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Gamma band plasticity in sensory cortex is a signature of the strongest memory rather than memory of the training stimulus

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ABSTRACT

Gamma oscillations (~30–120 Hz) are considered to be a reflection of coordinated neuronal activity, linked to processes underlying synaptic integration and plasticity. Increases in gamma power within the cerebral cortex have been found during many cognitive processes such as attention, learning, memory and problem solving in both humans and animals. However, the specificity of gamma to the detailed contents of memory remains largely unknown. We investigated the relationship between learning-induced increased gamma power in the primary auditory cortex (A1) and the strength of memory for acoustic frequency. Adult male rats ($n = 16$) received three days (200 trials each) of pairing a tone (3.66 kHz) with stimulation of the nucleus basalis, which implanted a memory for acoustic frequency as assessed by associatively-induced disruption of ongoing behavior, viz., respiration. Post-training frequency generalization gradients (FGGs) revealed peaks at non-CS frequencies in 11/16 cases, likely reflecting normal variation in pre-training acoustic experiences. A stronger relationship was found between increased gamma power and the frequency with the strongest memory (peak of the difference between individual post- and pre-training FGGs) vs. behavioral responses to the CS training frequency. No such relationship was found for the theta/alpha band (4–15 Hz). These findings indicate that the strength of specific increased neuronal synchronization within primary sensory cortical fields can determine the specific contents of memory.

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1. Introduction

A major advance in broadening our understanding of the neural substrates of learning and memory has involved a shift in emphasis from linear stimulus–response circuits to neural networks. Following Hebb's insights (Hebb, 1949), it is now generally accepted that coordinated neuronal activity forms during learning to represent and store relevant information, serve cognition and ultimately behavioral action. Gamma frequency oscillations (~30–120 Hz) are thought to reflect the synchronous activity of neurons both within and across cortical fields (Buzsáki & Wang, 2012). The time-scale of gamma oscillations is appropriate for synaptic integration (Salinas & Sejnowski, 2000; Volgushev, Chistiakova, & Singer, 1998) and spike timing dependent plasticity (STDP) (Bi & Poo, 1998; Isaac, Buchanan, Muller, & Mellor, 2009; Wespataat, Tennigkeit, & Singer, 2004). Particularly relevant to the domain of learning and memory, increased gamma activity has been linked to processes such as attention (Börgers, Epstein, & Kopell, 2008) and

short-term memory (Lutzenberger, Ripper, Busse, Birbaumer, & Kaiser, 2002; Pesaran, Pezaris, Sahani, Mitra, & Andersen, 2002). Moreover, the level of gamma activity at the time of encoding can predict the degree of later recall (Fell & Axmacher, 2011; Osipova et al., 2006; Sederberg et al., 2006, 2007). An increase in cortical gamma power also develops during simple associative auditory classical conditioning in humans (Miltner, Braun, Arnold, Witte, & Taub, 1999), underscoring its ubiquity and the potential applicability of appropriate animal models to mechanisms of human learning.

Animal models of associative learning have identified candidate neural substrates for the representation and storage of signal stimuli in the cerebral cortex. For example when a tone is paired with a reinforcer, receptive fields (RF) in the primary auditory cortex (A1) shift to emphasize the frequency of the conditioned stimulus (CS) (Bakin & Weinberger, 1990; Edeline & Weinberger, 1993; Gao & Suga, 2000; Kisley & Gerstein, 2001). Such representational plasticity has the main attributes of associative memory: associativity, specificity, consolidation and long-term retention (reviewed in Weinberger, 2007). Gamma activity may play a critical role in the development of cortically based associative learning. For example, an increase in gamma power within A1 predicts both specific CS-directed cortical plasticity and also behaviorally validated

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learning 24 h later, but only during initial acquisition, not during maintenance of the memory (Headley & Weinberger, 2011; Weinberger, Miasnikov, & Chen, 2006).

Heretofore, it has been assumed tacitly that enhanced gamma activity induced by a signal stimulus during learning reflects the increased salience or behavioral relevance of that stimulus, e.g., the CS in simple associative learning. However, there is an alternative possibility. It is well known that even when perceptual, acquisition and storage processes are functioning optimally, the *content* of the resultant memory can *differ* from the actual experience. Subjects trained identically do not all acquire the exact same content (Bieszczad & Weinberger, 2010a, 2010b, 2012; Ohl, Scheich, & Freeman, 2001; Polley, Steinberg, & Merzenich, 2006). Therefore, the greatest increase in gamma activity may actually reflect the stimulus that has gained the greatest strength through learning, rather than the training stimulus. The relative strength of memory for different stimuli along a sensory dimension cannot be determined during training, but rather depends on obtaining post-training stimulus generalization gradients (Bouton, 2007; Mostofsky, 1965). Discrimination learning (i.e., reinforced CS+ with non-reinforced CS−) is a well-documented example. The peak of the post-training generalization gradient is generally not at the CS+ but is displaced to a stimulus value that is farther away from the CS− (Purtle, 1973). Such “peak shift” has been thought to reflect the summation of an excitatory neural gradient centered on the CS+ and an inhibitory neural gradient centered on the CS− (Spence, 1937).

Recently, we found such shifted generalization peaks in simple associative conditioning, due to pre-training exposure to various tones that induced an inhibitory neural gradient in primary auditory cortex (A1) (Miasnikov & Weinberger, 2012). This disjunction between the training frequency and the peak of the generalization gradient provides a unique opportunity to determine whether enhanced gamma activity during learning is tied to the CS frequency or to the peak of the generalization gradient, i.e., to the tone that is most strongly represented in memory. If increased gamma activity reflects increased neural synchrony that is part of the substrate of auditory frequency memory, then the greatest increase in gamma should be tightly linked to the strongest memory, regardless of the training frequency. We report here the analysis of changes in gamma activity that had been recorded during the previous study. The same changes in gamma were analyzed two ways: based on the CS training frequency and based on the peak of the generalization gradient.

2. Materials and methods

As the present analysis concerns EEG activity obtained in our previous study (Miasnikov & Weinberger, 2012), the materials and methods are mainly the same and will be summarized 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.

2.1. Subjects and surgery

Sixteen adult male Sprague–Dawley rats (412 ± 28 g, mean $\pm$ sd) received an epidural recording electrode (stainless steel screw) into the calvaria over the right primary auditory cortex and screws over the frontal sinus to serve as references, while under general anesthesia. A concentric bipolar stainless steel stimulating electrode was implanted into the right (ipsilateral) caudal nucleus basalis (NB) (ventrolateral internal capsule, ventromedial lateral globus pallidus and nucleus basalis of Meynert), sites of cholinergic

projections to the auditory cortex (Bigl, Woolf, & Butcher, 1982; Moriizumi & Hattori, 1992). Stimulation of the nucleus basalis (NBstm) produced EEG activation: shift from lower frequency, higher voltage waves (e.g., theta and alpha) to higher frequency, lower voltage waves (especially gamma) in all animals (e.g., Celesia & Jasper, 1966; Dtri, Rasmusson, & Semba, 1997, 1999; Duque, Balatoni, Dtri, & Zaborszky, 2000). Implants were covered with a dental acrylic pedestal containing two aluminum hex threaded standoffs for mounting a thermistor assembly; all leads were connected to a miniature socket that could be led to a commutator. Subjects were allowed 1–2 weeks to recover from surgery.

2.2. Experimental design

To study stimulus-specific implanted memory, we first obtained behavioral baseline responses to many pure tone frequencies, then trained animals with one frequency and 24 h after the end of training, presented again many test frequencies. This protocol yielded pre- and post-training behavioral frequency generalization gradients (FGG). Pre-training gradients were obtained twice (Days 1–2), 200 trials/day total for the nine test frequencies (1.00–27.64 kHz), presented randomly (inter-stimulus intervals [ISI] = 53.8 ± 5.8 s, mean $\pm$ se). Day 2 behavioral data were used for the pre-training baseline because they were obtained within 24 h of the start of training. Training was conducted on Days 3–5. Each training trial consisted of a 2.0 s CS tone (3.66 kHz, 70 dB) followed after 1.8 s by NBstm overlapping the last 200 ms of CS presentation (CS–NBstm interval = 1.8 s), 200 trials/day (ISI = 54.5 ± 6.6 s, mean $\pm$ se). A post-training gradient was obtained on Day 6 (ISI = 51.3 ± 2.6 s, mean $\pm$ se) (Fig. 1A). The effect of pairing the CS with NBstm on memory was determined by subtracting the pre-training FGG on Day 2 from the post-training FGG on Day 6, yielding a difference frequency generalization gradient (Δ FGG) (see Section 2.4). A non-associative control group was not included because all previous studies of NB-induced memory implantation have shown that the effects of pairing tone with NBstm (tone–NBstm) are associative (McLin, Miasnikov, & Weinberger, 2002a; Miasnikov, Chen, Gross, Poytress, & Weinberger, 2008; Miasnikov, Chen, & Weinberger, 2006, 2008, 2011; Weinberger et al., 2006).

2.3. Stimuli

Training and testing took place while subjects rested quietly in an acoustically damped box ($23 \times 23 \times 31$ cm) contained in a double-walled acoustic chamber (Industrial Acoustics Co., Bronx, NY). Acoustic stimuli were 9 pure tones, 1.00–27.64 kHz, separated by ~ 0.58 octaves (2.0 s duration, cosine 10 ms rise/fall time [10–90%], 70 dB SPL), produced by Tucker–Davis Technologies (TDT, Alachua, FL) System 3 components, delivered via calibrated speakers positioned ~ 35 cm above the box floor. NBstm was a 0.2 s train of 100 Hz pulses, pairs of 0.2 ms opposite polarity, 100 μ A (S88 stimulator and PSIU6 isolation units, Grass Instrument Co., Quincy, MA). NBstm was subthreshold to affect ongoing or initiate new behavior, as observed in video monitoring.

2.4. Respiration behavior: state control, recording and analysis

To assess the implantation of memory, we measured disruption of the ongoing pattern of regular respiration by all of the tones, before and after training. Respiration was detected as breathing-related thermal fluctuations by a glass-encapsulated thermistor attached to a lightweight pedestal-mounted assembly pre-adjusted in such way that a sensor is positioned in front of a naris. The amplified signal was fed to an ADC module, stored in a computer, and the autocorrelation function (AC) was calculated

Fig. 1. Protocols for the presentation of tones and NB stimulation, behavioral state control and quantification of changes in ongoing respiration. (A) Detailed temporal relationships of stimuli for the various phases of the experiment: delivery of test tones (Days 1, 2 and 6) and CS tone paired with NBstm (Days 3–5). (B) Examples of measures of respiration/EEG corresponding to major behavioral states: quiet waking, exploring/grooming, slow-wave sleep and REM sleep. Shown are the EEG from primary auditory cortex (line 1) and respiration records (line 2). (B) During quiet waking (quiescent state), which was the state when stimuli were presented during testing and training, the EEG is less desynchronized (B1); the animals are not moving and respiration is regular and can be easily disrupted by tones (thick horizontal bars). (B2) Throughout the experiment, the respiration autocorrelation function (AC) was continuously calculated on-line over 4-s long epochs. When a randomly selected inter-trial interval had passed, the software compared the current value of the AC ($AC = 0.89$ for this particular trace) with pre-selected thresholds ($0.700 \leq AC \leq 0.975$) and triggered a stimulus when that criterion was satisfied. (B3) Quantification of a regular sinusoidal baseline (first 4 s) respiration record disrupted by CS tone presentation 24 h post-training. The “Respiration Change Index” (RCI, see Section 2) is sensitive to both increases and decreases in signal amplitude and frequency. The shaded area indicates the first 13-s portion of the peri-stimulus respiration record containing the majority of the tone-evoked change in respiration. The RCI values found within this epoch were used in the behavioral data analysis. (C–E) The behavioral states when test/training stimuli were not presented. (C) During periods of ongoing activity such as exploration or grooming, while the EEG is low-voltage fast (C1), the respiration pattern lacks regularity ($AC = 0.01$ for the trace shown) and is represented by the wide range of waveform shapes and amplitudes due to the variable depth of breathing supporting whole body movements and more nimble movements of naris affecting the flow of warm air during exhalation captured by the thermistor (C2). (D) During deep slow-wave sleep (SWS) the EEG has higher voltage, lower frequencies (D1); animals are not moving and respiration is extremely regular ($AC = 0.97$ for the trace shown) (D2). (E) During REM sleep, the EEG is low-voltage fast (E1) and breathing is shallower (hence, lower amplitude) and less regular ($AC = 0.34$ for the trace shown) (E2).

on-line. The AC window was 1.2 s wide for the 4 s epoch of analysis. As such, it always contained at least one peak and at least one trough; the values of the first peak and first trough were used in subsequent calculations.

The AC was used to present tones only when the subject was in a quiescent behavioral state, defined as four consecutive seconds of $0.700 \leq AC \leq 0.975$. This state control avoided giving stimuli when

very high levels of ACh were released, as during exploration or paradoxical sleep, or very low levels, as during slow-wave sleep (Giovannini et al., 2001; Jasper & Tessier, 1971), to prevent ceiling or floor effects (Fig. 1B–E).

The collected data were used to calculate a “Respiration Change Index” (RCI) on a second-by-second basis: $RCI_i = (|Post_i - Pre|) / (Post_i + Pre)$, where Post and Pre were the values of the power of

the respiration signal (McLin, Miasnikov, & Weinberger, 2002b; McLin et al., 2002a). An RCI value of zero would indicate no change and a value of 1.0 would indicate complete cessation of respiration. This index is sensitive to increases and decreases of both frequency and amplitude of respiration.

An example of tone-elicited disruption of respiration and its RCI quantification is provided in Fig. 1B. The nine test frequencies were presented before and after training. Each RCI value for each frequency and each subject was averaged and expressed as a “frequency generalization gradient” (FGG). Because respiration is a sensitive behavioral measure, and therefore can be disrupted by tones before training, pre-training frequency response profiles were obtained and compared to post-training FGGs. (Technically-speaking, “stimulus generalization” cannot occur before training as there is no training stimulus from which to generalize; rather, the pre-training behavioral profile actually constitutes a “behavioral tuning function”. For simplicity of narrative, we use “FGG” for pre- as well as post-training frequency responses.)

The behavioral respiration responses were averaged across the group as a function of *absolute acoustic frequency* for pre-training (Day 2) and post-training (Day 6) sessions. As noted above, the pre-training FGG (Day 2) was subtracted from the post-training FGG (Day 6) to yield the “difference frequency generalization gradient” (Δ FGG). This measure revealed the magnitude and frequency specificity of the effects of pairing the CS tone (3.66 Hz) with stimulation of the nucleus basalis.

As explained in the Introduction, the goal of this paper is to determine if learning-related changes in gamma power are most closely linked to the training (CS) frequency or to the frequency that has gained the greatest increased strength through learning. Therefore, the same brain-behavioral data were analyzed in two ways: (a) on the basis of absolute frequency, focusing on the CS frequency (“Absolute Frequency Basis”); (b) on the basis of the peak of each individual Δ FGG regardless of their absolute frequencies (“Peak Δ FGG Basis”). Comparison of these analyses can be conducted only for animals in which the peak of their Δ FGGs was not at the CS frequency. In the case of animals for which the peak of their Δ FGGs was at the CS frequency, it is impossible to determine which factor is critical (see Section 3.3). Statistical analyses used IBM SPSS statistics v.20 software (SPSS, Chicago, IL).

2.5. Recording and analysis of the EEG

The ongoing EEG was recorded by a DAM-50 pre-amplifier (1–1000 Hz, 1000 $\times$, WPI, Sarasota, FL) linked to an A/D converter of a Power 1401 System (CED, Cambridge, England, UK) and stored on a computer. Power in various EEG bands was analyzed before (Day 2) and after training (Day 6) using Fast Fourier Transform (FFT). Experimental records from Spike 2 (5.15, CED) data files were imported into a PostgreSQL (9.2) database (open source). FFT (RMS, Root Mean Square, power, $1.024 \text{ s} \times 0.98 \text{ Hz}$ bins; 24 ms/1024 ms, 2.3% window overlap) for respiration and EEG were computed using functions written in Python (open source). A Hanning window was applied to the waveform data in each time bin. The FFT data were also stored in the database. Power Change Index (PCI) values were computed and stored in the database using SQL (Structured Query Language) queries. (The database was queried from MATLAB [R2011a] using a Java and JDBC [Java Database Connectivity] interface and the figures were made.) The spectrum “pre-whitening” was performed within the 0–55 Hz frequency range via calculating the PCI values. We determined a Power Change Index (PCI) by subtracting pre-training from post-training power values according to the following formula: $\text{PCI}_i = (\text{Post}_i - \text{Pre}_i) / (\text{Post}_i + \text{Pre}_i)$ (Miasnikov et al., 2006); a negative value would indicate a decline and a positive value would indicate a rise in power relative to its pre-stimulus baseline. The PCI (also

referred to as the “Modulation Index”, e.g., Zinke et al., 2006) is a robust measure of stimulus-induced cortical activation manifested by the rising power of high- and falling power of low-frequency oscillations. The current report focuses on gamma band activity (30–55 Hz). For comparison with a lower frequency part of the EEG spectrum, we also analyzed the theta and alpha bands together (4–15 Hz).

3. Results

3.1. Behavior

Pairing tone and NBstm produced some significant changes from the pre-training (Day 2) respiratory responses. Fig. 2A presents group pre- and post-training tone frequency generalization gradients (FGGs). Prior to training, responses were not uniform but were greatest at 8.22 kHz for the group. Regardless, as the tones used both pre- and post-training were identical, it is the difference between the pre- and post-FGGs that reveals the effects of training.

The post-training FGG did not differ from the pre-training gradient at the most sensitive frequency of 8.22 kHz, or any other frequency except that of the CS frequency of 3.66 kHz ($p < 0.01$,

Fig. 2. Group pre/post-training behavior. (A) Group mean respiration responses shown as frequency generalization gradients (FGG) (mean $\pm$ se) for all test tone frequencies for the group of 16 subjects pre- and post-training. Maximum pre-training response was to 8.22 kHz. Nevertheless, there was no significant change in respiration at this frequency following training. In contrast, note the significant pre- to post-training augmentation of behavioral responses only to the CS (3.66 kHz, $p < 0.01$, 2-tailed here and on all other tests unless otherwise noted) and at the adjacent lower frequency (2.44 kHz, $p < 0.02$; post hoc Univariate and Within-Subject Contrast tests, Doubly Multivariate Repeated Measures Model). (B) The peak of the group Δ FGG (post- minus pre-training, mean $\pm$ se) was not at the CS training frequency (3.66 kHz), but at 2.44 kHz. Statistically significant paired comparisons are indicated by asterisks. The CS frequency on the abscissa is outlined by a frame in both plots. The presented plot is a modification of Fig. 5 in Miasnikov and Weinberger (2012).

2-tailed test here and elsewhere unless otherwise noted), and its lower neighbor of 2.44 kHz ($p < 0.02$). There were no significant changes for any other frequencies (all $p > 0.05$) (Fig. 2A). Fig. 2B presents the effects of training, i.e., the difference gradient (Δ FGG) (post- minus pre-training). Note that its peak is *not* at the CS frequency of 3.66 kHz, but at 2.44 kHz. Thus, while behavioral responses to the CS were significantly increased after training, so too were responses to 2.44 kHz, which was the peak of the Δ FGG.

As the maximum change in response was not at the CS frequency, it was possible to determine if changes in EEG power, particularly for the gamma band, were most strongly linked to the CS frequency or to frequency that elicited the maximum response

(peak of the Δ FGG, i.e., gained the greatest strength through learning).

3.2. Plasticity of EEG bands and general relationship to behavior

3.2.1. Changes in EEG bands across frequency

Fig. 3 shows examples of EEG responses obtained post-training (Day 6) to 2.44 kHz (Fig. 3A) and 3.66 kHz (Fig. 3B), i.e., the tones that produced significant increases in behavioral response after training. Note the increase in high frequency activity starting at tone onset (Fig. 3A1 and B1). Records filtered for the gamma band (30–55 Hz) at the same (Fig. 3A2 and B2) and an expanded time

Fig. 3. Examples of post-training EEG responses to (A) 2.44 kHz and (B) 3.66 kHz, showing that both frequencies induced increased gamma oscillations (compare pre-tone vs. during tone activity). (A1) “Raw” (1–55 Hz) and (A2, A3) digitally filtered (30–55 Hz) waveforms. Thick horizontal bars indicate tone presentation. (A3) A higher temporal resolution of (A2), most clearly showing increased gamma amplitude during the tone. (B) Parallel examples for the CS tone of 3.66 kHz. The structure of the plot is the same as in (A). Note that the increase in gamma activity was due to increased gamma band oscillations, rather than to other potential sources that might have had power within the gamma band, such as muscle activity (EMG) or other artifacts.

base (Fig. 3A3 and B3), show that this shift in dominant frequency spectrum involved an increase in gamma band oscillations for both tones.

Fig. 4 presents group averages of spectral EEG power across all nine test tones, during pre-training (Day 2), post-training (Day 6) and their difference (post- minus pre-training). During pre-train-

Fig. 4. Spectro-temporal (S-T) EEG bands response characteristics before and after training, and their differences. (A) Profiles of combined responses to all 9 test frequencies before (Pre, Day 2), after (Post, Day 6) and the effects of training (Post-Pre, Day 6–Day 2). S-T diagrams show that before training, the auditory cortical responses were dominated by tone-elicited increased power at higher frequencies (~30–55 Hz, gamma) and more prolonged reduced power at lower frequencies (~4–15 Hz, theta and alpha), with increased power that ramped up over time at the lowest band (~1–4 Hz, delta). Post-training, gamma increased while theta/alpha decreased. The effects of training are seen in the Post-Pre S-T diagram; gamma power was substantially increased both in level and duration during the first 5 s following tone onset, while theta/alpha was decreased and delta power did not change. The black bar denotes the 2.0 s tone presentation and the vertical dashed lines denote the 5.0 s period starting at tone onset during which most of the changes in power developed. (B) Quantification of power change from pre-tone baseline (Power Change Index [PCI], Section 2.4) in the gamma (red) and combined theta/alpha (T/A, blue) bands (mean $\pm$ se). The “Pre” plot shows that the largest portion of the T/A decreased response was limited to the first 5 s, while the increased gamma response is briefer, confined largely to the 2 s tone duration. The pairing procedure (“Post”) intensified each of these opposite changes, with both increasing in magnitude and duration. The differential response plot (“Post-Pre”) confirms the effectiveness of tone–NBstm pairing; gamma power increased in magnitude and lasted for 5 s while T/A power declined in magnitude and increased in duration, lasting for the 15 s recording period (note difference in scaling of ordinate). The EEG PCI index is biased towards negative values providing negative baselines (Pre and Post) but the bias has been eliminated on differential plots (Post-Pre). (C) Scattergram of the actual alpha (3.42–9.28 Hz, x-axis) vs. theta (9.28–15.14 Hz, y-axis) responses shown in (B). The points represent averaged responses to each of the nine tone frequencies used in the study. There was a significant positive linear correlation ($r = 0.81, p < 0.01$) between these two EEG frequency bands (see also McLin et al., 2003). As power within the two bands changed together, we combined the two into a single T/A low frequency band.

ing, tones elicited a several second decrease in low frequency power (~ 5 – 20 Hz) and a very brief increase in higher frequency (30–55 Hz, gamma) power (Fig. 4A). Twenty-four hours after the end of training (Day 6), the same general pattern was evident, except that the decrease in low frequencies was intensified, as was the increase in the gamma band. The effects of training are seen most clearly in the difference graph: low frequency power was reduced markedly during the first 5 s following tone onset, and remained lower for the 15 s shown on the plot. Gamma band power was increased substantially during the first 5 s epoch but was not changed thereafter. Quantification of these data are provided in Fig. 4B; the analysis of low frequency power is hereafter confined to the combined theta/alpha (T/A) band (4–15 Hz). The decrement in T/A power and the increment in gamma power are quite evident. Fig. 4C provides the rationale for merging the theta and alpha bands into a single T/A band. The changes (Post minus Pre) in power within these two bands were significantly positively linearly correlated ($r = 0.81$, $p < 0.01$) indicating the similarity in function at least for the employed learning task. This finding replicates and extends previous findings of decreased power in these two spectral components of the EEG following tone–NBstm pairing (McLin et al., 2003).

3.2.2. Frequency specificity of changes in EEG bands and behavior

Although these global data reveal opposite training effects on gamma and T/A power across acoustic frequency, they do not provide information about the stimulus specificity of such plasticity. This information is provided in Fig. 5 as changes in frequency tuning for the gamma and T/A bands. (The behavioral Δ FGG is also shown for comparison.)

The group average for the gamma band showed significantly increased power at and around the CS (1.50 kHz, $p < 0.02$; 2.44 kHz, $p < 0.001$; 3.66 kHz = CS, $p < 0.002$; 5.49 kHz, $p < 0.001$; 8.22 kHz, $p < 0.03$). Lower and higher frequencies did not develop such increases (1.00, 12.31, 18.45 and 27.64 kHz; all $p > 0.05$). The gamma band difference function is similar to the shape of the Δ FGG mem-

ory function (dashed line) to which it is significantly correlated ($r = 0.76$, $p < 0.02$).

There was a broad significant decline in power for T/A at and around the CS (1.50 kHz, $p < 0.001$; 2.44 kHz, $p < 0.001$; 3.66 kHz = CS, $p < 0.001$; 5.49 kHz, $p < 0.02$; 12.31 kHz, $p < 0.003$), but no change at the lowest (1.00 kHz) or higher frequencies (8.22, 18.45 and 27.64 kHz, all $p > 0.05$). The T/A difference function mirrors the shape of the Δ FGG memory function with which it is inversely correlated ($r = -0.87$, $p < 0.005$).

Therefore, both training induced decreased T/A power and increased gamma band power were significantly related to changes in the behavioral frequency generalization gradient.

3.3. Variability of individual peaks of behavioral frequency generalization gradients

Despite the significant correlation between frequency-specific behavior and changes in EEG power in both the gamma and T/A bands, averaging based on absolute acoustic frequency may not reveal the *closest* relationship between the plasticity of EEG power and the *specificity of implanted memory*. Thus, if individual memories differed across the cohort, i.e., if the peaks of the Δ FGGs differed between subjects, then the group average might underestimate the strength of the actual relationship between changes in gamma or T/A and behavior. Therefore, we asked whether the group average adequately represented the individual behavioral frequency generalization gradients. A two-way ANOVA (frequencies $\times$ subjects) for the effects of training disclosed that behavioral responses differed across frequency ($F_{(8,3174)} = 14.967$, $p < 0.001$), as was fully expected. More importantly, this analysis also revealed that subjects differed among themselves in their responses to tones ($F_{(15,3174)} = 7.207$, $p < 0.001$), and further that there was an interaction between the factors of subjects and frequencies ($F_{(120,3174)} = 1.310$, $p < 0.02$). Inspection of individual Δ FGG functions revealed that although each of the functions

Fig. 5. Specificity of changes across acoustic frequency for brain and behavior. Training induced changes in gamma and T/A power (right ordinate) are compared to implanted frequency memory (same Δ FGG as shown in Fig. 2B; left ordinate). Note the different scales and baselines specific for behavior (dotted) and EEG power (solid). The group average for gamma yielded a positive frequency tuning function that peaked at 2.44 kHz (not the CS) and was significantly greater than zero at and around the CS (Doubly Multivariate Repeated Measures ANOVA, Univariate and Within-Subject contrasts tests: 1.50 kHz, $p < 0.02$; 2.44 kHz, $p < 0.001$; 3.66 kHz = CS, $p < 0.002$; 5.49 kHz, $p < 0.001$; 8.22 kHz, $p < 0.03$). There were no significant changes at either extreme of the test frequency range (1.00, 12.31, 18.45 and 27.64 kHz; $p > 0.06$). The shape of the gamma tuning function (mean $\pm$ se) is similar to the Δ FGG memory function ($r = 0.76$, $p < 0.02$). The T/A group average tuning function (mean $\pm$ se) was negative, with a “peak” (trough) at 2.44 kHz and was significantly reduced at most frequencies, encompassing the CS (1.50 kHz, $p < 0.001$; 2.44 kHz, $p < 0.001$; 3.66 kHz = CS, $p < 0.001$; 5.49 kHz, $p < 0.02$; 12.31 kHz, $p < 0.003$). The lowest and highest frequencies were not significantly different (1.00, 18.45 and 27.64 kHz; $p > 0.05$), and neither was 8.22 kHz ($p > 0.05$). The T/A tuning function was negatively correlated with the Δ FGG memory tuning function ($r = -0.87$, $p < 0.005$).

Fig. 6. Comparison of changes in gamma and T/A power based on absolute frequency vs. based on individual Δ FGG peaks. (Inset) Distribution of the peaks of Δ FGGs. Note that only 5/16 animals (orange bars) exhibited the strongest memory for the training frequency of 3.66 kHz. The other eleven (green bars) showed a second cluster at the adjacent lower frequency (2.44 kHz, $n = 5$) or were spread across the spectrum from 1.00 to 27.64 kHz. Because of the variability in peaks of memory strength, the gamma and T/A tuning data were reanalyzed based on the positions of individual peak Δ FGGs. (A) S-T profiles and (A') quantification of changes (post- minus pre-training, 1st 5 s after tone onset, mean $\pm$ se) for gamma and T/A power based on responses to the CS frequency. (We focused on the first 5 s starting with tone onset, as this period encompassed the vast majority of change.) (B) S-T profiles and (B') quantification of changes (mean $\pm$ se) for gamma and T/A power based on peaks of their Δ FGGs. (1) Data for the entire group ($n = 16$), (2) data for animals with Δ FGG peaks not at the CS frequency ($n = 11$), and (3) data for subjects for whom the CS was the peak of their behavioral tuning function and therefore was also the peak of their Δ FGGs by definition. Black horizontal bars and vertical dashed lines in (A) and (B) denote tone presentation and 5 s analysis window, as in Fig. 4. Note: red arrows indicate critical statistical comparisons. The change in gamma power was smaller for Non-CS than CS subjects when their analysis was based on absolute frequency (A'2 vs. A'3, $p < 0.05$, 1-tailed), but was increased for Non-CS subjects when analyzed according to their Δ FGGs (B'2 vs. A'2, $p < 0.002$), eliminating their reduced gamma compared to the CS group (B'2 vs. B'3, $p > 0.05$). Overall, the findings show that increased gamma band oscillations are largest for the frequency that gained the greatest strength due to learning. Thus, the training frequency is not the determinant of maximal augmentation of gamma.

was tuned, the actual frequencies of the peaks varied broadly. Fig. 6 (inset) shows their frequency distribution. Only 5/16 animals had their peaks at the CS frequency, while 11/16 exhibited

strongest memory for other tones. Of these, the peaks of five were at 2.44 kHz while the peaks of the six remaining functions ranged from 1.00 to 27.64 kHz. We therefore conducted a further analysis

to determine if the relationships between gamma and/or T/A and behavior were stronger when based on the Δ FGG peak rather than based on absolute frequency.

3.4. EEG bands, gamma and T/A: absolute frequency vs. Δ FGG

Fig. 6 shows the effects of training on spectral-temporal profiles (post- minus pre-training) for gamma and T/A power based on responses to the CS frequency (Fig. 6A1) and based on peaks of the individual Δ FGGs (Fig. 6B1) for all animals ($n = 16$). Gamma was significantly larger for the latter than the former ($t_{(15)} = 3.808$, $p < 0.003$), indicating that analyses based only on the CS frequency underestimate the magnitude of gamma induced by learning (Fig. 6A'1 vs. B'1). Changes in T/A power did not differ statistically ($t_{(15)} = 1.150$, $p > 0.25$).

However, to fully understand the source, magnitude and specificity of this effect, it is necessary to separate data from animals for whom the CS was the peak of their generalization gradients from those for which a non-CS frequency was the tone that produced the greatest gain in strength due to learning. The rationale is that the peaks of the Δ FGGs for the “CS” subjects are the same as the CS frequency by definition, so these subjects cannot reveal whether maximum gamma, T/A or both are induced by the CS or by the tones that are at the peak of individual Δ FGGs. Therefore, the data were divided into two groups based on whether the peak of individual Δ FGGs was at the CS frequency ($n = 5$) or at a Non-CS frequency ($n = 11$). Next, we separately determined the magnitude of gamma and T/A changes elicited by the CS frequency (Fig. 6A and A', Absolute Frequency Basis) and by the tone that induced the largest response (peak) in the Δ FGGs (Fig. 6B and B', Peak Δ FGG Basis).

3.4.1. Absolute frequency

The first issue concerns the EEG power changes when the data are organized in the standard manner of grouping the subjects based on absolute acoustic frequency focusing on responses to the CS training frequency. Do the Non-CS and the CS groups differ? The increased power for the gamma band and decreased power for the T/A band are evident for the entire group (Fig. 6A1 and A'1). However, if gamma is more closely linked to the Δ FGG peak than to the CS frequency, then it should be smaller for the Non-CS group (Fig. 6A2 and A'2) than for the CS group (Fig. 6A3 and A'3). This proved to be the case ($t_{(14)} = 1.85$, $p < 0.05$ 1-tailed), indicating that analyzing the Non-CS group on the basis of absolute frequency that focuses on the CS provides a significant underestimate of magnitude of gamma increase during learning.

Although the T/A decrease based on the Δ FGG appears larger for the Non-CS group (Fig. 6A'2 vs. A'3), it failed to reach statistical significance ($t_{(14)} = 1.57$, $p > 0.05$ 1-tailed) for the first 5 s, but was significant across the entire 15 s period due to the tonic nature of reduction of power ($t_{(14)} = 2.22$, $p < 0.05$). Overall, these results show that animals whose peaks were *not* at the CS frequency had smaller changes in EEG power than those whose peaks were at the CS frequency, particularly for the gamma band. Therefore, group brain–behavior relationships were, indeed, not fully captured by basing data analysis on absolute acoustic frequency.

3.4.2. Δ FGG analysis

The next issue concerns the peaks of the individual generalization gradients, which differed across animals for the Non-CS group. Does analysis based on the Δ FGG yield a greater magnitude of change in gamma, T/A power, or both, than analysis based on absolute frequency? Yes, the Non-CS group did exhibit a significant increase in gamma power based on the peak Δ FGG (Fig. 6A'2 vs. B'2) ($t_{(10)} = 5.007$, $p < 0.002$). Thus, for subjects in which a non-CS frequency gained the greatest increased strength through learning,

analysis based on absolute frequency underestimates the relationship between gamma band activity and memory.

Interestingly, while the prior analysis based on absolute frequency had yielded a change in gamma that was significantly *smaller* for the Non-CS than the CS group (above), analysis based on the peaks of the Δ FGGs showed *no difference* between the two ($t_{(14)} = 0.63$, $p > 0.50$). In other words, basing the analysis on the Δ FGG for the Non-CS group eliminated its significantly smaller increase in gamma power vs. the CS group. This is additional evidence that analysis based on absolute frequency does not reveal the closest relationship between gamma and behavior (see Fig. 5).

Fig. 7. (A) Relationship of learning-induced increase in gamma to absolute acoustic frequency (bottom x-axis) and Δ FGG (top x-axis) for the Non-CS group ($n = 11$). Note that the peak of the gamma increase occurs at the peak of the Δ FGG (distance to peak = 0.0 octaves). In contrast, the peak gamma increase is not at the CS frequency (3.66 kHz, absolute frequency). The magnitude of difference in gamma between the peak Δ FGG and the CS is significant (asterisk, $t_{(10)} = 5.007$, $p < 0.002$). Only the peak Δ FGG developed a significant increase relative to the CS frequency. Gamma was significantly smaller at 2.44 kHz based on Δ FGG because 5 subjects had their original peak at this frequency (asterisk, $p < 0.05$). Specificity is further shown by the absence of any other significant differences. Univariate ANOVA (reference $\times$ octave distance to reference) where the reference was either the CS (absolute frequency) or a peak Δ FGG yielded no effect for the reference ($F_{(1,157)} = 0.896$, $p > 0.30$) but significant effect for the distance ($F_{(7,157)} = 2.420$, $p < 0.03$); the reference $\times$ distance effect was not significant ($F_{(7,157)} = 1.992$, $p > 0.05$). The Pair-wise comparison of the data at each distance relative to references yielded no significant effects for all other distances (Paired Samples t -test: -1.749 , $p > 0.05$; -1.166 , $p > 0.70$; 0.583 , $p > 0.80$; 1.166 , $p > 0.95$; 1.749 , $p > 0.80$; 2.332 , $p > 0.95$). (B) Scattergram of individual measures of gamma magnitude at the CS frequency (x-axis) vs. the gamma magnitude at individual peak Δ FGGs (y-axis). Black dots indicate subjects in Non-CS group and open dots indicate CS-group (peak of Δ FGG at the CS frequency). Note that 10/11 Non-CS subjects had clearly greater gamma induced at their individual peak Δ FGGs vs. the CS frequency ($p < 0.01$, Wilcoxon Sign-Rank test). The values for the CS subjects (shown for convenience) are necessarily on the diagonal of equal value because the peaks of their Δ FGG are at the CS frequency by definition.

There was no significant change in the T/A band for the Non-CS group, when data analyses were based on the Δ FGG vs. the absolute frequency ($t_{(10)} = 1.156$, $p > 0.25$). Therefore, in contrast to gamma oscillations, decreased power in the T/A band is not tightly linked to the acoustic frequency that gained the greatest strength through learning vs. the CS training frequency.

3.5. Specificity of findings based on absolute frequency and Δ FGG analyses to changes in gamma and T/A power

3.5.1. Gamma power

As analysis based on Δ FGG for the Non-CS group revealed a greater magnitude of increased gamma at the individual most effective frequencies (peaks of individual Δ FGGs) than analysis

based on the CS frequency, the major issue of *specificity* can now be addressed. If increased gamma activity reflects activity that is part of the substrate of specific auditory frequency memory, then the greatest increase in gamma should *match* the tone that gained the most strength in memory but should not match other frequencies.

Fig. 7A presents changes in gamma band activity (post- minus pre-training) across the Non-CS group both for absolute frequency and Δ FGG bases. Note that the peak of the increase in gamma does coincide with the peak of individual behavioral Δ FGGs. In contrast for the analysis based on absolute frequency, the peak is *not* at the CS frequency. As revealed in Fig. 6 (A'2 vs. B'2), the magnitude of increased gamma at the peak of the Δ FGG is significantly greater than at the CS frequency ($p < 0.002$). Reinforcing the conclusion that the greatest increase in gamma band activity occurs specifically at the frequency that gained the most strength through learning is the finding that gamma was *reduced* at the adjacent lower absolute frequency of 2.44 kHz (-0.583 octaves relative to peak Δ FGG, $t_{(9)} = 2.307$, $p < 0.05$). This reflects the fact that five subjects had the peak of their behavioral response gradients at 2.44 kHz (Fig. 6, inset). There were no other significant differences (all other

Fig. 8. Entire group ($n = 16$) data for the relationship of changes in EEG bands to behavior. (A) Gamma activity. Axes are the same as in Fig. 7. Adding the CS group to the Non-CS group does not change the findings (see Fig. 7); the peak of the gamma increase remains at the peak of the Δ FGG (distance to peak = 0.0 octaves) vs. the CS frequency (3.66 kHz). The magnitude of gamma at the peak Δ FGG is significantly greater than at the CS (asterisk, $t_{(15)} = 3.808$, $p < 0.003$). As in the case for the Non-CS group only, gamma was significantly smaller at 2.44 kHz ($p = 0.05$). Specificity remains evident in the absence of any other significant comparisons in gamma between absolute frequency and peak Δ FGG. Univariate ANOVA (reference $\times$ octave distance to reference) where the reference was either the CS (absolute frequency) or a peak Δ FGG yielded no effect for the reference ($F_{(1,237)} = 0.481$, $p > 0.45$) but significant effect for the distance ($F_{(7,237)} = 5.702$, $p < 0.001$); the reference $\times$ distance effect was not significant ($F_{(7,237)} = 1.308$, $p > 0.20$); nor were pair-wise comparisons (Paired Samples t -test: -1.749 , $p > 0.05$; -1.166 , $p > 0.65$; 0.583 , $p > 0.80$; 1.166 , $p > 0.90$; 1.749 , $p > 0.80$; 2.332 , $p > 0.95$). (B) Theta/alphas activity. In contrast to gamma, maximum decline in T/A activity was neither at the peak Δ FGG nor at the CS frequency, and there were no significant differences between the different methods of analysis.

Fig. 9. Relationships of peak frequencies in behavioral memory and gamma. (A) Distributions of occurrence of peak Δ FGG (open bars, same as shown in Fig. 6 inset) and peak gamma enhancement (closed bars) along the tone frequency axis. Note that only 3/16 of the animals exhibited the largest enhancement in gamma for the training frequency of 3.66 kHz, although the majority of gamma peaks ($4 + 3 + 5 = 12/16$) were found in the vicinity of the CS. Note the similarity between the two distributions: they did not differ statistically ($p > 0.70$, independent-samples Mann–Whitney U test; $p > 0.90$, two-sample Kolmogorov–Smirnov test), consistent with a close relationship. (B) Scattergram of the peak position of change in gamma (y-axis) vs. the peak position of change in behavioral memory (peak Δ FGG, x-axis) on a subject-by-subject basis. Dashed line: linear regression line estimate for all subjects; the linear correlation is significant ($r = 0.74$, $p < 0.01$). Solid line: linear regression line estimate for subjects with peaks that were closest to the CS; the linear correlation is greater ($r = 0.83$, $p < 0.001$). Open circles: the two subjects with peaks in Δ FGG found furthest away from the CS. Circles around the closed ones indicate that more than one subject occupied the same spot.

frequencies, $p > 0.05$), showing the specificity of the link between maximum increase in gamma and the peak of the behavioral Δ FGG (Fig. 7).

To what extent does this group level finding pertain to individual animals? Fig. 7B shows the relationship between the amounts of gamma at the CS frequency vs. at the peak Δ FGG. Note that 10/11 of the animals exhibited a greater gamma increase at peak Δ FGG than at the CS. The individual differences between the two measures were statistically significant (Wilcoxon, $p < 0.007$). Thus, regardless of the frequency at the peak Δ FGGs of animals in the Non-CS group, increases in their gamma band activity are greater than gamma induced by the CS training frequency.

As the foregoing comparison was based on the Non-CS group ($n = 11$), it might be that the specificity of the difference no longer obtains when all of the animals are considered together. Therefore, we combined the Non-CS group ($n = 11$) with the CS group ($n = 5$) and reanalyzed the data based on all the subjects ($n = 16$). The results for gamma are shown in Fig. 8A. As noted previously (Fig. 6A'1 vs. B'1), the magnitude of increase in gamma at the Δ FGG peaks is significantly greater than at the CS frequency ($p < 0.003$). The significant decrease in gamma at 2.44 kHz seen in the previous analysis of the Non-CS group also is evident for the entire group of all subjects ($t_{(14)} = 2.147$, $p = 0.05$). Also demonstrating specificity between maximum increase in gamma and behavioral peak of the Δ FGGs, there were no other differences in gamma for Δ FGG vs. absolute frequency analyses (all other frequencies, $p > 0.05$).

3.5.2. T/A Power

Fig. 8B shows the results of parallel analyses for the T/A band ($n = 16$), which had developed a decrease in power to most tones following training (Fig. 5). In contrast to the findings for the gamma band, analyses based on Δ FGG actually reduced the relationship between changes in the T/A band and behavior. First, the significant negative correlation between T/A and behavior based on absolute frequency ($r = -0.87$, Fig. 5) was lost ($r = 0.05$, $p > 0.10$). Second, the amount of decreased power at the CS frequency did not become larger, but was actually somewhat smaller, although not-significantly ($t_{(15)} = 1.150$, $p > 0.25$).

3.6. Gamma band activity and memory

If the maximum increases (peaks) in gamma band activity are a potential substrate of the frequency that gained the greatest strength through learning, then their distributions across subjects should not differ, regardless of the peak acoustic frequency. Fig. 9A shows the distribution of subjects for both measures. Note that only 3/16 of the animals exhibited the largest enhancement in gamma exactly at the CS frequency of 3.66 kHz. Nonetheless, the two distributions did not differ statistically ($p > 0.70$, Mann–Whitney U test).

Within-subject findings are presented in Fig. 9B. The scattergram shows a significant positive ($\text{tg } [\alpha] = 0.36$) linear correlation ($r = 0.74$, $p < 0.01$) between the frequencies at the peaks of behavior (Δ FGG) and gamma for all 16 subjects. Two were outliers. Therefore, the correlation was recalculated omitting these two subjects. The results remain a positive ($\text{tg } [\alpha] = 0.62$) linear correlation for subjects with response peaks that were closer to the CS ($r = 0.83$, $p < 0.001$).

The overall relationship between gamma activity and behavioral memory across frequency previously was determined on the basis of absolute frequency for the entire group ($n = 16$) (Fig. 5). The correlation was significant ($r = 0.76$, $p < 0.02$). The same relationship was calculated between gamma activity and memory based on the Δ FGG. The result is shown in Fig. 10. Their correlation was significant ($r = 0.84$, $p < 0.005$). Note in particular that the peaks of the behavior and gamma match.

4. Discussion

4.1. Resume of gamma findings

This report focuses on the relationship between associatively induced gamma band activity in sensory cortex and behaviorally validated memory. The latter was implanted by pairing a tone with stimulation of the nucleus basalis. Previously, increased gamma activity had been identified as a neural signature of association,

Fig. 10. Group ($n = 16$) gamma tuning (right ordinate) and change in respiration response (behavioral index of implanted memory, left ordinate), both based on the peak of individual Δ FGGs rather than based on absolute frequency. Note the different scales. The group peak of maximum respiration change is at the peak Δ FGG by definition. However, the peak of gamma tuning was free to develop at any octave distance from the behavioral peak. Nonetheless, note that the gamma peak coincides with the peak of the behavioral response, i.e., the largest increase in gamma power developed for the tone frequency that gained the greatest strength through learning. Also, the magnitude of the behavioral response based on individual Δ FGGs is about twice as large as it is when measured based on absolute frequency (~ 0.08 vs. ~ 0.04 units of Δ RCl, Fig. 2B, respectively), a difference that is statistically significant ($t_{(15)} = 3.808$, $p < 0.003$). Moreover, the correlation between the change in behavior and change in gamma power was larger for the analysis based on Δ FGG vs. absolute frequency ($r = 0.84$, $p < 0.005$ vs. $r = 0.76$, $p < 0.02$, Fig. 5, respectively). Thus, accounting for individual differences in the tone that gained the greatest strength through learning reveals a closer relationship between increased gamma power and implanted memory than the standard alternative approach based on the analysis of absolute training frequency.

e.g., when a sensory stimulus develops the ability to predict a reinforcer (Gruber, Keil, & Müller, 2001; Headley & Weinberger, 2011; McLin, Miasnikov, & Weinberger, 2003; Miltner et al., 1999). Such a neural correlate provides an important step in understanding the mechanisms underlying the acquisition and storage of information, and ultimately the production of adaptive behavior.

However, an enduring tacit assumption has been that the critical brain–behavior relationship is necessarily between the signal training stimulus and the increase in gamma band activity. Indeed, we shared this assumption until recently, when serendipitous findings provided a conspicuous reminder that what is best learned and remembered very often is *not* the training stimulus. In the case of simply pairing a tone with stimulation of the nucleus basalis, we observed that the peak of the difference generalization gradient (post-training minus pre-training, Δ FGG) was *not* at the CS frequency of 3.66 kHz, but at 2.44 kHz (Fig. 2). This “peak shift” had previously been accounted for by a pre-training inhibitory neural gradient produced by a habitatory decrement caused by repeated presentation of tones during the pre-training period (Miasnikov & Weinberger, 2012).

However, further detailed analyses of those behavioral data presented in this report revealed that while the behavioral group mean did exhibit the peak shift, there was also considerable variation of individual Δ FGG peaks across the cohort of 16 trained rats (Fig. 6 inset and Fig. 9A). The entire group could be subdivided into a small group of animals ($n = 5$) for which the individual peaks of behavioral change (post- minus pre-training FGGs) were at the CS frequency, and a larger group ($n = 11$) for which the individual peaks of behavioral responses were at various non-CS frequencies (Fig. 6 inset). Such variability provided an opportunity to determine whether the increase in gamma activity was more strongly associated with the CS frequency or with the frequency that had gained the greatest strength through learning.

Thus, we reanalyzed the data based on the peaks of the change in the individual generalization gradients for subjects whose greatest gain in memory was not at the CS. This revealed that they developed greater increases in gamma for their peak Δ FGGs than for the CS frequency (Fig. 6A/2 vs. B/2). This increase proved to be highly specific, occurring only at the peak Δ FGG. (The Δ FGG analysis yielded a significant *reduction* at 2.44 kHz which had a peak behavior in absolute frequency [Fig. 7A].) Moreover, a further analysis showed that within subjects this difference was highly reliable (Fig. 7B). Further, the Δ FGG analytic approach remained superior to the absolute frequency (CS) based approach even when those animals whose peak gamma was at the CS frequency ($n = 5$) were included (Fig. 8A). These findings demonstrate that maximal increased gamma band oscillations during learning is a signature of the stimulus that gained the greatest strength, not the training frequency. Further evidence that increased gamma activity indexes neural processes that could dictate specific memory was evident in the close relationships between the distribution of peaks in gamma and in behavior (Fig. 9A), the significant relationship between individual frequencies at peak behavior and peak gamma (Fig. 9B), and the match between the peak of the increase in gamma and peak of the increase in behavior, regardless of the absolute frequencies involved (Fig. 10).

4.2. Resume of theta/alpha findings

Initial analyses of the theta/alpha band based on absolute frequency indicated that a parallel decrease in T/A activity accompanies the conditioned increase in gamma activity (Fig. 5). This finding confirmed our previous results, also based on absolute frequency (McLin et al., 2003). However, when the behavioral data were analyzed at a finer grain based on individual peaks of Δ FGGs, the T/A decline in power no longer mirrored the rise of gamma

power. Unlike changes in gamma activity, there was no statistically significant improvement in the relationship between theta/alpha activity and memory (Figs. 6 and 8).

The fact that T/A power is not as closely linked to specific memory as is gamma power in this study should not be interpreted to indicate that the two bands are always independent. For example, within the hippocampal formation, theta oscillations modulate gamma activity during the learning of item–context associations (Tort, Komorowski, Manns, Kopell, & Eichenbaum, 2009) and across cortical regions, theta modulates gamma during auditory attention (Doesburg, Green, McDonald, & Ward, 2012). In the present study theta was not analyzed separately from alpha because of prior findings of parallel associative decreases in both bands (McLin et al., 2003). Their similar magnitude of decrease due to learning was verified in the present study (Fig. 4C). The general decrease in T/A power does indicate that the specific relationship between gamma power and memory is *not* simply an aspect of a general “cortical activation” pattern that may develop during learning. Rather, the results indicate that increased gamma is a *signature of acquired specific meaning* that is expressible in specific behavior. In contrast, the decrease in theta and alpha power appears to index processes yet undetermined that are not as closely involved as gamma in the stimulus features that enter into the contents of memory.

4.3. Relation to previous findings

Previously, we reported that memory implantation was accompanied by an increase in gamma activity and a decrease in theta and alpha activity (McLin et al., 2003). That study found that the group peak of the post-training generalization gradient was at the CS frequency; there was no observable peak shift. However, the previous study did not repeatedly present tones preceding training, and therefore did not involve habituation effects to various test tone frequencies that can account for peak shift (Miasnikov & Weinberger, 2012). Moreover, that previous study involved prolonged training (~15 consecutive days as it was customary in the field at that time, e.g., Kilgard & Merzenich, 1998). While the former study yielded very well ordered results, it also fostered the standard assumption that neural correlates of learning are necessarily specific to the training stimulus. This position, implicitly assumed since the beginning of research on neurophysiological correlates of learning and memory, fails to adequately account for the effects of prior experience or individual learning dynamics on current learning.

4.4. The cholinergic system, gamma, cortical plasticity and specific memory

The cholinergic system, engaging muscarinic receptors in the cortex, may be a mechanism that links three cardinal processes: (a) enhanced neuronal synchronization, as indexed by gamma activity, (b) specific cortical plasticity and (c) specific behavioral memory (Weinberger, 2003). For example, pairing a tone with stimulation of the cholinergic nucleus basalis (NBstm) produces associative shifts in frequency receptive fields (Bakin & Weinberger, 1996; Bjordahl, Dimyan, & Weinberger, 1998; Dimyan & Weinberger, 1999; Ma & Suga, 2003; Miasnikov, McLin, & Weinberger, 2001) and expanded representation in cortical frequency maps (Kilgard & Merzenich, 1998). NBstm and cholinergic agonists also increase gamma activity (Cape & Jones, 2000; Grossberg & Versace, 2008; McLin et al., 2002b; Metherate, Cox, & Ashe, 1992; Rodriguez, Kallenbach, Singer, & Munk, 2004), while tone paired with NBstm induces associative increased gamma activity (McLin et al., 2003). Most importantly, and less well known, tone paired

with NB stimulation also implants specific, behaviorally validated memory.

In a series of studies, using the sensitive behavioral measures of CS-elicited changes in ongoing heart rate or respiration, memory implantation has been shown to be associative and specific (McLin et al., 2002a), rapidly-acquired (Miasnikov et al., 2006), consolidated over time (Miasnikov et al., 2011; Weinberger, Miasnikov, & Chen, 2009) and is retained at least for weeks (Miasnikov et al., 2011). Implanted memory is not an artifact of putative local or spreading rewarding (Wilson & Rolls, 1990) or punishing stimulation because it is induced by low currents, producing brief EEG activation without overt behavioral change and the level of current controls the specificity of memory rather than the strength of learning (Weinberger et al., 2006). Also, NBstm inducing memory is motivationally neutral (Miasnikov, Chen, Gross, et al., 2008) and implanted memory is dependent on central muscarinic receptors (Miasnikov, Chen, & Weinberger, 2008). Therefore, the cholinergic system may play a pivotal enabling role in the formation of cortically-based associative memory.

4.5. Functional significance: a schema

As noted in the Introduction, gamma band activity is indicative of a particular mode of neural processing, specifically one in which neurons act in a synchronized manner. Coordinated spike activity can reflect the reorganization of the same number of neuronal discharges in a local area into “packets” or bursts of activity that tend to occur during the negative phase of gamma, that is, when extracellularly recorded gamma oscillations reflect maximal intracellular depolarization (Buzsáki, Anastassiou, & Koch, 2012). This activity pattern results in more effective communication with efferent target populations (Fries, 2005; Salinas & Sejnowski, 2001).

Given the previous evidence for the role of the nucleus basalis cholinergic system in gamma, specific cortical plasticity and the implantation of specific behavioral memory, we suggest the following schema. First, when the NB is activated during associative learning by circuits yet to be fully identified for all tasks (but in auditory fear conditioning, likely involving projections from the auditory thalamic magnocellular medial geniculate nucleus to the amygdala and then to the nucleus basalis (Weinberger, 2004, 2011), it releases ACh that engages cortical mAChRs. Second, mAChRs acting on cells and circuits that provide representations of the signal stimulus (e.g., CS in classical conditioning and S+ for instrumental learning) in primary (and other) sensory cortical fields strengthens responses to the signal stimuli in “non-CS” cells, thus increasing the population representing the CS. Enhanced representation of signal stimuli is observed as a shift of tuning, and if sufficiently extended across A1, increased area of its representation. At the same time, or shortly thereafter, ACh also increases coordinated cellular activity, observed as an increase in gamma power, initially locally. Third, the increase in gamma power, combined with the increase in the number of CS representational cells, exerts a stronger influence on target neuronal populations, some of which were also initially activated by other aspects of the learning situation, e.g., those encoding the reinforcer and contextual stimuli, interoceptive signals about bodily state, cells sensitive to the release of stress hormones, and cells involved in recall of similar experiences. *In toto*, these changes create a widely distributed network of neurons that essentially encode the entire learning experience. Fourth, targets involving networks underlying motor planning and execution will therefore become more strongly influenced by the representations of signal stimuli, increasing the probability that they will produce relevant behavior, i.e., overt evidence of associative learning and memory. Finally, we suggest that the

particular changes in synaptic strengths underlying differential plasticity and memory strength for various tonal frequencies are a reflection not only of the training stimuli but also of their relative strengths based on prior experiences, i.e., subjects are not *tabulae rasae*.

In the current NB-based studies, we bypass the circuitry between a reinforcer and the NB by direct stimulation of the latter, potentially initiating the subsequent hypothetical steps outlined above. Also, of importance, basic association in the present line of inquiry is revealed by the use of sensitive behavioral measures such as disruption of the regular pattern of respiration. Seeking evidence of implanted associative memory by recording an arbitrary instrumental response could also be accomplished by determining the effects of the tone paired with NB stimulation on an ongoing operant response.

4.6. General implications and future directions

The major implication of the current observations is that coordinated neural activity that develops during associative learning, and is indexed by increased gamma power, actually is a *substrate mode of processing for the formation of memory*. In so doing, it provides a novel explanatory path for both the *strength and specific content of (at least) associative memory*. Relative memory strength is indexed by the post-training magnitude of behavioral responses across the generalization gradient, more specifically across the *difference gradient* (ΔFGG), which reflects the effects of training on frequency response. Likewise, the specific content of memory is revealed by the profile of the ΔFGG , particularly the location of its peak. Both behavioral strength and specificity appear to be closely linked to gamma band activity. In fact, synchronized neuronal activity, as indexed by gamma, becomes a candidate mechanism underlying both memory strength and memory specificity.

Future studies will need to incorporate the various frequency bands of gamma. Thus, although a strong relationship between the gamma band of 30–55 Hz and memory was found, higher frequency activity, also considered to be gamma, has been implicated in cortical function and cognition (Edwards, Soltani, Deouell, Berger, & Knight, 2005), even to the point of being differentially specific to various cortical lamina (Ainsworth et al., 2011). Moreover, future studies should increase the ability to determine the spatial domain of gamma, by the use of multiple indwelling electrodes, which would also provide for the determination of important local and distal network operations such as phase synchronization, which has been implicated in memory (Fell & Axmacher, 2011).

From a methodological perspective, there is a renewed conceptual basis for determining what is actually learned in a learning experience, rather than continuing with the assumption that a statistically significant neural signature necessarily identifies a specific substrate of memory. Thus, the standard analysis based on the training stimulus (i.e., the CS and absolute frequency in the present case) exhibited a significant correlation between gamma activity and behavior. However, it was not the strongest relationship. This proved to be the relationship between maximum increase in gamma and the signal that gained the greatest strength through learning. Therefore, caution should be exercised if one is interested not merely in finding a neural correlate (e.g., of the training stimulus), but finding the strongest neural correlate. Future studies of neural signatures of learning and memory, even if unable to obtain generalization information to determine the relative memory strengths for stimuli along a dimension, would gain perspective and influence by making clear that a closer relationship between brain and memory might be revealed by individualized analyses based on “what was learned”, i.e., the contents of memory.

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