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REMODELING SENSORY CORTICAL MAPS IMPLANTS SPECIFIC BEHAVIORAL MEMORY

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Abstract—Neural mechanisms underlying the capacity of memory to be rich in sensory detail are largely unknown. A candidate mechanism is learning-induced plasticity that remodels the adult sensory cortex. Here, expansion in the primary auditory cortical (A1) tonotopic map of rats was induced by pairing a 3.66-kHz tone with activation of the nucleus basalis, mimicking the effects of natural associative learning. Remodeling of A1 produced *de novo* specific behavioral memory, but neither memory nor plasticity was consistently at the frequency of the paired tone, which typically decreased in A1 representation. Rather, there was a specific match between individual subjects' area of expansion and the tone that was strongest in each animal's memory, as determined by post-training frequency generalization gradients. These findings provide the first demonstration of a match between the artificial induction of specific neural representational plasticity and artificial induction of behavioral memory. As such, together with prior and present findings for detection, correlation and mimicry of plasticity with the acquisition of memory, they satisfy a key criterion for neural substrates of memory. This demonstrates that directly remodeling sensory cortical maps is *sufficient* for the specificity of memory formation.

Key words: acetylcholine, auditory cortex, brain stimulation, neurophysiology, nucleus basalis.

INTRODUCTION

The neural basis of memory remains a central problem in neuroscience. A prevalent approach has been to determine the brain regions that are necessary for memory formation. For example, the medial temporal lobe has been identified as a requisite for the establishment of recent declarative memory, although not for long-term storage which has been attributed largely to the cerebral cortex (Squire et al., 2004). A less frequent but complementary research focus is on how the actual *contents* of memory become stored. *Memory content* includes particular sensory information about experienced events that is initially provided by transient neural activity across the several sensory modalities. Sensory cortical areas are particularly well suited to represent details of experiences because they include neurons with highly specific receptive fields. Moreover, primary sensory fields are convenient targets for the study of the representations of *remembered* experiences because they contain organized dimensions of content-specific representations (Gilbert and Wiesel, 1992; Weinberger, 1995), which facilitated the discovery of learning and memory-related plasticity in primary auditory (A1) (Weinberger, 1995), somatosensory (S1) (Diamond et al., 1999) and visual (V1) (Super, 2002) fields.

Regardless of the brain region or type of learning-related plasticity under consideration as a memory substrate, certain commonly accepted criteria need to be satisfied. First, behavioral evidence of memory formation should be accompanied by (a) *detection* of a neural change. Further, the neural plasticity detected should be (b) *correlated* with the behavioral parameters of learning. Additionally, (c) *mimicry* should be demonstrable, i.e., artificial production of the neural change should produce behavioral signs of memory that *mimic* its natural induction (Martin et al., 2000). Satisfaction of these criteria is required to conclude that a candidate neural change is sufficient for memory.

However, neural plasticity that can account for memory *contents* also requires an additional criterion, that of (d) *specificity*. Thus, it is not adequate to simply find neural plasticity (i.e., detection) that is related to with behavioral expression of memory by their co-emergence (i.e., correlation), because such plasticity might be involved in, e.g., processes that enable the acquisition and storage of a particular experience, rather than encoding a sensory aspect (or content) of the experience itself. Consequently, neural candidates for memory contents have also to match the specific details of those contents. Therefore, in order to conclude sufficiency, both natural and also (c) *mimicked* plasticity ought to match the specific contents of the behavioral memory, e.g., that of a specific sound. Furthermore, specificity at the group-level, while important, is

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Abbreviations: A1, primary auditory cortex; AC, autocorrelation function; BF, best frequency; CF, characteristic frequency; CS, conditioned stimulus; Exc, excitatory; FGG, frequency generalization gradients; FRA, Frequency response area; MGv, ventral division of the medial geniculate nucleus; NB, nucleus basalis; NBstm, stimulation of the cholinergic nucleus basalis; RCI, Respiration Change Index; S1, primary somatosensory cortex; SWS, slow-wave sleep; V1, primary visual cortex.

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inadequate to fully meet the criterion of content-specificity. Individuals seldom form identical memory, even within a group that has undergone the same training. Therefore a neural change in individual subjects needs to match the content of the individual subject's memory in order to be a valid candidate substrate of those contents.

The primary auditory cortex has been studied more extensively than any other primary sensory field for neural substrates of learning and memory. As such, neural plasticity in A1 has met the cardinal criteria outlined above. The (a) *detection* of associative plasticity (e.g., increased evoked potentials and unit discharges to a signal tone) has been established across tasks and species for more than 50 years (reviewed in Scheich et al., 2011; Weinberger, 2011). More recently, combined behavioral studies of memory and auditory neurophysiology have revealed (b) *correlation*, in that associative learning can produce signal-specific persistent associative shifts in receptive field tuning to favor representation of a tone-frequency that signals reinforcement (Bakin and Weinberger, 1996; Weinberger, 2004). Furthermore, representational tuning shifts across A1 expand the signal-frequency area in the tonotopic map (Recanzone et al., 1993) where they appear to encode the level of acquired stimulus importance (Rutkowski and Weinberger, 2005) and serve as a substrate for strengthening specific memory (Polley et al., 2006; Bieszczad and Weinberger, 2010c, 2012). Moreover, representational plasticity correlates of learning have the same attributes as behavioral memory (e.g., associativity, specificity, consolidation and long-term retention) (Weinberger, 2007) and are ubiquitous, developing in humans and animals in a wide variety of tasks (Ohl and Scheich, 2005).

Brain stimulation techniques have been used to satisfy the third criterion of (c) *mimicry* for auditory learning and A1 plasticity. For example, stimulation of the cholinergic nucleus basalis (NBstm) paired with the presentation of an auditory tone induces representational plasticity in A1 that has the same major features as plasticity induced during natural learning, i.e., associativity, specificity, consolidation and long-term retention (Weinberger, 2007). Moreover it is dependent on muscarinic acetylcholine receptors (Miasnikov et al., 2001; Zhang et al., 2006; Chen and Yan, 2007; Zhang and Yan, 2008). Perhaps most importantly, this procedure also implants *de novo* behavioral memory that also has the main characteristics of natural behavioral memory (McLin et al., 2002; Miasnikov et al., 2011). Thus, NBstm procedure successfully mimics natural memory formation by artificially inducing A1 representational plasticity and also implanted auditory memory.

However, there has not yet been any established link between mimicry of A1 representational plasticity and mimicry of behavioral memory. For example, whether or not the induction of plasticity in A1 by stimulation of the nucleus basalis is sufficient to implant of behavioral memory with this procedure is unknown. This issue could be resolved by addressing the fourth criterion for sufficiency, that of (d) *specificity*, to determine whether there are matches in NB-induced plasticity and implanted memory at the level of the individual. Studies of *natural* auditory learning and memory in rodents have shown at the group-level that neural plasticity in A1 is significantly related to the training frequency (Gonzalez-Lima and Scheich, 1986; Bakin and Weinberger, 1996; Edeline and Weinberger, 1993; Recanzone et al., 1993; Kisley and Gerstein, 2001; Fritz et al., 2003; Reed et al., 2011). Recent experiments have focused on the fact that identical training can induce different representational changes in A1 in individual subjects, and discovered that these individual differences in natural learning correlate with the strength of the specific memory an animal had acquired during training (Ohl et al., 2001; Polley et al., 2006; Bieszczad and Weinberger 2010a,b, 2012). Similarly, a recent study of artificially implanted memory has shown that the NBstm procedure is susceptible to a "peak shift" learning phenomenon in which the training can implant a specific auditory memory that is unique in individual animals and different from the actual frequency of the paired tone – despite their identical training (Miasnikov and Weinberger, 2012). Therefore, the ultimate specificity of mimicked and natural behavioral memory may depend not on the parameters of training, but on the specificity of the reorganization of frequency-representation in A1 within an individual subject.

One paper has studied a link between mimicry of A1 representational plasticity and mimicry of behavioral memory by exploring the degree of match in specificity between NB-induced A1 plasticity and memory. A significant relationship was found between the magnitude of increase in evoked potential amplitude for frequencies at or adjacent to the conditioned stimulus frequency (CS) and the magnitude of change in behavioral heart rate or respiration measures of memory (Miasnikov et al., 2006). However, this study did not demonstrate specificity of A1 plasticity and behavior for the same unique frequency. The conclusion that cortical plasticity is actually highly specific to memory requires an individual analysis of the match in frequency-specificity between NB-induced plasticity in A1 and NB-induced memory. The purpose of the present study was to investigate this open issue of individual matches in *specificity* to determine the role of A1 reorganization for the induction of auditory memory.

Because the area of representational gain is known to encode both stimulus importance (Rutkowski and Weinberger, 2005) and strength of frequency-specific memory (Bieszczad and Weinberger, 2010c) in natural learning, we focused on the relationship between frequency-representational A1 area and its specificity to memory.

EXPERIMENTAL PROCEDURES

The general methods were identical to those previously reported (Miasnikov et al., 2011) and thus are only briefly reported here. All procedures were performed in accordance with the University of California, Irvine,