

The level of cholinergic nucleus basalis activation controls the specificity of auditory associative memory

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Received 6 March 2006; revised 6 April 2006; accepted 8 April 2006

Available online 5 June 2006

Abstract

Learning involves not only the establishment of memory per se, but also the specific details of its contents. In classical conditioning, the former concerns *whether* an association was learned while the latter discloses *what* was learned. The neural bases of associativity have been studied extensively while neural mechanisms of memory specificity have been neglected. Stimulation of the cholinergic nucleus basalis (NBs) paired with a preceding tone induces CS-specific associative memory. As different levels of acetylcholine may be released naturally during different learning situations, we asked whether the level of activation of the cholinergic neuromodulatory system can control the degree of detail that is encoded and retrieved. Adult male rats were tested pre- and post-training for behavioral responses (interruption of ongoing respiration) to tones of various frequencies (1–15 kHz, 70 dB, 2 s). Training consisted of 200 trials/day of tone (8.0 kHz, 70 dB, 2 s) either paired or unpaired with NBs (CS-NBs = 1.8 s) at moderate ($65.7 \pm 9.0 \mu\text{A}$, one day) or weak ($46.7 \pm 12.1 \mu\text{A}$, three training days) levels of stimulation, under conditions of controlled behavioral state (pre-trial stable respiration rate). Post-training (24 h) responses to tones revealed that moderate activation induced both associative and CS-specific behavioral memory, whereas weak activation produced associative memory lacking frequency specificity. The degree of memory specificity 24 h after training was positively correlated with the magnitude of CS-elicited increase in γ activity within the EEG during training, but only in the moderate NBs group. Thus, a low level of acetylcholine released by the nucleus basalis during learning is sufficient to induce associativity whereas a higher level of release enables the storage of greater experiential detail. γ waves, which are thought to reflect the coordinated activity of cortical cells, appear to index the encoding of CS detail. The findings demonstrate that the amount of detail in memory can be directly controlled by neural intervention.

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Keywords: Auditory cortex; Encoding; Acetylcholine; Association

1. Introduction

Neural mechanisms are responsible not only for the establishment of memory per se, but also for the specific details of its contents. The issue of specificity is central to the problem of how the brain represents and stores the details of experiences and thus constitutes a core problem in the neurobiology of learning and memory. Consideration of classical (Pavlovian) conditioning can clarify the difference between the establishment and specificity of memory.

The former concerns *whether* learning occurred while the latter concerns *what* was learned. For example, validation of associative memory can be provided by the use of a control group in which the conditioned (CS) and unconditioned (US) stimuli are not paired. This reveals *whether* an association was formed. The possibilities for specificity are much greater because the potential contents of memory are practically unlimited. For instance, even when learning occurs to a pure tone cue, subjects may have learned that a single stimulus parameter or combination thereof predicts reward, punishment or their absence, e.g., a sudden change in the stimulus environment (regardless of modality), a sound, a sound in a particular area of space, a sound with a

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particular timbre, a pure tone of a particular frequency range (e.g., “high” vs. “low”), a pure tone of an absolute frequency (e.g., 5.5 kHz), as well as aspects of the learning context, etc.

The specific details of what was learned ordinarily cannot be determined during training but rather can be assessed afterward by the use of appropriate tests. For example, subjects may be trained with a single stimulus (e.g., in simple conditioning) or two stimuli (e.g., in discrimination learning) but later tested with many values along a stimulus dimension (e.g., acoustic frequency), in the absence of reinforcement (i.e., extinction) (Mackintosh, 1974; Mostofsky, 1965; Pavlov, 1960). Preferential responses to the training stimulus indicate that subjects learned about the particular parameters of the training stimulus while responses to most other stimuli, as well as the training stimulus, indicate that learning was not specific to the training stimulus but rather general along the tested dimension. For example, in the case of training with a pure tone, the former outcome implies that subjects learned about the signal importance of one particular dimension of the environment (the actual frequency of the conditioned stimulus) while the latter implies that subjects did not, but may have learned that tones in general have a signal function (Mackintosh, 1974).

The neural bases of associativity have been studied extensively (Christian & Thompson, 2003; Davis, Falls, Campeau, & Kim, 1993) while those of specificity have received scant attention. Studies near the middle of the last century (1950s–1970s) revealed that learning alters the processing of signal stimuli in sensory cortices (John, 1961; Thompson, Patterson, & Teyler, 1972). More recently, hybrid experimental designs that have combined the basic protocols of the field of sensory neurophysiology with those from learning/memory have revealed that associative learning systematically modifies the processing and representation of sensory information in the auditory, somatosensory, and visual cortices (Diamond, Petersen, & Harris, 1999; Edeline, 2003; Feldman & Brecht, 2005; John, 1961; Rauschecker, 1999; Thompson et al., 1972; Weinberger, 1995). Such learning-induced plasticity can be highly specific. For example, the frequency tuning of neurons in the primary auditory cortex can be shifted toward or even to the frequency of a CS during classical and instrumental conditioning (Weinberger, 2004c); see also (Ohl & Scheich, 2004; Weinberger, 2004b).

Pairing a tone with stimulation of the cholinergic nucleus basalis (NB) induces the same type of receptive field plasticity in the primary auditory cortex that develops during standard classical and instrumental conditioning (Weinberger, 2003) and, accordingly, also expanded representation of the paired tone in the tonotopic map in the primary auditory cortex (Kilgard et al., 2001; Kilgard & Merzenich, 1998).

This report concerns an unusual approach to the neurobiology of learning and memory. Beyond the induction of cortical plasticity, it concerns the induction of actual

behavioral memory by direct activation of the nucleus basalis. [We use the phrase “behavioral memory” to distinguish it from neural plasticity that develops during brain stimulation (e.g., LTP) or learning (e.g., neural correlates) because plasticity is often called “memory”; hereafter, “memory” refers to information storage that is behaviorally validated.] We chose to determine if activation of the cholinergic NB can induce memory because of the known involvement of cholinergic mechanisms in learning and memory (Deutsch, 1971; Flood, Landry, & Jarvik, 1981; Power, Vazdarjanova, & McGaugh, 2003).

Previously, we found that pairing a tone with stimulation of the nucleus basalis does induce memory, and that such memory is both associative and contains detail about the absolute frequency of the conditioned stimulus. Rats that received extensive pairing of a single tone with NB stimulation (NBs) (3000 trials over 15 days) later exhibited behavioral frequency response profiles (for both the interruption of ongoing respiration and changes in heart rate) that were maximal at the CS frequency in the absence of NBs. In contrast, rats receiving unpaired stimulation failed to develop such behavioral CS-specificity (McLin, Miasnikov, & Weinberger, 2002b, 2003). Recently, we have found that specific associative memory can be induced rapidly with a single training session of 200 trials (Miasnikov, Chen, & Weinberger, 2006).

The present study approaches the issue of the neural mechanisms of both associativity and specificity. To date, stimulation of the nucleus basalis has been shown to simultaneously induce behavioral memory that is both associative and specific. However, these two cardinal features of learning are not necessarily coupled, as evidenced by learning in which some or many of the details of an experience are not encoded or are forgotten. This long-recognized distinction is the root of studies of human recognition memory that are concerned with the cognitive and neurobiological differences between memory for detail vs. memory largely limited to a “sense of familiarity” (Rugg & Yonelinas, 2003). We asked whether the level of activation of the cholinergic system can control the degree of detail of a tonal conditioned stimulus by training different groups with different levels (“moderate” and “weak”) of NB stimulation. We further asked whether weak stimulation could produce the same effects as moderate stimulation, by tripling the number of training trials. Some findings for the group receiving moderate stimulation have been reported in another context (Miasnikov et al., 2006).

2. Materials and methods

The materials and methods were identical to those previously reported for the group that received the moderate level of NB stimulation (Miasnikov et al., 2006), except as otherwise noted, and thus will be described only briefly. All procedures were performed in accordance with the University of California Irvine Animal Research Committee and the NIH Animal Welfare guidelines. During training and testing, subjects were continuously monitored by video cameras.

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