RESEARCH ARTICLE

EFFECTS OF MEMORY CONSOLIDATION ON HUMAN HIPPOCAMPAL ACTIVITY DURING RETRIEVAL

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Abstract

Day-to-day memories undergo transformation from short-term to long-term storage, a process called memory consolidation. Animal studies showed that memory consolidation requires protein synthesis and the growth of new hippocampal synapses within 24 h. To test for effects of memory consolidation in the human, we examined brain activation during the retrieval of information at 10 min and at 24 h following learning using functional magnetic resonance imaging (fMRI), an indirect measure of synaptic activity. Learning instructions were adjusted to yield a comparable retrieval quantity and retrieval quality at 10 min and 24 h after learning. The left hippocampal formation exhibited enhanced activity during the retrieval at the 24 h lag compared to the retrieval at the 10 min lag. Moreover, the activity in the left anterior hippocampal formation showed stronger correlations with retrieval quantity and retrieval quality at the 24 h lag than at the 10 min lag. This suggests that the relation between left anterior hippocampal activity and retrieval success became closer as consolidation progressed. These fMRI results in the human hippocampal formation may correspond to the neurobiological results in the animal hippocampal formation of a strengthening and growth of synaptic connections within 24 h.

Key words: episodic memory, hippocampus, remember/know, fMRI, neuroimaging

Introduction

In cognitive neuroscience, the term memory consolidation refers to two-way interactions between medial temporal and neocortical regions for the long-term storage of explicit memories. One view of memory consolidation posits a time-limited role of the hippocampus for the retrieval of declarative information with memories eventually becoming entirely supported by neocortical structures (Squire and Zola-Morgan, 1991; Squire and Alvarez, 1995). The multiple trace theory (MTT), on the other hand, suggests that the hippocampus is continuously involved in the retrieval of episodic information and that over time and upon reactivation multiple related memory traces are formed in the hippocampus (Nadel and Moscovitch, 1997; Nadel et al., 2000). These so-called systems consolidation processes are time-consuming and in the human may take months or years to completion (e.g., Knowlton and Fanselow, 1998).

In neurobiology, memory consolidation refers to molecular and cellular events that fix preliminary alterations in synaptic strength in order to transform fragile memory traces into more stable representations. These processes occur within hours after learning. Long-term retention requires that within 24 h after learning gene expression be activated to give rise to the synthesis of new proteins and possibly to the growth of new synaptic connections in the hippocampal formation and other memory systems (Milner et al., 1998; Kandel, 2001).

While the molecular and cellular underpinnings of memory consolidation within the first 24 h after learning have been vigorously investigated in animals, research on the 24 h memory consolidation in the human is sparse. Yet, it is possible to indirectly measure retrieval-related brain activity in the human with the blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) method. The BOLD response is believed to relate to changes in excitatory (glutamatergic) neurotransmission and can be considered an indirect measure for all aspects of presynaptic and postsynaptic processing (Magistretti and Pellerin, 1999; Logothetis et al., 2001; Raichle, 2001; Bonvento et al., 2002; Lauritzen and Gold, 2003; Logothetis, 2003; Zonta et al., 2003).

The two standard approaches in neuroimaging studies of human memory consolidation and retrieval were to either have participants learn items and retrieve them only minutes after learning in the same session (Lepage et al., 1998; Schacter and Wagner, 1999) or to have participants retrieve autobiographical information from the past (e.g., Haist, 2001; Maguire et al., 2001). The problem with retrospective studies of memory consolidation is that it remains unknown exactly when information was acquired, how well it was learned, or how often and when the last time a certain memory was retrieved and thus re-encoded. Moreover, memories may change character over time. Autobiographical memories may become less episodic (‘event’-like, rich in details, authentic, personal) and more semantic (‘fact’-like) over time (e.g., Cermak and O'Connor, 1983). The final representational status of the tested memories should be equivalent across time lags if brain activity differences at test are to reflect effects of time lag rather than effects of memory systems. Prospective studies allow investigators to determine with much greater precision the time, strength, and nature of learning, and – to some degree – the rehearsal of the learning material between study and test.

With such a prospective approach and a comparable retrieval performance between time lags, Stark and Squire (2000) found a non-significant trend towards a retrieval-related fMRI signal increase in the left and right anterior and posterior hippocampal region at 24 h versus 30 min following study. They found no such activity increase if retrieval performance remained unequated between study-test intervals. The same negative result was obtained by Dupont et al. (2001) who had participants silently recall the same list of words 20 min and 24 h following learning without controlling for performance differences in the retrieval across time lags.

In this study, we indirectly measured retrieval-related brain activity with BOLD fMRI 10 min and 24 h after the experimentally controlled learning of word pairs. Our analyses focused on time lag-related activity differences within the medial temporal lobes (MTL). The following methodological considerations were applied:

First, our interest concerned common effects of time lag across several hippocampal memory tasks avoiding task-specific effects. We therefore looked at the main effect of time lag in a two (time lag) - by - two (memory task) ANCOVA and at the cognitive conjunction of memory tasks (Price and Friston, 1997; Cabeza et al., 2002). We used two paired-associate word learning tasks, a high-associative and a low-associative task, that differed in their efficacy of establishing associations in long-term memory. Both task instructions fostered a deep encoding of the single words. However, while the low-associative task instruction provided for a poor learning of additional semantic word-word associations, the high-associative task instructions automatically led to the establishment of many semantic word-word associations (Henke et al., 1999).

Second, we used incidental learning instructions to avoid intentional rehearsing and re-encoding of the word pairs between study and test.

Third, different lists of word pairs were used for each task and each study-test interval to avoid repetition effects and re-encoding due to repeated testing.

Fourth, we empirically and statistically controlled for a comparable retrieval quality and quantity between the two time lags. This is important because the natural process of forgetting might lead to weaker memory traces and thus a bias in the retrieval-related fMRI response at the 24 h lag compared to the 10 min lag. The empirical control of retrieval performance can be achieved by increasing the number of learning trials (e.g., Stark and Squire, 2000) or by varying the learning instructions to adjust the depth of stimulus processing (Heckers et al., 2002). We used the first method for the low-associative memory task and the second method for the high-associative memory task. The ANCOVA and the conjunction analysis allowed testing for common effects of time lag on retrieval, independently of the specific learning procedures used.

Fifth, even with the number of retrieval events equated, the quality of the retrieved information ('event'-like, 'fact'-like) may still largely differ between time lags. We therefore assessed and statistically controlled the quality of the retrieved information by using Tulving's (1985) Remember/Know procedure. Accordingly, Old (studied) - New (not studied) decisions in the test given for recognition were followed by Remember/Know decisions for Old answers. A Remember response implied that the whole study episode was recollected (e.g., one's own thoughts at the first encounter with an item). A Know response implied item familiarity without recollection of the study episode. It has been suggested that the hippocampal formation, defined here as the CA regions, dentate gyrus and subicular complex (Cohen and Eichenbaum, 1993), mediates recollection while the perirhinal cortex mediates familiarity-based recognition (Eldridge et al., 2000; Brown and Aggleton, 2001; Yonelinas et al., 2002; Davachi et al., 2003). On the other hand, Remember and Know answers have been considered qualitatively equal, hippocampal-dependent recognition processes which simply differ in the amount of the retrieved information (Manns et al., 2003). Whichever account is favored, the control for potential Remember/Know differences between time lags appears essential for the study of time lag effects on retrieval-related hippocampal activity.

These precautions allowed us to isolate relatively pure effects of study-test intervals on retrieval-related hippocampal activity.

Materials and Methods

Participants

Twelve healthy right-handed volunteers (seven men) of different educational levels (9-18 school years; mean: 14.8, SD: 2.7) and ages (20-45 years; mean: 27.6, SD: 6.9) participated in this study. Participants were either students at the University of Zurich or worked at the financial services department of a Swiss bank where advertisements of this study were posted. Participants had above-