Linking brain and behavior in sleep-dependent learning and memory consolidation

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The modulation of our brains' neural circuitry by ongoing life experience ("neuronal plasticity") remains an exciting and intensely studied topic. Such experience-based changes in neuronal structure and function underlie the critical adaptive processes of learning and memory formation. Current research seeks to understand these phenomena at numerous levels of analysis, including genetics, molecular biology, biochemistry, cell biology, developmental biology, neurobiology, cognitive neuroscience, psychology, and even philosophy. Over the last decade, it has become increasingly clear that the processes of learning and memory consolidation and integration can occur over extended periods of time, measured in days or even years (1–4). At the same time, evidence has continued to build supporting an important role for sleep in at least some aspects of these processes (refs. 5–8, but see ref. 9). A complete understanding of the role of slow and sleep-dependent mechanisms in these phenomena will require the concerted application of tools from all these fields of research. In this issue of PNAS, Schwartz *et al.* (10) use a visual texture discrimination task (TDT) to demonstrate how elegantly functional magnetic resonance imaging (fMRI) studies can contribute to this field.

In the TDT, originally described by Karni and Sagi (11), subjects evaluate stimuli similar to those in Fig. 1 by identifying both a central fixation letter (e.g., L in Fig. 1*A*, T in Fig. 1*B*) and the orientation of an array of three diagonal bars in the upper left visual quadrant (e.g., horizontal in Fig. 1*A*, vertical in Fig. 1*B*). Training of the TDT leads to highly specific improved identification of the orientation of the diagonal bar array. This improvement does not transfer to targets in other visual quadrants or to backgrounds of vertical bars (11), and, in the case of monocular training, does not transfer to the contralateral eye (11, 12). But perhaps most importantly, posttraining improvements develop only over several hours and in a sleep-dependent manner (12–16). Improvement is not seen even 12 h after training, unless sleep occurs during this period (Fig. 2*A*). With such sleep, improvement continues over additional days and nights, even in the absence of additional training (Fig. 2*B*). But when subjects are sleep deprived the first night after training, subsequent improvement is prevented (Fig. 2*B*, red bar). In addition, overnight improvements correlates with the amounts of both deep, slow wave sleep (SWS) early in the night and REM sleep late in the night (Fig. 2 *C* and *D*). Thus, optimal learning of this task appears to require posttraining events occurring during subsequent SWS and REM sleep.

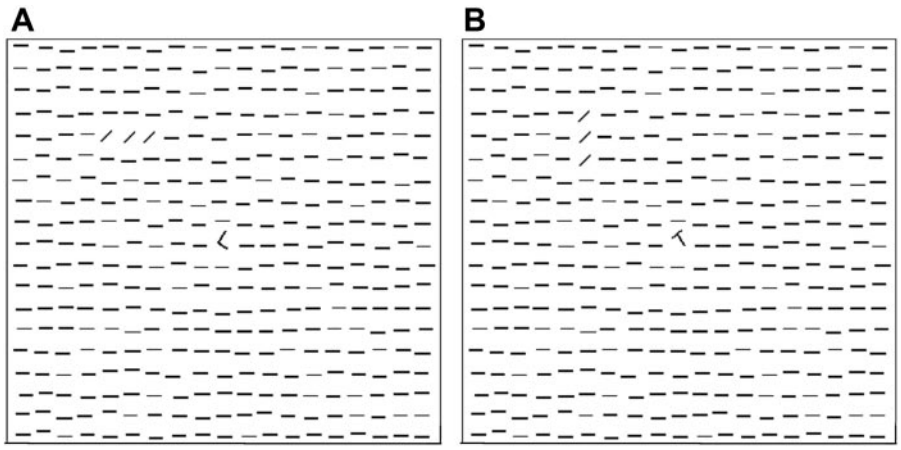

Fig. 1. Sample texture discrimination task stimuli. Screens consist of a background of horizontal bars with a rotated letter ("T" or "L") at the central fixation point and an array of three diagonal bars (in either a horizontal row or a vertical column) in the upper left visual field. (*A*) The letter "L" at fixation, three diagonal bars in a row in the upper left. (*B*) The letter "T" at fixation, three diagonal bars in a column in the upper left.

Little was known of the nature of brain basis of TDT improvement (17) until now. Schwartz *et al.* (10) now report compelling evidence of a retinotopically precise increase in visual cortical activity 24 h after a single session of TDT training. They hypothesized that exposure to information in a highly localized region of the visual field would lead to cortical changes similarly constrained to the corresponding region of the retinotopically organized visual cortex.

Such a study would normally be quite difficult, requiring subjects to be scanned before and 24 h after training. But there are inherent limitations of test–retest reliability in fMRI (18). Changes across time in the homogeneity of the magnetic field in the scanner, together with more practical issues, such as the inevitable inaccuracies in repositioning the subject's head in exactly the same position the second time, and equally inevitable changes in the subject's vigilance level between the two scanning sessions, could seriously diminish the signal-to-noise ratio and, hence, the sensitivity of the technique.

But in an ingenious experimental design, Schwartz *et al.* (10) circumvent these problems by taking advantage of the earlier findings that monocular training does not transfer to the contralateral eye. Because each eye "learns" the TDT independently, it is possible to train one eye but not the other, and then test them

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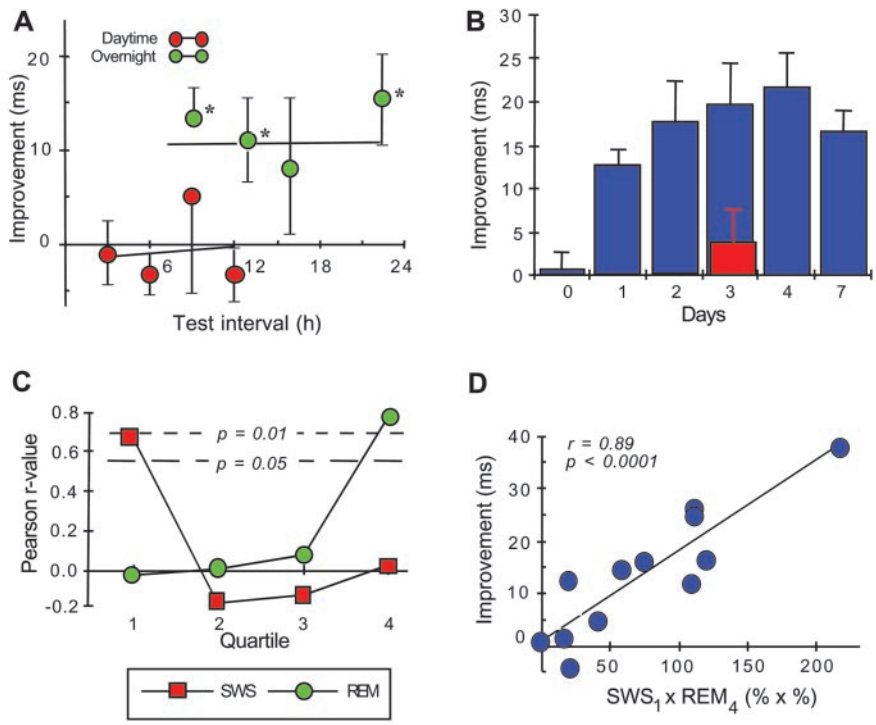

Fig. 2. Sleep-dependent learning of a texture discrimination task. Each subject was retested only once, and each point represents a separate group of subjects. (*A*) Improvement across a night's sleep. Subjects were trained and then retested either 3–12 h later on the same day (red circles) or after 8–24 h after a night's sleep (green circles). All told, $n = 57$, with $n = 7$–9 for individual points. (*B*) Improvement across a week. Subjects were retested the same day as training (day = 0) or after 1–7 days ($n = 122$) (blue bars). Subjects were sleep deprived the night after training and retested after a total of 3 days ($n = 11$) (red bar). Error bars = SEM. (*C*) Overnight improvement was correlated with the amount of both SWS (red squares) and REM (green circles) in each quarter of the night, and the Pearson correlation coefficient plotted ($n = 12$). (*D*) The percent of time spent in SWS during the first quarter of the night (SWS_1) was multiplied by the percent REM for the last quarter of the night (REM_4) for each subject, and plotted against the individual's overnight improvement. From Stickgold and colleagues (15, 16). [Reprinted with permission from ref. 7 (Copyright 2001, AAAS, www.sciencemag.org).]

both in a single session; and because a given region of visual space (such as the portion of the upper left visual quadrant in which the diagonal bar arrays are presented) maps to precisely the same cortical regions through each eye, comparing the responses of the cortex to identical visual input coming through the trained and untrained eye becomes equivalent to comparing responses from the same eye before and after training. In addition, standard visual field probes could be used to map the visual world onto visual cortex to determine whether the learning-induced changes involved the same cortical regions as normally process information coming from the target region of the TDT stimuli. This is exactly what Schwartz *et al.* (10) have done, and the results are impressive.

Their findings demonstrate highly localized plastic changes in the dynamic neural properties of the human visual system 24 h after training on this texture discrimination task. Significant training-dependent monocular increases in the response to test stimuli were only seen in a restricted region of primary visual cortex (V1), a single clump of 88 voxels in the lower bank of the right calcarine sulcus. All 88 voxels lay within the region of cortex stimulated by visual input from a small curved bar covering the same portion of the upper left quadrant of visual space in which the target diagonal bar arrays were displayed. Thus, training led to a specific increase in sensitivity of cortical neurons to target stimuli in just that portion of V1 that processes incoming visual signals from the region in which the target arrays were displayed.

Although no other training-dependent monocular increases were seen, this does not necessarily mean that there were no other training-induced changes. Indeed, the one disadvantage of their technique is that changes in V2 or higher processing regions would not be detectable, because monocularly driven cells are restricted to V1 (19). For example, if training-induced changes occurred in V4 (e.g., see ref. 20), they may be equally reactivated by input through the trained and untrained eye. Thus the argument that the brain's response to the untrained eye would be equivalent to its response to the trained eye at baseline only holds for V1, and the question of upstream training-induced changes remains unanswered. This reservation aside, the clear demonstration that training leads to increased stimulus-driven activity in the precise region of V1 that processed the visual input from target stimuli is gratifying.

How do the changes in activation patterns reported by Schwartz *et al.* relate to the question of sleep-dependent learning and memory consolidation? Exactly when the increases in cortical activation seen by Schwartz *et al.* developed is not known. It could have developed (*i*) by the end of training, (*ii*) several hours later but before sleep, (*iii*) after the early, SWS-rich portion of the night, or (*iv*) only after the full night of sleep. Dissecting this time course is an important task for the future that will clarify the time and sleep dependency of these brain changes.

A separate question is whether these cortical circuits are reactivated during sleep as well as during postsleep testing. Such replay of experience-dependent activity during sleep have already been reported in rat hippocampus after training on spatial learning tasks (21, 22) and in human cortex after training on an implicit motor sequence task (23). Improvement on both spatial learning tasks and simple motor sequence tasks has been shown at the behavioral level to be at least partially sleep dependent (24, 25).

Additional brain-based evidence for slow, experience-dependent changes in cortical activity comes from other studies. Changes in human auditory evoked response potentials after training on a complex auditory discrimination task have been shown to develop over 24–48 h (26), and changes in single cell responses in the monocularly deprived kitten increase after subsequent sleep deprivation (27). In the rat, zif-268, an immediate early gene associated with synaptic plasticity, is specifically upregulated in the cortex during REM sleep after exposure to a rich sensorimotor environment (28), and in a shock avoidance task, retention of learning is highly correlated with REM sleep-associated pontogeniculooccipital waves (29).

What is needed now are studies that begin to explain how these experience-based changes in brain activity contribute to the processes of learning and memory consolidation. The study of Schwartz *et al.* (10) suggests that the careful combination of behavioral and brain imaging techniques will play a major role in answering this challenge.

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