., Franowicz, M. N. & Goldman-Rakic, P. S. 2001 Coding specificity in cortical microcircuits: a multiple-electrode analysis of primate prefrontal cortex. *J. Neurosci.* **21**, 3646–3655.
- Cools, R. & Robbins, T. W. 2004 Chemistry of the adaptive mind. *Phil. Trans. R. Soc. A* **362**, 2871–2888. (doi:10.1098/rsta.2004.1468)
- Courtney, S. M., Petit, L., Maisog, J. M., Ungerleider, L. G. & Haxby, J. V. 1998 An area specialized for spatial working memory in human frontal cortex. *Science* **279**, 1347–1351. (doi:10.1126/science.279.5355.1347)
- Cowan, N. 1988 Evolving conceptions of memory storage, selective attention, and their mutual constraints within the human information processing system. *Psychol. Bull.* **104**, 163–171. (doi:10.1037/0033-2909.104.2.163)
- Cowan, N. 1999 An embedded-process model of working memory. In *Models of working memory: mechanisms of active maintenance and executive control* (eds A. Miyake & P. Shah), pp. 62–101. Cambridge, UK: Cambridge University Press.

- Cohen, J. D., Dunbar, K. & McClelland, J. L. 1990 On the control of automatic processes: a parallel distributed processing account of the Stroop effect. *Psychol. Rev.* **97**, 332–361.
- Curtis, C. E. & D'Esposito, M. 2003 Persistent activity in the prefrontal cortex during working memory. *Trends. Cogn. Sci.* **7**, 415–423. (doi:10.1016/S1364-6613(03)00197-9)
- Curtis, C. E., Rao, V. Y. & D'Esposito, M. 2004 Maintenance of spatial and motor codes during oculomotor delayed response tasks. *J. Neurosci.* **24**, 3944–3952. (doi:10.1523/JNEUROSCI.5640-03.2004)
- D'Esposito, M., Postle, B. R. & Rypma, B. 2000 Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. *Exp. Brain Res.* **133**, 3–11. (doi:10.1007/s002210000395)
- D'Esposito, M., Cooney, J. W., Gazzaley, A., Gibbs, S. E. & Postle, B. R. 2006 Is the prefrontal cortex necessary for delay task performance? Evidence from lesion and fMRI data. *J. Int. Neuropsychol. Soc.* **12**, 248–260.
- Druzgal, T. J. & D'Esposito, M. 2003 Dissecting contributions of prefrontal cortex and fusiform face area to face working memory. *J. Cogn. Neurosci.* **15**, 771–784. (doi:10.1162/089892903322370708)
- Durstewitz, D., Seamans, J. K. & Sejnowski, T. J. 2000a Dopamine-mediated stabilization of delay-period activity in a network model of prefrontal cortex. *J. Neurophysiol.* **83**, 1733–1750.
- Durstewitz, D., Seamans, J. K. & Sejnowski, T. J. 2000b Neurocomputational models of working memory. *Nat. Neurosci.* **3**, 1184–1191. (doi:10.1038/81460)
- Engel, A. K., Fries, P. & Singer, W. 2001 Dynamic predictions: oscillations and synchrony in top-down processing. *Nat. Rev. Neurosci.* **2**, 704–816. (doi:10.1038/35094565)
- Fiebach, C. J., Rissman, J. & D'Esposito, M. 2006 Modulation of inferotemporal cortex activation during verbal working memory maintenance. *Neuron* **51**, 251–261. (doi:10.1016/j.neuron.2006.06.007)
- Friston, K. J. & Buchel, C. 2000 Attentional modulation of effective connectivity from V2 to V5/MT in humans. *Proc. Natl Acad. Sci. USA* **97**, 7591–7596. (doi:10.1073/pnas.97.13.7591)
- Friston, K. J., Frith, C. D., Liddle, P. F. & Frackowiak, R. S. 1993 Functional connectivity: the principal-component analysis of large (PET) data sets. *J. Cereb. Blood Flow Metab.* **13**, 5–14.
- Funahashi, S. & Inoue, M. 2000 Neuronal interactions related to working memory processes in the primate prefrontal cortex revealed by cross-correlation analysis. *Cereb. Cortex* **10**, 535–551. (doi:10.1093/cercor/10.6.535)
- Funahashi, S., Bruce, C. J. & Goldman-Rakic, P. S. 1989 Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J. Neurophysiol.* **61**, 331–349.
- Funahashi, S., Bruce, C. J. & Goldman-Rakic, P. S. 1993 Dorsolateral prefrontal lesions and oculomotor delayed-response performance: evidence for mnemonic "scotomas". *J. Neurosci.* **13**, 1479–1497.
- Fuster, J. M. (ed.) 1985 *The prefrontal cortex and temporal integration cerebral cortex: vol. 4, association and auditory cortices*. New York, NY: Plenum Press.
- Fuster, J. M. 1995 *Memory in the cerebral cortex*. Cambridge, UK: The MIT Press.
- Fuster, J. 1997 *The prefrontal cortex: anatomy, physiology, and neuropsychology of the frontal lobes*. New York, NY: Raven Press.
- Fuster, J. M. 2000 Cortical dynamics of memory. *Int. J. Psychophysiol.* **35**, 155–164. (doi:10.1016/S0167-8760(99)00050-1)
- Fuster, J. M. 2003 *Cortex and mind*. New York, NY: Oxford University Press.
- Fuster, J. M. & Alexander, G. E. 1971 Neuron activity related to short-term memory. *Science* **173**, 652–654. (doi:10.1126/science.173.3997.652)
- Fuster, J. M., Bauer, R. H. & Jervey, J. P. 1985 Functional interactions between inferotemporal and prefrontal cortex in a cognitive task. *Brain Res.* **330**, 299–307. (doi:10.1016/0006-8993(85)90689-4)
- Gazzaley, A., Rissman, J. & Desposito, M. 2004 Functional connectivity during working memory maintenance. *Cogn. Affect. Behav. Neurosci.* **4**, 580–599.
- Gazzaley, A., Cooney, J. W., McEvoy, K., Knight, R. T. & D'Esposito, M. 2005a Top-down enhancement and suppression of the magnitude and speed of neural activity. *J. Cogn. Neurosci.* **17**, 507–517. (doi:10.1162/0898929053279522)
- Gazzaley, A., Cooney, J. W., McEvoy, K., Knight, R. T. & D'Esposito, M. 2005b Top-down enhancement and suppression of the magnitude and speed of neural activity. *J. Cogn. Neurosci.* **17**, 1–11. (doi:10.1162/0898929053279522)
- Gibbs, S. E. & D'Esposito, M. 2005 A functional MRI study of the effects of bromocriptine, a dopamine receptor agonist, on component processes of working memory. *Psychopharmacology (Berlin)* **180**, 644–653. (doi:10.1007/s00213-005-0077-5)
- Goldman-Rakic, P. S. 1987 Circuitry of the prefrontal cortex and the regulation of behavior by representational memory. In *Handbook of physiology. Sec 1. The nervous system*, vol. 5, section I (eds F. Plum & V. Mountcastle), pp. 373–417. Bethesda, MD: American Physiological Society.
- Goldman-Rakic, P. 1988 Topography of cognition: parallel distributed networks in primate association cortex. *Annu. Rev. Neurosci.* **11**, 137–156. (doi:10.1146/annurev.ne.11.030188.001033)
- Hazy, T. E., Frank, M. J. & O'Reilly, R. C. 2006 Banishing the homunculus: making working memory work. *Neuroscience* **139**, 105–118. (doi:10.1016/j.neuroscience.2005.04.067)
- Hickok, G., Buchsbaum, B., Humphries, C. & Muftuler, T. 2003 Auditory-motor interaction revealed by fMRI: speech, music, and working memory in area Spt. *J. Cogn. Neurosci.* **15**, 673–682.
- Kanwisher, N., McDermott, J. & Chun, M. M. 1997 The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J. Neurosci.* **17**, 4302–4311.
- Kieras, D. E., Meyer, D. E., Mueller, S. & Seymour, T. 1999 Insights into working memory from the perspective of the EPIC architecture for modeling skilled perceptual-motor and cognitive human performance. In *Models of working memory: mechanisms of active maintenance and executive control* (eds A. Miyake & P. Shah), pp. 183–223. Cambridge, UK: Cambridge University Press.
- Kimberg, D. Y., D'Esposito, M. & Farah, M. J. 1997 Cognitive functions in the prefrontal cortex-working memory and executive control. *Curr. Dir. Psychol. Sci.* **6**, 185–192. (doi:10.1111/1467-8721.ep10772959)
- Klein, I., Paradis, A. L., Poline, J. B., Kosslyn, S. M. & Le Bihan, D. 2000 Transient activity in the human calcarine cortex during visual-mental imagery: an event-related fMRI study. *J. Cogn. Neurosci.* **12**(Suppl. 2), 15–23. (doi:10.1162/089892900564037)
- Knight, R. T., Staines, W. R., Swick, D. & Chao, L. L. 1999 Prefrontal cortex regulates inhibition and excitation in distributed neural networks. *Acta Psychol. (Amst)* **101**, 159–178. (doi:10.1016/S0001-6918(99)00004-9)

- Kraemer, D. J., Macrae, C. N., Green, A. E. & Kelley, W. M. 2005 Musical imagery: sound of silence activates auditory cortex. *Nature* **434**, 158. (doi:10.1038/434158a)
- Kubota, K. & Niki, H. 1971 Prefrontal cortical unit activity and delayed alternation performance in monkeys. *J. Neurophysiol.* **34**, 337–347.
- Logie, R. H. 1995 *Visuo-spatial working memory*. Hove, UK: Erlbaum.
- Maguire, E. A., Mummery, C. J. & Buchel, C. 2000 Patterns of hippocampal-cortical interaction dissociate temporal lobe memory subsystems. *Hippocampus* **10**, 475–482. (doi:10.1002/1098-1063(2000)10:4<475::AID-HIPO14>3.0.CO;2-X)
- Marslen-Wilson, W. D. & Tyler, L. K. 2007 Morphology, language and the brain: the decompositional substrate for language comprehension. *Phil. Trans. R. Soc. B* **362**, 823–836. (doi:10.1098/rstb.2007.2091)
- McIntosh, A. R. 1998 Understanding neural interactions in learning and memory using functional neuroimaging. *Ann. NY Acad. Sci.* **855**, 556–571. (doi:10.1111/j.1749-6632.1998.tb10625.x)
- McIntosh, A. R. 2000 Towards a network theory of cognition. *Neural Netw.* **13**, 861–870. (doi:10.1016/S0893-6080(00)00059-9)
- Miller, B. T. & D'Esposito, M. 2005 Searching for “the top” in top-down control. *Neuron* **48**, 535–538. (doi:10.1016/j.neuron.2005.11.002)
- Miller, E. K. & Cohen, J. D. 2001 An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci.* **4**, 167–202. (doi:10.1146/annurev.neuro.24.1.167)
- Miller, E. K., Li, L. & Desimone, R. 1993 Activity of neurons in anterior inferior temporal cortex during a short-term memory task. *J. Neurosci.* **13**, 1460–1478.
- Miyake, A. & Shah, P. (eds) 1999 *Models of working memory: mechanisms of active maintenance and executive control*. Cambridge, UK: Cambridge University Press.
- Miyashita, Y. & Chang, H. S. 1988 Neuronal correlate of pictorial short-term memory in the primate temporal cortex. *Nature* **331**, 68–70. (doi:10.1038/331068a0)
- Mottaghy, F. M., Gangitano, M., Sparing, R., Krause, B. J. & Pascual-Leone, A. 2002 Segregation of areas related to visual working memory in the prefrontal cortex revealed by rTMS. *Cereb. Cortex* **12**, 369–375. (doi:10.1093/cercor/12.4.369)
- Murray, D. J. 1968 Articulation and acoustic confusability in short-term memory. *J. Exp. Psychol.* **78**, 679–684. (doi:10.1037/h0026641)
- Nakamura, K. & Kubota, K. 1995 Mnemonic firing of neurons in the monkey temporal pole during a visual recognition memory task. *J. Neurophysiol.* **74**, 162–178.
- Nobre, A. C., Allison, T. & McCarthy, G. 1994 Word recognition in the human inferior temporal lobe. *Nature* **372**, 260–263. (doi:10.1038/372260a0)
- Norman, D. A. & Shallice, T. 1986 Attention to action: willed and automatic control of behavior. In *Consciousness and self-regulation*, vol. 4 (eds R. J. Davidson, G. E. Schwartz & D. Shapiro), pp. 1–18. New York, NY: Plenum Press.
- O'Reilly, R. C., Braver, T. S. & Cohen, J. D. 1999 A biologically based computational model of working memory. In *Models of working memory: mechanisms of active maintenance and executive control* (eds A. Miyakawa & P. Shah), pp. 62–101. Cambridge, UK: Cambridge University Press.
- O'Reilly, R. C., Noelle, D. C., Braver, T. S. & Cohen, J. D. 2002 Prefrontal cortex and dynamic categorization tasks: representational organization and neuromodulatory control. *Cereb. Cortex* **12**, 246–257. (doi:10.1093/cercor/12.3.246)
- Patterson, K. 2007 The reign of typicality in semantic memory. *Phil. Trans. R. Soc. B* **362**, 813–821. (doi:10.1098/rstb.2007.2090)
- Paulesu, E., Frith, C. D. & Frackowiak, R. S. 1993 The neural correlates of the verbal component of working memory. *Nature* **362**, 342–345. (doi:10.1038/362342a0)
- Petrides, M. 1994 Frontal lobes and working memory: evidence from investigations of the effects of cortical excisions in nonhuman primates. In *Handbook of neuropsychology*, vol. 9 (eds F. Boller & J. Grafman), pp. 59–84. Amsterdam, The Netherlands: Elsevier Science B.V.
- Petrides, M. 2005 Lateral prefrontal cortex: architectonic and functional organization. *Phil. Trans. R. Soc. B* **360**, 781–795. (doi:10.1098/rstb.2005.1631)
- Postle, B. R. 2005 Delay-period activity in the prefrontal cortex: one function is sensory gating. *J. Cogn. Neurosci.* **17**, 1679–1690. (doi:10.1162/089892905774589208)
- Postle, B. R., Desposito, M. & Corkin, S. 2005 Effects of verbal and nonverbal interference on spatial and object visual working memory. *Mem. Cogn.* **33**, 203–212.
- Ranganath, C. & D'Esposito, M. 2001 Medial temporal lobe activity associated with active maintenance of novel information. *Neuron* **31**, 865–873. (doi:10.1016/S0896-6273(01)00411-1)
- Ranganath, C., Cohen, M. X., Dam, C. & D'Esposito, M. 2004 Inferior temporal, prefrontal, and hippocampal contributions to visual working memory maintenance and associative memory retrieval. *J. Neurosci.* **24**, 3917–3925. (doi:10.1523/JNEUROSCI.5053-03.2004)
- Repovs, G. & Baddeley, A. 2006 The multi-component model of working memory: explorations in experimental cognitive psychology. *Neuroscience* **139**, 5–21. (doi:10.1016/j.neuroscience.2005.12.061)
- Rissman, J., Gazzaley, A. & D'Esposito, M. 2004 Measuring functional connectivity during distinct stages of a cognitive task. *Neuroimage* **23**, 752–763. (doi:10.1016/j.neuroimage.2004.06.035)
- Robbins, T. W. 2007 Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. *Phil. Trans. R. Soc. B* **362**, 917–932. (doi:10.1098/rstb.2007.2097)
- Rowe, J., Friston, K., Frackowiak, R. & Passingham, R. 2002 Attention to action: specific modulation of corticocortical interactions in humans. *Neuroimage* **17**, 988–998. (doi:10.1016/S1053-8119(02)91156-0)
- Ruchkin, D. S., Grafman, J., Cameron, K. & Berndt, R. S. 2003 Working memory retention systems: a state of activated long-term memory. *Behav. Brain Sci.* **26**, 709–728, discussion 728–777.
- Sawaguchi, T. 2001 The effects of dopamine and its antagonists on directional delay-period activity of prefrontal neurons in monkeys during an oculomotor delayed-response task. *Neurosci. Res.* **41**, 115–128. (doi:10.1016/S0168-0102(01)00270-X)
- Shallice, T. 1988 *From neuropsychology to mental structure*. Cambridge, UK: Cambridge University Press.
- Shimamura, A. P. 2000 The role of the prefrontal cortex in dynamic filtering. *Psychobiology* **28**, 207–218.
- Silver, M. A., Ress, D. & Heeger, D. J. 2006 Neural correlates of sustained spatial attention in human early visual cortex. *J. Neurophysiol.* **97**, 229–237. (doi:10.1152/jn.00677.2006)
- Singer, W. & Gray, C. M. 1995 Visual feature integration and the temporal correlation hypothesis. *Annu. Rev. Neurosci.* **18**, 555–586. (doi:10.1146/annurev.ne.18.030195.003011)
- Stuss, D. T. & Alexander, M. P. 2007 Is there a dysexecutive syndrome? *Phil. Trans. R. Soc. B* **362**, 901–915. (doi:10.1098/rstb.2007.2096)
- Tallon-Baudry, C., Bertrand, O. & Fischer, C. 2001 Oscillatory synchrony between human extrastriate areas during visual short-term memory maintenance. *J. Neurosci.* **21**, RC177.

- Tomita, H., Ohbayashi, M., Nakahara, K., Hasegawa, I. & Miyashita, Y. 1999 Top-down signal from prefrontal cortex in executive control of memory retrieval. *Nature* **401**, 699–703. (doi:10.1038/44372)
- Toni, I., Rowe, J., Stephan, K. E. & Passingham, R. E. 2002 Changes of cortico-striatal effective connectivity during visuomotor learning. *Cereb. Cortex* **12**, 1040–1047. (doi:10.1093/cercor/12.10.1040)
- Vallar, G. & Shallice, T. 1990 *Neuropsychological impairments of short-term memory*. Cambridge, UK: Cambridge University Press.
- Vuilleumier, P. & Driver, J. 2007 Modulation of visual processing by attention and emotion: windows on causal interactions between human brain regions. *Phil. Trans. R. Soc. B* **362**, 837–855. (doi:10.1098/rstb.2007.2092)
- Wang, X. J. 2001 Synaptic reverberation underlying mnemonic persistent activity. *Trends Neurosci.* **24**, 455–463. (doi:10.1016/S0166-2236(00)01868-3)
- Wood, J. N. & Grafman, J. 2003 Human prefrontal cortex: processing and representational perspectives. *Nat. Rev. Neurosci.* **4**, 139–147. (doi:10.1038/nrn1033)
- Yoon, J. H., Curtis, C. E. & D'Esposito, M. 2006 Differential effects of distraction during working memory on delay-period activity in the prefrontal cortex and the visual association cortex. *Neuroimage* **29**, 1117–1126. (doi:10.1016/j.neuroimage.2005.08.024)
- Zelano, C., Bensafi, M., Porter, J., Mainland, J., Johnson, B., Bremner, E., Telles, C., Khan, R. & Sobel, N. 2005 Attentional modulation in human primary olfactory cortex. *Nat. Neurosci.* **8**, 114–120. (doi:10.1038/nn1368)