

Memory Consolidation: Tracking Transfer with Functional Connectivity

Every day we store memories of innumerable new experiences. Our extraordinary ability to retrieve so many of them at a later time is due in no small part to the consolidation of these memories, a process that continues offline long after the experiences themselves are over.

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The standard model of declarative memory consolidation proposes that memories are initially stored in hippocampal networks that take advantage of that structure's fast learning rate to bind together disparate neocortical areas [1]. Over time, direct neocortico-neocortical connections are established, and the hippocampus is no longer needed [2,3]. Although first proposed more than a century ago, this model remains controversial, with alternatives such as the multiple trace theory [4] still under consideration. Lesion studies have not resolved the controversy, which centres on the role of the hippocampus in long-term memory retrieval. Some studies show temporally graded retrograde amnesia following hippocampal damage [5], while others show continued hippocampal dependence even after many years [6]. Similarly, some experiments show decreased hippocampal activation after memory consolidation [7], while others show increased hippocampal activation [8]. The central question thus remains: does the hippocampus become less involved in declarative memory retrieval over time, and is it eventually replaced by direct connections between neocortical areas?

An elegant new study by Takashima *et al.* [9] has recently shed light on this debate. Using a face-location association task, the authors examined memory by presenting faces as a retrieval cue for their associated locations. Two balanced sets of stimuli were learned on successive days, with a test session for both sets 15 minutes after the learning session on the second day (Figure 1). Consolidation theory suggests that stimuli presented on the first day (remote) will have consolidated over the 24 hour delay before testing, while stimuli presented on the second day (recent) will not

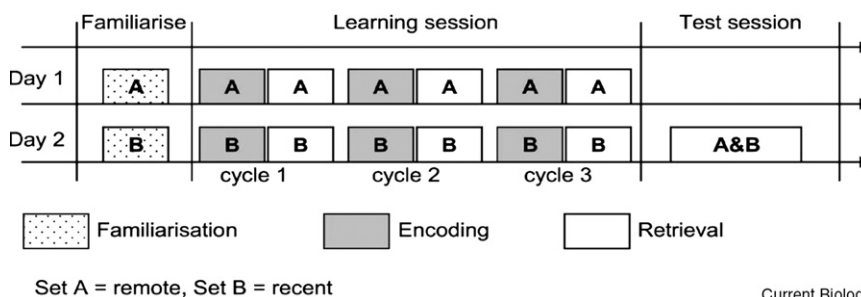
have had time to consolidate. Takashima *et al.* [9] performed functional magnetic resonance imaging (fMRI) during the test session, allowing comparison of responses to these two stimulus sets. Because the task involved faces and locations, the authors expected to find activity in two specific neocortical regions, the fusiform face area (FFA) which responds to face stimuli, and the posterior parietal cortex (PPC), which is involved in representation of egocentric space [10]. On the basis of the standard model of consolidation, they predicted weakening of connections between these neocortical regions and the hippocampus, and strengthening of direct neocortico-neocortical interconnections across the retention period.

When they compared the results for remote against recent pictures during the test session, Takashima *et al.* [9] did indeed find decreased activation in the hippocampus and increased activation in the FFA and PPC, reflecting a consolidation-related shift away from the hippocampus and towards the neocortex. More importantly, they performed a psychophysiological interaction analysis looking at the functional connectivity between different areas. This showed that

connectivity between hippocampus and PPC, between hippocampus and FFA, and between hippocampus and early visual areas believed to be involved in reconstructing images at retrieval [11] were all decreased in the consolidated condition. Furthermore, connectivity between the FFA and PPC, and between the FFA and early visual areas was increased in the same condition. These results provide the first human evidence that memory-related connections between neocortical areas which are initially linked through the hippocampus shift towards an exclusively neocortical network after a period of off-line consolidation.

Interestingly, Takashima *et al.* [9] found no link between consolidation and behavioural performance. This is worth noting because the literature frequently equates consolidation with performance gain, or in the case of declarative memory, with protection against deteriorated performance [12]. The new findings remind us that the primary purpose of consolidation seems to be to allow both rapid learning and long-term storage. Performance gains are an important potential consequence, but are not always present or measurable.

The standard model of systems level consolidation proposes that the hippocampal hub is gradually replaced by direct connections between neocortical areas involved in the reconstruction of the memory [11]. However, it is possible that there are intermediate stages of consolidation when the hippocampal linking role is transiently taken by a neocortical area (Figure 2). Previous work has suggested that the medial prefrontal



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Figure 1. The experimental design used by Takashima *et al.* [9].

On two successive days, participants were first familiarised with a different set of 60 face photos then taught to associate each photo with a spatial location on the screen. Three cycles of presentations (with the same association each time) ensured that learning was possible. After the learning session on the second day, they were presented with a face and asked for the location. Adapted with permission from [9].

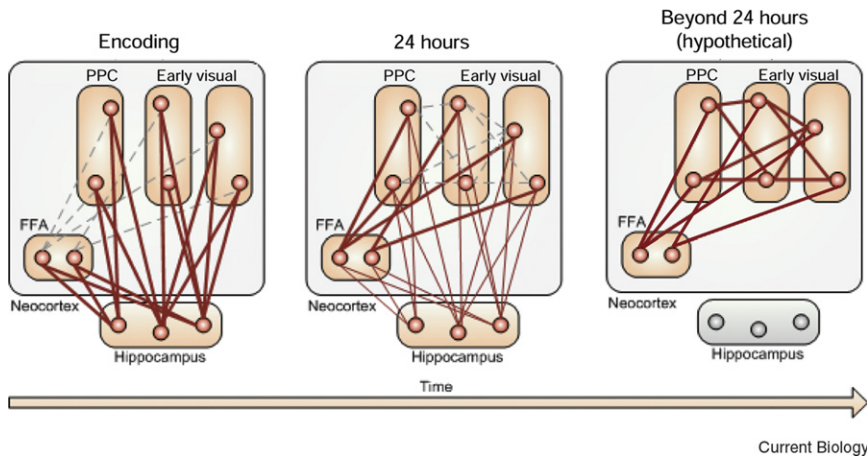


Figure 2. Schematic diagram illustrating a hypothetical model of consolidation in the Takashima *et al.* experiment [9].

Cortical modules in FFA, PPC, and early visual regions are initially bound together through the hippocampus. Over 24 hours connections between these modules and the hippocampus weaken and the FFA begins to take over the linking role. Subsequently, further consolidation may result in a gradual strengthening of direct interconnections between PPC and early visual areas. Adapted with permission from [2].

cortex may perform this temporary linking function as it is increasingly active after consolidation [7,12,13]. Interestingly, such activation was not apparent in the new Takashima study [9]. Instead, the FFA showed enhanced connectivity with both PPC and early visual areas after 24 hours and may thus take the hub-like linking role in this face-location association task. Under this interpretation, Takashima *et al.*'s data could suggest that the location of the temporary hub which links neocortical areas after initial consolidation is task-specific.

The timescale of systems level consolidation also remains a controversial issue. Takashima *et al.* [9] found a decrease in hippocampal involvement after just one night, while some other studies have shown an initial increase followed by a subsequent decrease [12]. Schema theory, or the idea that new information is easier to learn if it fits into an existing mental framework, suggests that the speed of progress towards hippocampal independence depends on how strongly the neocortical networks that need to be strengthened have already been established through previous consolidation [14]. Neocortical networks for remembering faces are frequently used and firmly ingrained, hence consolidation of this information should be more rapid, which could explain the overnight changes seen by Takashima *et al.* [9].

While demonstrating significant transfer of connectivity in just 24 hours, the new study deliberately leaves open the question of when within that retention period the transfer takes place. In particular, it does not comment on the role of sleep. Over the past decade, a number of studies looking at both declarative and procedural memory have found that sleep is important in the consolidation process [15,16]. Evidence includes the observation that a 12 hour retention period including sleep can lead to improved performance when an equivalent period of wake does not [16], and that post-learning sleep deprivation can lead to a long-lasting impairment [12]. When and how this sleep-dependent consolidation occurs remains open for debate. Some existing models suggest that slow-wave sleep is necessary to coordinate hippocampal sharp-wave ripples with thalamic spindles which are believed to be involved in plasticity [15]. Others argue that both slow-wave sleep and rapid-eye-movement sleep are needed [17]. Fascinatingly, work in both rats [18] and humans [19] has shown activity-dependent reactivation during sleep, consistent with a broadly Hebbian mechanism for strengthening neocortical-neocortical connections.

An earlier publication demonstrated that face-location associations are remembered better after a retention interval containing sleep than after a comparable interval of wakefulness

[20], so it seems likely that the plasticity observed by Takashima *et al.* [9] occurred during sleep. We therefore propose two extensions to their experiment which would elucidate the role of sleep in this transfer of connectivity. First, polysomnographic monitoring of brain activity during sleep in the retention interval would allow examination of the sleep stages and properties associated with such transfer, thus facilitating an examination of the respective roles of slow wave and rapid eye movement sleep. Second, functional imaging during the same period could allow visualisation of how connectivity transfer evolves across a night of sleep, clarifying not only the role of each sleep stage, but also the order in which changes occur.

Offline memory reorganisation is now widely accepted, but competing theories offer different mechanisms. Carefully designed studies such as the one by Takashima *et al.* [9] are invaluable in providing clear evidence to distinguish between models. More work along the lines we propose, and doubtless many alternative designs, will help to clarify important details such as whether neocortical hubs take over the binding role and precisely how sleep contributes to consolidation.

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Olfaction: When Nostrils Compete

In vision, alternating percepts occur when two different visual stimuli are presented separately to the two eyes. By analogy, simultaneous presentation of two different odorants separately to the two nostrils has now been shown to cause alternating odor percepts, an effect termed ‘binaral rivalry’.

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Binocular rivalry is a fascinating perceptual phenomenon that occurs when spatially incompatible images are presented to corresponding visual fields of both eyes. Rather than forming one well-blended percept, the two images compete for perceptual exclusivity, leading to alternating periods of perceptual dominance and suppression that switch abruptly every few seconds [1–3]. Scientific descriptions of this effect date back to 1760 [4], and today binocular rivalry remains a powerful method to investigate the neural bases of visual awareness. In this issue of *Current Biology*, Zhou and Chen [5] present evidence for binaral rivalry — olfactory perceptual alternations that occur when two different odorants are presented to opposite nostrils. The experimental paradigm presented here may herald a new research direction in the human sense of smell, opening up the possibility of gaining unique insights into the mechanisms of olfactory awareness.

In the main ‘binaral’ experiment, subjects were presented with dichorhnic mixtures [6,7], i.e., two different odorants delivered simultaneously to opposite nostrils. One nostril was exposed to butanol, a

straight-chain alcohol that smells like a marker pen. The other nostril was exposed to phenethyl alcohol, an aromatic alcohol that smells like roses. On each trial, subjects intermittently sampled from the two bottles, making a single sniff, and then used a bipolar rating scale (with anchors ‘marker’ and ‘rose’) to indicate how similar the odor was to marker or rose. In order to minimize sensory habituation, trials recurred every 20–30 sec. Over the course of 20 samplings, each of the subjects experienced perceptual switches between marker and rose, which varied both in the frequency of the switches as well as their magnitude: some subjects reported fairly modest effects, judging the maximal similarity of the mixture to either rose or marker between 62 and 70% (where 50% represents equal similarity to rose and marker), while others experienced more striking effects (maximal similarity, 82–94%).

Interestingly, when each subject’s ratings of whether the mixture smelled similar to either rose or marker were averaged across the 20 samplings, the mean rating across subjects was 53.9% similar to marker and 46.1% similar to rose. This analysis highlights the value of examining *trial-by-trial responses* during dichorhnic stimulation, a practice that is not

typically adopted in odor mixture studies. If one were to focus solely on group-averaged data, collapsed across trials, one would conclude that delivery of two odorants to different nostrils elicits a mixed percept that is 53.9% marker-like and 46.1% rose-like, essentially a composite odor containing roughly equal proportions of the two stimuli. Such a finding would be consistent with those observed in prior odor mixture studies [7–9]. But as shown by Zhou and Chen [5], a very different conclusion is reached when considering the data on a subject-by-subject and trial-by-trial basis. It would be valuable to reappraise the data from the earlier mixture studies to determine whether within-subject percepts fluctuated between odors across trials.

In a complementary ‘monorhinal’ experiment, the same subjects were presented with physical — rather than dichorhnic — mixtures of butanol and phenethyl alcohol. Thus, instead of separate odorant presentations to different nostrils, both odorants were presented to both nostrils. Again, each subject experienced perceptual switches, with a high degree of intersubject variability in the number of switches and the magnitude of perceptual changes. According to Zhou and Chen [5], this experiment provides evidence for a cortical basis of olfactory rivalry, relating their findings to the phenomenon of monocular rivalry — a less studied effect in which alternating visual percepts are elicited when two competing visual images are both presented to both eyes [10]. The