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Doubts about double dissociations between short- and long-term memory

Charan Ranganath and Robert S. Blumenfeld

Center for Neuroscience and Department of Psychology, University of California at Davis, 1544 Newton Ct, Davis, CA 95616, USA

Historically, psychologists and neuroscientists have distinguished between processes supporting memory for events across retention delays of several seconds (short-term memory, STM), and those supporting memory for events across longer retention delays of minutes or more (long-term memory, LTM). Dissociations reported in some neuropsychological studies have contributed to a popular view that there must be neurally distinct memory stores that differentially support STM and LTM. In this article, we review evidence from recent studies regarding dissociations between STM and LTM. We suggest that the evidence reveals problems with claims of selective STM or LTM impairments, which in turn questions whether theories of memory need to propose neurally distinct stores for short- and long-term retention. We consider alternative ways to explain the neural mechanisms of memory across different retention intervals.

Introduction

In 1957, Scoville and Milner published a case report on 'H.M.', a patient who underwent a bilateral medial temporal lobe resection for the treatment of intractable epilepsy [1]. Research on H.M. revolutionized the study of memory for two reasons: First, following the surgery, H.M. was virtually unable to form new memories for events, suggesting that the medial temporal lobes are essential for new episodic memory formation. Second, clinical testing indicated that H.M. could exhibit intact performance on tests of memory with short retention delays of a few seconds (short-term memory, or STM tasks), despite his severe impairments on tests of memory with longer retention delays (long-term memory, or LTM tasks). Subsequent research identified patients who seemed to exhibit impaired immediate memory in the face of normal memory performance at long retention delays, suggesting a neuropsychological double dissociation between STM and LTM [2].

These findings, along with other neuropsychological and behavioral results, have been used to advance the idea that there must be at least two kinds of memory stores: one that is used to retain information across short delays (spanning several seconds) and another that is used to retain information across longer delays (spanning minutes, hours, days, etc.). Although the 'multi-store' view has been challenged [3–6] (see Box 1), it is widely cited as fact, based on initial reports of dissociations between STM and LTM (e.g. [7,8]). However, there has been an accumulation of new evidence since these initial

Box 1. Psychological models of processes contributing to STM and LTM

Although psychological models have long distinguished between processes supporting STM and LTM, they did not necessarily suggest neurally distinct memory stores. For example, Hebb [65] proposed a 'dual-trace mechanism', suggesting: (1) that STM and LTM can be supported by the re-activation of distributed networks of strongly interconnected neurons, which he termed a 'cell assembly'; and (2) that STM can additionally be supported by 'reverberating activity' within a cell assembly. In a similar vein, Atkinson and Shiffrin [66] noted: 'Our account of short-term and long-term storage does not require that the two stores necessarily be in different parts of the brain or involve different physiological structures. One might consider the short-term store simply as being a temporary activation of some portion of the long-term store.'

In contrast to this view, neuropsychological results suggested dissociations between STM and LTM tasks. Related work focused on functional and neuropsychological dissociations between primacy and recency effects in verbal list learning, which were assumed to reflect long-term and short-term retention processes, respectively (this view has been rejected in more recent studies). These dissociations led many to conclude that there must be a memory store that specifically supports temporary retention of information, independent of the memory store that supports retention across long delays [2].

The idea of a temporary memory store was further developed by Baddeley and Hitch [67] in their influential 'working memory' (WM) model. The Baddeley and Hitch model proposed that short-term retention (or 'maintenance') and manipulation of information across short delays is mediated by interactions between a 'central executive' and different short-term 'buffers' for different types of information (i.e. visuospatial and phonological). Based largely on neuropsychological evidence, it was assumed that each of these short-term buffers is a temporary memory store, separate from the stores for long-term retention. The Baddeley and Hitch model has been remarkably successful, to the point that the term 'working memory' is now often used to describe all types of STM tasks.

More recent models have attempted to explain relationships between STM and LTM without suggesting structurally distinct stores for temporary and long-term retention. For example, Cowan's model [3], like that of Baddeley and Hitch, has a 'central executive' that mediates goal-directed control processes. However, in Cowan's model active maintenance is accomplished by activating the same representations that support LTM, rather than by transferring information to temporary memory buffers. Similar ideas have been advanced by neuroscientists [4,5], and computational modelers [68]. Although there are substantial differences between these activation-based and structural accounts, such as the Baddeley and Hitch model, there have been few experimental efforts to directly contrast the two types of models.

Corresponding author: Ranganath, C. (cranganath@ucdavis.edu).
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reports, and there have been few efforts to evaluate previously reported dissociations within the context of these recent findings.

The goal of this article is to evaluate current neuropsychological evidence for dissociations between STM and LTM. More specifically, we will evaluate evidence relevant to the idea that medial temporal lobe lesions selectively affect LTM, whereas lesions to other regions, such as the perisylvian cortex or the prefrontal cortex, selectively affect STM. After reviewing this evidence, we conclude that claims of dissociations between STM and LTM are not well-supported. Finally, we consider theoretical alternatives to the multi-store view of memory.

Do the medial temporal lobes contribute to STM?

As noted above, patients with medial temporal lobe lesions can perform normally on many STM measures, despite their severely impaired LTM performance. Consequently, it has been proposed that medial temporal cortical areas (including perirhinal, parahippocampal and entorhinal cortex), along with the hippocampus, comprise a 'medial temporal lobe memory system' that is specifically necessary for LTM, but not STM [9,10]. By contrast, other temporal lobe areas, such as inferior temporal area TE, have been associated with functions more relevant to perception and STM.

Although the idea that the medial temporal lobes are not required for STM is widespread (e.g. [7,8]), there have been few rigorous attempts to test STM for different types of information in patients with restricted medial temporal damage. Such patients can clearly exhibit intact attention and concentration, and can hold in mind instructions to perform many complex tasks. Additionally, patients with medial temporal damage can exhibit intact STM for simple visual features or shapes ([9] and Prisko, unpublished data), and even intact immediate memory for the gist of lengthy, complex stories [11]. Such observations suggest that, despite their LTM impairments, patients with medial temporal damage can actively retain many kinds of information across short delays.

However, it is unclear whether all forms of STM are spared following medial temporal lobe lesions. For example, most clinical tests of STM involve simple and overlearned materials (e.g. words, digits, etc.) that are well-represented in cortical areas outside of the medial temporal region. Therefore, it might be more appropriate to investigate STM for materials that are more likely to be uniquely processed by the medial temporal region, such as complex, novel objects [12,13]. Interestingly, several lines of evidence suggest that medial temporal regions – particularly the perirhinal cortex – play an essential role in STM for complex, novel visual objects.

For example, neuropsychological studies have examined retention of novel visual objects in human amnesic groups that included patients with extensive medial temporal lobe lesions [14–18]. All but one of these studies reported memory deficits in medial temporal lobe amnesics across retention delays as short as 2–10s (see Figure 1). One could argue that STM deficits in these patients might have been caused by damage extending into temporal cortical areas adjacent to the medial temporal lobes, such as area TE. However, results from controlled lesion studies in monkeys suggest that medial temporal lesions that include the perirhinal cortex can cause severe STM deficits for novel objects, even when damage to adjacent areas is minimal [19–27]. Interestingly, one of these studies even reported impaired performance with a zero second retention delay [20]. These data seriously question the assumption that the medial temporal lobes are not necessary for any form of STM.

Results from single-unit recording studies of monkeys [28–31] complement the lesion evidence by demonstrating that perirhinal and entorhinal neurons exhibit persistent, object-selective activity during retention delays in STM tasks – a putative neural mechanism for active maintenance (see Box 2). Consistent with these findings, neuroimaging studies of humans have reported perirhinal, parahippocampal, entorhinal, and hippocampal activity during the performance of STM tasks with novel visual objects [32–35], faces [36], or scenes [37,38]. This activity is enhanced for novel stimuli relative to repeated stimuli [34,36,38], and enhanced for stimuli that are successfully remembered after both short and long delays [34,37].

In summary, the available evidence indicates that medial temporal lesions can impair retention of information about complex objects across short delays and that medial temporal regions exhibit persistent activity during active maintenance of novel visual objects. These findings provide compelling evidence for the idea that, at least under some circumstances, medial temporal cortical regions are necessary for, and contribute to normal STM.

Do patients with perisylvian cortex lesions show selective STM deficits?

Another kind of evidence cited to support the idea of neurally distinct short- and long-term memory stores comes from studies of patients with severe impairments in phonological STM [39]. These patients typically have damage to left perisylvian cortex and/or underlying white matter (Ravizza, S. *et al.*, unpublished data). Such patients can show intact LTM for meaningful words [2,40], suggesting that STM can be impaired without affecting LTM.

However, this inference is problematic because the types of tasks and measures used to assess STM and LTM differ in several ways that have nothing to do with the retention interval. For example, in the span tasks used to assess phonological STM, one must immediately recall a short sequence of spoken digits in the correct order. In a typical LTM task, one must learn a long list of meaningful words (presumably presented at a slow rate), and recall performance is assessed across multiple learning trials. At the most basic level, comparisons between such tests are confounding differences in retention interval and/or list length with differences in the type of information to be maintained (e.g. meaningless digits versus meaningful words). Therefore, to test whether patients with phonological STM deficits can exhibit intact phonological LTM, it is at least necessary to test memory for information that is difficult to encode semantically or visually. Crucially, patients with phonological STM deficits exhibit severely

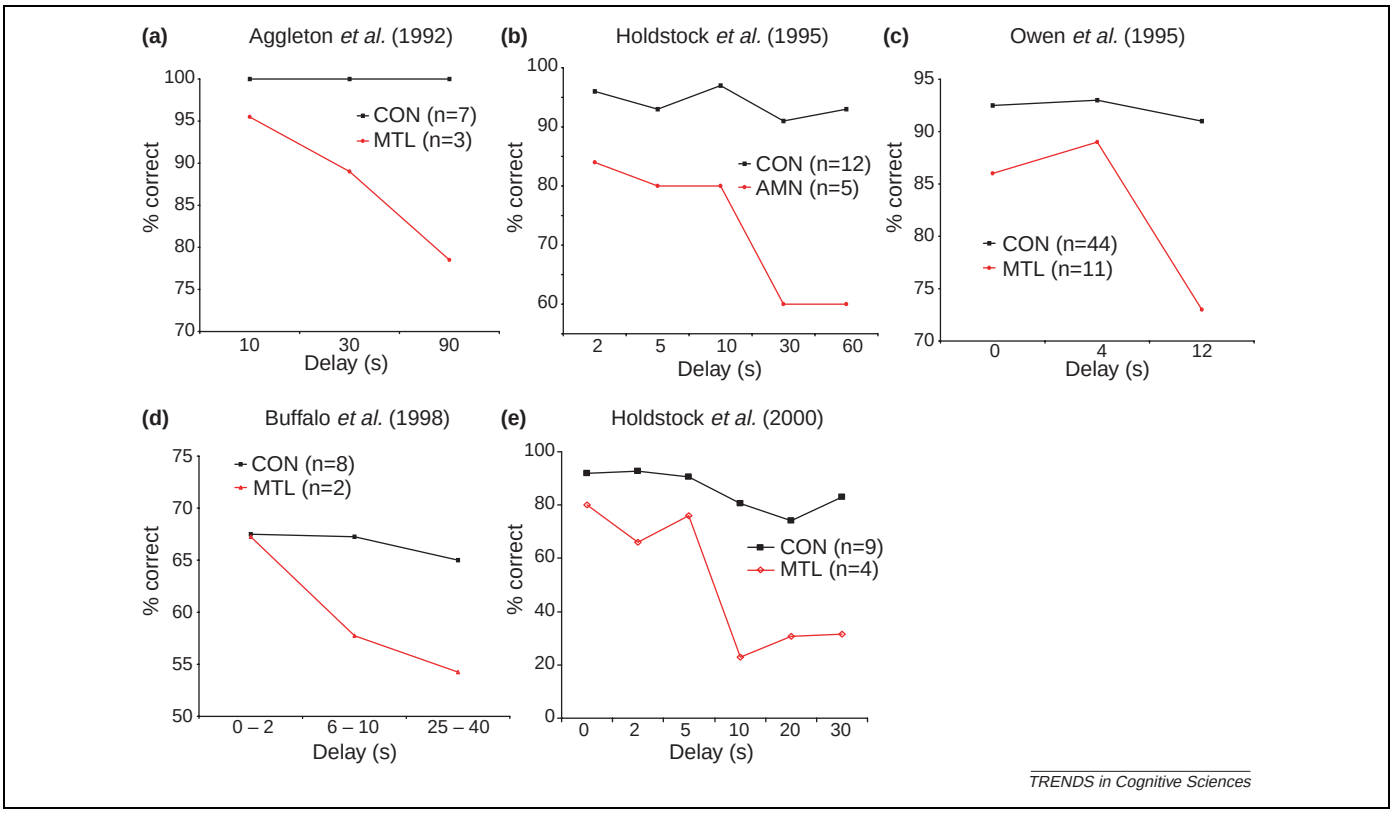

Figure 1. Recognition memory for novel visual objects across short retention intervals in patients with medial temporal lesions. **(a)** Results from an alcoholic control group (CON) and a group of 3 patients with medial temporal damage following viral encephalitis (MTL) [18]. **(b)** Results from a healthy control group (CON) and a mixed amnesic patient group (AMN) consisting of three patients with medial temporal damage following viral encephalitis, one patient with bilateral thalamic damage, and one patient with a fornix lesion following surgical removal of a colloid cyst [14]. **(c)** Results from a healthy control group (CON) and a group of 11 patients who underwent unilateral amygdalo-hippocampectomies (MTL) for treatment of epilepsy [15]. **(d)** Results from a healthy control group (CON) and from two patients with bilateral temporal lobe damage due to herpes simplex encephalitis (MTL) [16]. **(e)** Results from a healthy control (CON) group and from four patients with bilateral temporal lobe lesions due to encephalitis or meningitis (MTL) [17]. Each graph shows percentage accuracy as a function of the retention interval, plotted from results depicted in the original reports.

impaired LTM for auditorily-presented, meaningless non-words [41–44]. Thus, the overall pattern of results suggests that patients with perisylvian lesions can exhibit normal LTM for information that can be encoded visually or semantically, but they clearly have deficiencies in phonological STM *and* LTM. Accordingly, there is no reason to believe that these patients exhibit a dissociation between STM and LTM.

Does the prefrontal cortex disproportionately contribute to STM?

Another area that is often cited as specifically supporting STM is the prefrontal cortex [7]. Indeed, the discovery that prefrontal neurons exhibit persistent, stimulus-selective activity during short memory delays [45] has fueled intensive research on neural STM signals in the prefrontal cortex. However, this phenomenon is not specific to prefrontal cortex (see Box 2). Recent studies have shown that several neocortical areas exhibit persistent, stimulus-specific activity during short retention delays [46,47]. More crucially, results from neuropsychological studies do not suggest that the lateral prefrontal cortex is a critical site for short-term storage *per se*. Lesion studies in monkeys and humans have failed to find consistent effects of lateral prefrontal damage on the retention of objects or verbal information across short delays, and the effects that have been reported were attributed to deficiencies in task learning, attention, or response selection, rather than mnemonic deficits [15,48–55].

For example, D'Esposito and colleagues [55] recently examined verbal STM performance in patients with unilateral prefrontal lesions. Results from this study showed that digit span (an STM measure used to assess deficits in the patients with perisylvian lesions described earlier) was normal in these patients, consistent with results of a previous meta-analysis of neuropsychological studies [53]. Patients and controls next performed tasks in which either one letter or 3–4 letters (the load was matched to the digit span of each patient) were retained across a 6.5s delay. On some trials, distracting words were presented during the retention delay, whereas on other trials the delay was unfilled. As shown in Figure 2, patients with prefrontal lesions performed normally, even when retaining multiple letters in the face of distraction. These findings are difficult to reconcile with the view that the prefrontal cortex is necessary for verbal short-term storage.

Neuropsychological evidence additionally suggests that prefrontal lesions can affect performance on LTM tasks. Whereas patients with prefrontal lesions can perform at or near normal levels on LTM tasks when given structured encoding tasks and simple test formats, they exhibit impaired performance when forced to initiate strategies to actively encode information or when given tests that require strategic processing during retrieval [56,57].

Box 2. Different types of neural signals for short-term memory

Results from single-unit recording studies of monkeys and neuroimaging studies of humans suggest that there are two classes of neural signals that might disproportionately contribute to STM relative to LTM (Figure I). One class would be best described as 'active' STM signals, in that they are primarily seen under circumstances when one is attempting to actively maintain information across short delays. Most research has focused on persistent, stimulus-specific activity, which is thought by many to be a neural correlate of rehearsal or active maintenance (Figure Ib). The ability of persistent activity to maintain information across short delays has been described in biologically-plausible computational models based on known properties of neocortical neurons [68]. In addition to persistent activity, another active STM signal has been described as 'match enhancement'. This refers to an enhanced response to a stimulus that matches one that has been maintained across a delay period (Figure Ic). Match enhancement effects have been reported in lateral prefrontal, inferior temporal, and medial temporal cortex in both single-unit recording studies in monkeys [69,70] and neuroimaging studies of humans [71,72].

A second class of neural signals that might contribute to STM can be described as 'passive', because they are seen in response to a stimulus even if it is not task-relevant [69]. The most commonly observed passive STM signal is a reduction in neural responses to recently encountered stimuli, relative to stimuli that have not been recently encountered (Figure Id). Available evidence implicates several mechanisms – including neural adaptation, synaptic plasticity, and neuromodulatory influences – that bring about activity reductions to recently encountered items [73]. It has been proposed that activity reductions in the perirhinal cortex could signal the occurrence of a recently encountered item [74]. If so, some mechanisms for neural activity reductions might selectively support LTM (e.g. synaptic plasticity), whereas others might selectively support STM (e.g. neural adaptation) [73]. Interestingly, repetition-related activity reductions in the perirhinal cortex are lag-sensitive, such that the effects are most pronounced at short lags between the first and second exposure [74,75]. This characteristic is similar to the behavioral influence of familiarity on human recognition decisions, which is also lag-sensitive and more prominent at short retention intervals [76].

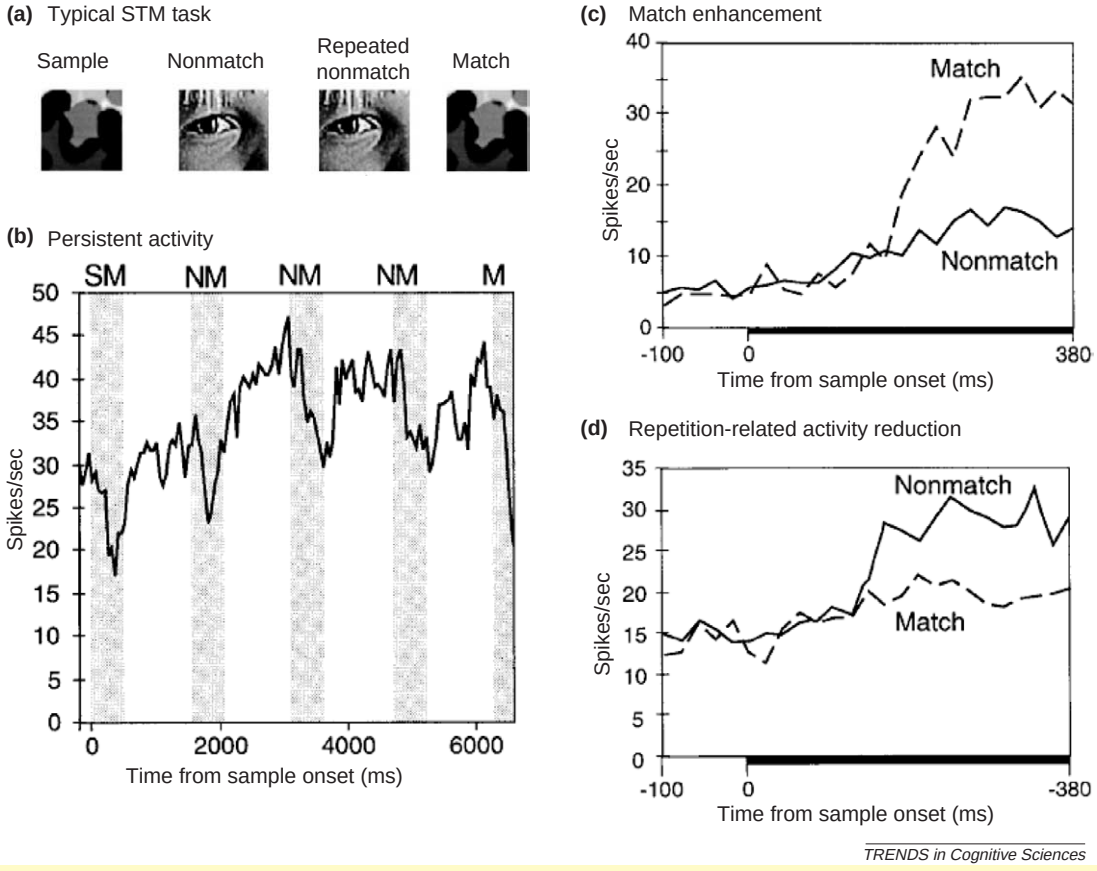

Figure I. Examples of neural STM signals recorded from the entorhinal cortex. **(a)** In a typical STM task used in single-unit recording studies, a sample object must be retained across a delay and compared with a series of test objects, until a matching object is presented. In some tasks, as in the figure, nonmatching test objects are repeated, allowing researchers to differentiate between neural signals sensitive to item repetition and signals more specifically sensitive to the item that is being actively maintained. **(b)** Recordings from a neuron showing persistent activity during the retention of an object. The periods of presentation of the sample (SM), nonmatching test objects (NM), and the matching test object (M) are denoted by gray bars. Note that persistent activity in this neuron remains robust, even following presentation of nonmatching test items. **(c)** Recordings from a neuron showing match enhancement. These effects are not seen for repeated nonmatching items. **(d)** Recordings from a neuron showing reduced activity in response to nonmatching items. These neurons also show reduced activity to repeated nonmatching items, suggesting that they are generally sensitive to stimulus repetition. Adapted from Ref. [28].

Considered along with the range of nonmnemonic deficits induced by prefrontal lesions [58,59], these findings suggest that the prefrontal cortex is not a short-term storage buffer, but rather that it is necessary for implementing control processes that can contribute to both STM and LTM performance [47,56,60,61].

How can the lesion findings described above be reconciled with neuroimaging and single-unit recording studies showing persistent prefrontal activity during maintenance of information across short delays? One possibility is that persistent activity in prefrontal cortex serves to modulate activity in posterior cortical regions that represent

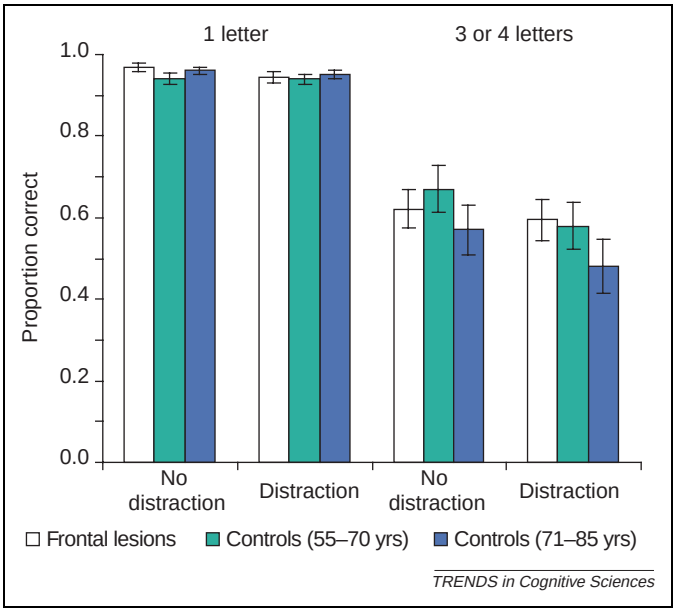

Figure 2. Results showing intact STM in patients with prefrontal lesions [55]. In this study, patients with unilateral prefrontal lesions and two control groups completed STM tasks that required maintenance of letters across a 6.5 s delay. Each subject was pre-tested to identify STM capacity and then completed the STM task with either 1 item, or 3 or 4 items corresponding to the subjects' capacity. On some trials, subjects maintained the letters across an unfilled retention delay, whereas on others, visual distracters were presented during the delay. Recall performance was intact in patients with prefrontal lesions, even when they had to retain multiple items across a distracter-filled retention delay.

information that is being maintained. Results from studies combining lesion and physiology techniques are consistent with this possibility. Specifically, these studies have shown that prefrontal lesions might disrupt STM task performance through dysregulation of task-relevant activity in posterior cortical areas. For example, in one study, activity was recorded from inferior temporal temporal neurons before and after cooling probes were used to induce reversible prefrontal lesions. Before cooling, inferior temporal neurons showed persistent sample-specific activity during the delay period of the memory task. However, this effect was attenuated by prefrontal cooling [62], suggesting that top-down feedback from prefrontal regions was critical for supporting robust STM-related activity in inferior temporal cortex. Another study investigated STM performance and electrophysiological activity in human patients with prefrontal lesions [54]. Behaviorally, the patients were impaired at retaining information across short delays when distracting sounds were presented during the memory delay. Concurrent event-related potential recordings showed that this effect was accompanied by increased neural responses to the distracters in posterior cortical areas. The authors interpreted the results to reflect disinhibition of posterior cortical areas following prefrontal lesions. These findings indicate that, rather than being a short-term storage buffer, the prefrontal cortex provides top-down feedback to support maintenance of information that is represented in posterior cortical areas.

Theoretical alternatives to the multi-store view

As described earlier, most arguments for neurally distinct short- and long-term memory stores are based on reported neuropsychological dissociations between STM and LTM. However, consideration of these reports in the context of more recent findings suggests a more complex picture. Contrary to popular belief, neuropsychological evidence indicates that medial temporal damage can impair STM under some circumstances. Medial temporal cortical regions, like other neocortical regions [47], also exhibit persistent activity during memory delays, a neural signal that might specifically support STM. Neuropsychological evidence also indicates that individuals with phonological STM deficits following perisylvian damage also show LTM deficits when tested appropriately. Finally, neuropsychological evidence suggests that the prefrontal cortex – an area popularly identified with STM – contributes to both STM and LTM in a circumscribed manner. Put together, these findings raise serious doubts about popular claims regarding double dissociations between STM and LTM. It follows that there are good reasons to question whether STM and LTM must be supported by separate neocortical memory stores or systems. Indeed, there are several alternative ways to characterize the neural mechanisms that support STM and LTM.

One possibility is that there are no large-scale cortical areas that uniquely support STM or LTM, but there might be neural circuits that differentially support STM and LTM within the same cortical area. By this view, one might not expect gross lesion studies to reveal double dissociations between STM and LTM, because the underlying memory 'stores' might be at a much finer spatial scale. Such a division of labor might be crucial for normal episodic memory formation [63]. For example, a short-term storage buffer might be necessary for encoding of temporal sequences or spatial maps by relating or binding aspects of events that unfold over time [63].

Another possibility is that distinctions between neural mechanisms of STM and LTM can be explained through differences in the dynamics of activation within the same neocortical memory circuits [4]. The simplest model would suggest that: (i) LTM and STM are supported by reactivation of neocortical memory networks either in response to an external stimulus or through internal, top-down signals for memory retrieval; and (ii) STM can additionally be supported by a family of neural signals, including persistent stimulus-specific activity, match enhancement, and repetition-related activity reductions (Box 2). According to this view, the crucial differences among neocortical memory stores or systems is not their contribution to memory at different retention intervals, but rather the types of information they process and represent [64]. Thus, one could easily assume that that there are multiple memory stores, each representing different types of information across short and long delays.

Conclusions

In conclusion, we have learned a great deal since the initial studies of H.M. and other patients with memory disorders. We argue here that the emerging pattern of evidence raises doubts about popular claims of dissociations between STM and LTM. This provokes new questions regarding how best to characterize the neural mechanisms that support STM and LTM (see also Box 3).

Box 3. Questions for future research

- Are there any neocortical areas or neural circuits that selectively support perception versus active maintenance versus long-duration memory storage [64]?
- Are there fundamental differences in the types of encoding or retrieval processes that are typically engaged during STM and LTM tasks [77]?
- Can persistent activity represent signals that are useful for STM in the absence of conscious awareness?
- How do network-level interactions between different neocortical areas support active maintenance of information across short delays [4]?
- Does persistent activity during short-term maintenance contribute to successful LTM for sequences or spatial maps [63]?
- What is the relationship between synchronized neural oscillations and neural STM signals?
- What kinds of memories, if any, are represented in prefrontal cortical networks [4]?
- Is the hippocampus or entorhinal cortex necessary for representing or retaining information about spatial and/or arbitrary non-spatial relations across short delays [78]?
- Subcortical areas, such as the mediodorsal thalamic nucleus, have been implicated in both STM and LTM. What are the roles of these areas, and how are their contributions to STM and LTM different from neocortical areas?

Clearly, more research will be necessary to determine whether these questions are best answered by models that propose neurally distinct short-term and long-term stores or by models that do not assume distinctions based on retention intervals.

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