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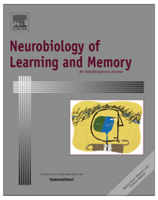

Learning strategy refinement reverses early sensory cortical map expansion but not behavior: Support for a theory of directed cortical substrates of learning and memory

Gabriel A. Elias [a], Kasia M. Bieszczad [a,b], Norman M. Weinberger [a,*]

[a] Center for the Neurobiology of Learning and Memory and Department of Neurobiology and Behavior, University of California, Irvine, CA 92697-3800, United States
[b] Behavioral and Systems Neuroscience, Department of Psychology, Rutgers University, Piscataway, NJ 08854-8020, United States

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ABSTRACT

Primary sensory cortical fields develop highly specific associative representational plasticity, notably enlarged area of representation of reinforced signal stimuli within their topographic maps. However, overtraining subjects after they have solved an instrumental task can reduce or eliminate the expansion while the successful behavior remains. As the development of this plasticity depends on the learning strategy used to solve a task, we asked whether the loss of expansion is due to the strategy used during overtraining. Adult male rats were trained in a three-tone auditory discrimination task to bar-press to the CS+ for water reward and refrain from doing so during the CS− tones and silent intertrial intervals; errors were punished by a flashing light and time-out penalty. Groups acquired this task to a criterion within seven training sessions by relying on a strategy that was "bar-press from tone-onset-to-error signal" ("TOTE"). Three groups then received different levels of overtraining: Group ST, none; Group RT, one week; Group OT, three weeks. Post-training mapping of their primary auditory fields (A1) showed that Groups ST and RT had developed significantly expanded representational areas, specifically restricted to the frequency band of the CS+ tone. In contrast, the A1 of Group OT was no different from naïve controls. Analysis of learning strategy revealed this group had shifted strategy to a refinement of TOTE in which they self-terminated bar-presses before making an error ("iTOTE"). Across all animals, the greater the use of iTOTE, the smaller was the representation of the CS+ in A1. Thus, the loss of cortical expansion is attributable to a shift or refinement in strategy. This reversal of expansion was considered in light of a novel theoretical framework (*CONCERTO*) highlighting four basic principles of brain function that resolve anomalous findings and explaining why even a minor change in strategy would involve concomitant shifts of involved brain sites, including reversal of cortical expansion.

1. Introduction

That primary ("early") sensory cortical fields are deeply involved in learning and memory is now well established. In contrast to traditional assumptions that primary sensory cortical fields function only as stimulus analyzers, associative learning is now known to specifically modify the representations of stimuli in animals and humans in the primary auditory (A1) (Scheich et al., 2011; Weinberger, 2011), somatosensory (S1) (Galvez, Weiss, Weible, & Disterhoft, 2006; Pleger, Blankenburg, Ruff, Driver, & Dolan, 2008), visual (V1) (Hager & Dringenberg, 2010; Miller et al., 2008), olfactory (Li, Howard, Parrish, & Gottfried, 2008) and gustatory (Ifuku, Hirata, Nakamura, & Ogawa, 2003) cortices. Most extensively studied in A1, learning can shift acoustic frequency tuning to strengthen the encoding of sounds that predict reinforcement (Bakin & Weinberger, 1990; Edeline & Weinberger, 1993; Kisley & Gerstein, 2001), which can also produce increased cortical representational area for a tone signal within the tonotopic "map" of A1 (Recanzone, Schreiner, & Merzenich, 1993; Rutkowski & Weinberger, 2005).

Highly specific learning-induced tuning shifts and increased area are instances of a previously unknown type of learning-dependent plasticity, "highly-specific associative representational plasticity". (For brevity, hereafter we generally use simply "representational plasticity".) Whereas "plasticity" is very widely applied to almost any instance of non-transient neural change, representational plasticity consists of systematic modification of the processing of a

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[*] Corresponding author at: 309 Qureshey Research Laboratory, Center for the Neurobiology of Learning and Memory, University of California, Irvine, CA 92697-3800, United States. Fax: +1 (949) 824 4576.
E-mail address: nmweinbe@uci.edu (N.M. Weinberger).

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parameter of sound, e.g., acoustic frequency. A defining feature of representational plasticity is that it cannot be known as the animal is actively learning during training trials. Rather, it is detected by sensory neurophysiological testing in trained subjects with a wide range of stimulus values, outside of the training context. This procedure can reveal whether cortical plasticity is limited to a particular stimulus or is a manifestation of a global modification in the cortical processing of a stimulus parameter. The implications of representational plasticity transcend local plasticity because representational plasticity alters not merely responses to a current stimulus, but rather the processing of future stimuli along a sensory dimension. Furthermore, the amount of expansion of representational plasticity can encode both the acquired importance of sensory stimuli (Rutkowski & Weinberger, 2005) and the strength of specific memory (Bieszczad & Weinberger, 2010c).

Representational plasticity in A1 is ubiquitous as it develops across species (including humans), types of learning, varieties of tasks, motivational valences and other sound parameters (Scheich, Brechmann, Brosch, Budinger, & Ohl, 2007; reviewed in Weinberger, 1995, 2004, 2007). Further evidence implicating primary sensory cortex in mnemonic processes is that representational plasticity in A1 has the same attributes as important features of memory, e.g., associativity, specificity, rapid formation, consolidation and long-term retention (reviewed in Weinberger, 2007). Moreover, directly enhancing A1 responses to a tone, by pairing it with stimulation of the cholinergic nucleus basalis (NB) (Bakin & Weinberger, 1996; Kilgard & Merzenich, 1998), implants specific behavioral memory (McLin, Miasnikov, & Weinberger, 2002) that also shares the major attributes of natural memory (Miasnikov, Chen, & Weinberger, 2006, 2011; Miasnikov & Weinberger, 2012; Weinberger, Miasnikov, & Chen, 2006) and does so by increasing its area of representation (Bieszczad, Miasnikov, & Weinberger, 2013).

Although representational plasticity is a reliable process that appears to favor behaviorally important sensory events, the factors that are responsible for its development during instrumental learning are not well understood. Learning strategy has been identified as an unexpectedly important influence (Berlau & Weinberger, 2008; Bieszczad & Weinberger, 2010a, 2010b, 2010c). Thus, most tasks can be solved in more than one way and whether or not representational plasticity develops seems to depend not on whether or how well a task is learned, but rather on how it is solved. For example, there is no unique solution to the problem of obtaining water rewards contingent on making bar-presses in the presence of a tone, while withholding them during silent intertrial intervals to avoid an error signal (flashing light) that initiates a time-out "penalty" period. Although apparently a very simple task, different strategies can be employed because a tone has different components: an onset, a plateau (steady state) and an offset. The problem could be solved simply by starting to respond at tone onset and stopping at tone offset ("tone duration" strategy, ON–OFF). However, subjects could also obtain rewards by responding from tone onset, past tone offset until receiving an error signal ("tone-onset-to-error" strategy, TOTE).

Rats trained in this instrumental reward task learn to solve the problem regardless of whether they use the ON–OFF or TOTE strategies. However, representational plasticity, particularly an expanded representation of the CS+, develops in A1 only if animals use the TOTE strategy (Berlau & Weinberger, 2008; Bieszczad & Weinberger, 2010b). Indeed, use of the TOTE strategy is more critical for the formation of representational plasticity than is motivational level (Bieszczad & Weinberger, 2010a). Furthermore, the magnitude of the tone signal's representation is a function of the extent to which animals use the TOTE strategy: the greater the use of TOTE, the greater the representational area (Bieszczad & Weinberger, 2010b).

Although learning strategy has been identified as an important factor for the development of representational plasticity, its role in the maintenance of representational plasticity is unknown. This is particularly important because learning-related representational expansions in A1 can diminish or completely disappear when training is continued, usually for weeks, after a task has been solved; this process that has been referred to as "renormalization" (Reed et al., 2011). This type of loss of learning-induced plasticity is a general and enigmatic process transcending the auditory system, e.g., visual cortex (Yotsumoto, Watanabe, & Sasaki, 2008), somatosensory cortex (Ma et al., 2010), motor cortex (Tennant et al., 2012). The goal of this experiment was to determine if the maintenance or loss of cortical representational plasticity is linked to the behavioral strategy employed in learning. Beyond the specific question at hand, the findings have extensive implications for a general theory of neural systems underlying learning and memory.

2. Methods

2.1. Subjects

The subjects were male Sprague–Dawley rats (300–325 g, $n = 21$) from Charles River Laboratories (Wilmington, MA). They were individually housed in a vivarium (temperature maintained at 22 °C, 12/12 h light/dark cycle, lights on 7 am), with *ad libitum* access to food and water before the onset of training. During training with water restriction (see Section 2.3), continuous access to water was restored on the weekends and supplements were provided after training sessions to maintain weight, as necessary. All procedures were conducted with care to minimize pain or discomfort and were in accordance with the University of California, Irvine, Animal Research Committee and the NIH Animal Welfare guidelines.

2.2. Experimental groups and treatments

The main goal of this experiment was to determine if the maintenance or loss of cortical representational plasticity is linked to the behavioral strategy employed during learning. As the loss of expanded representation has been reported in cases of prolonged training after subjects had initially learned to solve an instrumental task (e.g., Reed et al., 2011), we studied the effects of three different amounts of such overtraining.

First, animals were divided into three groups and were trained on the same three-tone discrimination task (3TD) to the same criterion. Specifically, they were trained to bar-press for water reward contingent on the presence of a CS+ tone, and not to press during presentation of either of two CS− tones (Low CS− and High CS−) (see Section 2.3.2.2). Training continued until each subject reached criterion, defined as three consecutive sessions during which its coefficient of variation (CV) for performance (P, see also Section 2.4.1) was $\leqslant 0.10$ (CV = standard deviation/mean of daily performance level). Second, they received different amounts of continued training after reaching criterion. Group ST ($n = 11$) received no additional training. Group RT ($n = 6$) continued to be trained for one week (5 sessions), and then underwent a two-week retention period prior to further treatment. Group OT ($n = 10$) was given more extensive overtraining of three weeks. Third, to determine the frequency specificity of learning, all groups underwent a stimulus generalization test after they completed training (or retention in the case of Group RT) (see Section 2.3.2.3). (The only exception to this sequence is that Group RT underwent a single training session after its retention interval to determine how well it remembered the task.) Fourth, all groups underwent mapping of the frequency representation of their primary auditory