

Detection of an inhibitory cortical gradient underlying peak shift in learning: A neural basis for a false memory

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ABSTRACT

Experience often does not produce veridical memory. Understanding false attribution of events constitutes an important problem in memory research. “Peak shift” is a well-characterized, controllable phenomenon in which human and animal subjects that receive reinforcement associated with one sensory stimulus later respond maximally to another stimulus in post-training stimulus generalization tests. Peak shift ordinarily develops in discrimination learning (reinforced CS+, unreinforced CS–) and has long been attributed to the interaction of an excitatory gradient centered on the CS+ and an inhibitory gradient centered on the CS–; the shift is away from the CS–. In contrast, we have obtained peak shifts during single tone frequency training, using stimulation of the cholinergic nucleus basalis (NB) to implant behavioral memory into the rat. As we also recorded cortical activity, we took the opportunity to investigate the possible existence of a neural frequency gradient that could account for behavioral peak shift. Behavioral frequency generalization gradients (FGGs, interruption of ongoing respiration) were determined twice before training while evoked potentials were recorded from the primary auditory cortex (A1), to obtain a baseline gradient of “habituated” neural decrement. A post-training behavioral FGG obtained 24 h after three daily sessions of a single tone paired with NB stimulation (200 trials/day) revealed a peak shift. The peak of the FGG was at a frequency lower than the CS while the cortical inhibitory gradient was at a frequency higher than the CS frequency. Further analysis indicated that the frequency location and magnitude of the gradient could account for the behavioral peak shift. These results provide a neural basis for a systematic case of memory misattribution and may provide an animal model for the study of the neural bases of a type of “false memory”.

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1. Introduction

Learning and memory concern the acquisition and storage, respectively, of experience. Experience consists of the multiplicity of sensory events in the several sensory systems. How experiences are represented and retained in the brain constitute central problems in neuroscience. An accurate record of experience requires precision by perceptual, acquisition and storage processes. Yet even when they are all functioning in an optimal manner, the content of the resultant memory can be different from the actual experience. “Peak shift” constitutes such a case. It consists of the systematic displacement of behavioral performance from a training stimulus (e.g., tone) to another stimulus (e.g., another tonal frequency) despite the fact that only the former had been reinforced. Peak shift is found in both classical and instrumental

discrimination training, across sensory modalities and dimensions, in both humans and animals (Purtle, 1973). For example, if a 1.0 kHz tone is rewarded (CS+) while a 1.2 kHz tone is not rewarded (CS–), then the peak of the post-training frequency generalization gradient will probably not be found at the CS+ frequency but rather at a lower frequency, e.g., 0.7 kHz. Note that the peak is shifted away from the CS– to a lower frequency, in this case, because the CS– is higher than the CS+. (The opposite occurs when the CS– is lower than the CS+.) In short, although discrimination training might be thought to promote accuracy of memory of the CS+, actually peak shift reveals an impairment of veridicality of the memory of an experience.

Spence (1937, 1942) proposed that within a stimulus dimension (e.g., acoustic frequency) rewarded stimuli (S+) produce a surrounding gradient of excitation and non-rewarded stimuli (S–) produce a gradient of inhibition. He further held that the two gradients combine algebraically with the sum dictating the gradient of resultant behavior. Insofar as the sum of the gradients would cause the peak of excitation to be displaced from the CS+, away from the CS–, Spence’s theory could in principle explain peak shift (Fig. 1).

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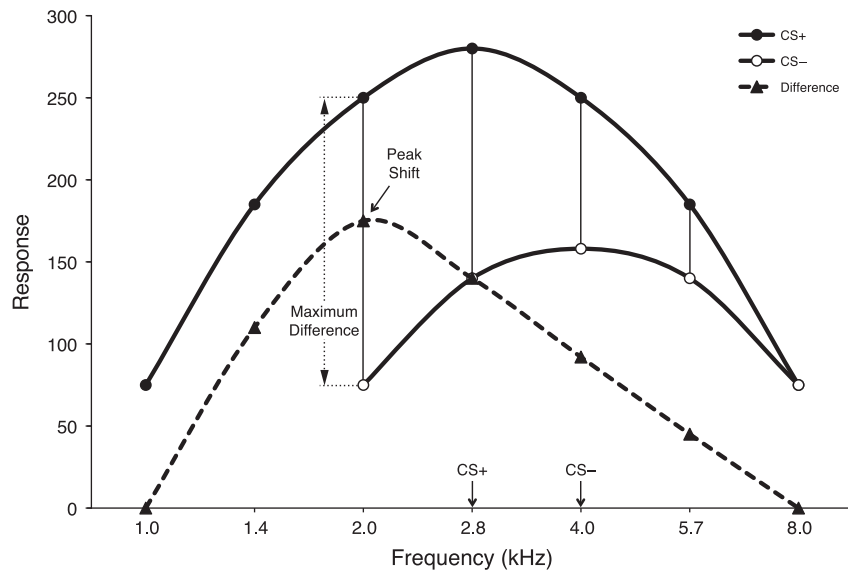


Fig. 1. Hypothetical schema to explain peak shift in frequency discrimination learning (after Spence, 1937). Spence postulated that in discrimination training within a sensory dimension, two gradients are formed: a gradient of excitation centered on the CS+ (●) and inhibition centered on the CS- (○). The algebraic sum was thought to determine the behavioral gradient of generalization. The vertical black lines show the difference between the two gradients. Note that the maximum difference (▲) is not at the CS+ (2.8 kHz) but is shifted to the adjacent stimulus frequency value on the low frequency side (2.0 kHz), away from the CS- (4.0 kHz). The dashed line shows the hypothesized resultant behavioral frequency generalization gradient, exhibiting a peak shift. For illustrative purposes, the inhibitory gradient is depicted above the response baseline rather than as negative values below the baseline.

Although Spence's ideas were published about 75 years ago, his formulation remains the dominant explanation (Bouton, 2007).

As research on peak shift has been confined almost exclusively to behavioral studies, the existence of putative explanatory neural gradients has remained unexplored. In approaches to the neural bases of this phenomenon, the hypothesized "inhibitory" gradient is of prime consideration because it is said to be the mechanism of peak shift. However, the term "inhibition" should be considered in an appropriate context. Spence's theory refers to behavioral gradients related to excitatory and inhibitory conditioning discovered by Pavlov (1927), not to neurophysiological excitation or inhibition. Thus, neural gradients that could account for peak shift need not be gradients of cellular inhibition *per se*, e.g., strengthening of inhibitory post-synaptic potentials (IPSPs). Other neural processes can oppose excitation, such as decrement in pre-synaptic transmitter release (Castellucci & Kandel, 1974), depotentiation (Fujii, Saito, Miyakawa, Ito, & Kato, 1991) and synaptic depression (Simons-Weidenmaier, Weber, Plappert, Pilz, & Schmid, 2006). Our use of the term "inhibition" is thus intended only in a general functional sense, i.e., to refer to neural processes that could reduce the effectiveness of neural excitation regardless of their particular neuronal bases.

We have reliably observed peak shift along the dimension of acoustic frequency in our previous studies of "implanted memory" (e.g., Miasnikov, Chen, & Weinberger, 2006, 2011). Memory is implanted by pairing a tone with electrical stimulation of the nucleus basalis (NBstm) (McLin, Miasnikov, & Weinberger, 2002; Miasnikov et al., 2006, 2011; Weinberger, Miasnikov, & Chen, 2006, 2009), which projects to (Mesulam, Mufson, Wainer, & Levey, 1983) and releases acetylcholine (ACh) into the cerebral cortex (Lehmann, Nagy, Atmadja, & Fibiger, 1980). Post-training behavioral measures reveal that animal subjects behave as though they had undergone standard training with a normal environmental reinforcement, i.e., they exhibit conditioned responses. Implanted memory has the major characteristics of natural associative memory. It is associative, can be acquired rapidly, is specific (conditioned responses to the CS and adjacent frequencies), and shows consolidation over days and long-term retention over weeks

(reviewed in Weinberger, 2007; see also Miasnikov et al., 2011). Moreover, implanted memory is not an artifact of unintended reward or punishment because NBstm as used in our studies is motivationally neutral (Miasnikov, Chen, Gross, Poytress, & Weinberger, 2008a). Rather, the nucleus basalis appears to be "downstream" of motivational systems and may constitute a "final common path" to the cortex. Implanted auditory memory requires that NBstm release ACh that engages muscarinic receptors (Miasnikov, Chen, & Weinberger, 2008b). Accordingly, elucidation of the neural bases of peak shifts of implanted memory may be applicable to natural memory given that the former has the major attributes of the latter.

However, in contradistinction to natural associative memory, we obtained peak shifts in the *absence* of overt discrimination training. Rather, peak shift appears in post-training frequency generalization gradients, after a single tone has been merely paired with brief stimulation of the nucleus basalis (Miasnikov et al., 2006, 2011). Thus, while behavioral responses to the CS frequency were enhanced compared to non-associative controls, the peak of the post-training generalization gradient was at a neighboring frequency.

Previous studies of implanted memory have used relatively weak (~65 μ A) levels of NBstm that produce only a few seconds of cortical activation. The present study was initiated to determine if a higher, but still moderate, level of stimulation (~100 μ A) that activates the cortex would maximize the specificity of learning, that is produce the largest behavioral responses *precisely at the CS frequency*. However, it soon became apparent that peak shift still developed. Therefore, we took the opportunity to explore its possible neural mechanisms.

2. Materials and methods

The materials and methods were same as those previously reported (Weinberger et al., 2009), and 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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