Research

Precise memory for pure tones is predicted by measures of learning-induced sensory system neurophysiological plasticity at cortical and subcortical levels

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Despite identical learning experiences, individuals differ in the memory formed of those experiences. Molecular mechanisms that control the neurophysiological bases of long-term memory formation might control how precisely the memory formed reflects the actually perceived experience. Memory formed with sensory specificity determines its utility for selectively cueing subsequent behavior, even in novel situations. Here, a rodent model of auditory learning capitalized on individual differences in learning-induced auditory neuroplasticity to identify and characterize neural substrates for sound-specific (vs. general) memory of the training signal's acoustic frequency. Animals that behaviorally revealed a naturally induced signal-"specific" memory exhibited long-lasting signal-specific neurophysiological plasticity in auditory cortical and subcortical evoked responses. Animals with "general" memories did not exhibit learning-induced changes in these same measures. Manipulating a histone deacetylase during memory consolidation biased animals to have more signal-specific memory. Individual differences validated this brain-behavior relationship in both natural and manipulated memory formation, such that the degree of change in sensory cortical and subcortical neurophysiological responses could be used to predict the behavioral precision of memory.

[Supplemental material is available for this article.]

Variability in learning, memory, and behavior derives from multiple factors (Patchett 1977; Engineer et al. 2004; Toledo-Rodriguez and Sandi 2007, Bieszczad and Weinberger 2010a,b, 2012; Strait et al. 2012; Truong et al. 2014; Stegman et al. 2019) each with their own neural generators that have distinct effects on function (Schreiner and Polley 2014; Weinberger 2015; McGann 2015). Therefore, a powerful use of within-group variability is to explain magnitude-of-effect in individual behavioral performance by differences in learning-induced neural function. Indeed, a major goal in behavioral neuroscience is to understand brain-behavior relationships enough to gain the ability to manipulate function and drive behavior in a desired direction by promoting neuroplasticity (Bieszczad et al. 2013; Tyler et al. 2017; Takesian et al. 2018). However, to harness plasticity mechanisms in a useful way after the form of experience-induced plasticity between groups is identified, its function and magnitude of effect must be determined at the level of the individual. Therefore, individual differences in learning and memory provide the opportunity to use variability to understand brain-behavior relationships.

Previous work has identified distinct functions for different forms of auditory system plasticity related to the behavioral relevance of acoustic frequency (Bieszczad and Weinberger 2010a,b, c; Froemke et al. 2013; Jeanne et al. 2013; Znamenskiy and Zador 2013) including at different time scales (Weinberger et al. 1991; Ohl et al. 2001; Fritz et al. 2003). For example, in the auditory cortex, rapid changes in neural tuning properties correlate with selective attention to sound frequency during active tasks (Fritz et al. 2003; Francis et al. 2018), while long-term changes in tuning bandwidth may be related to frequency-specific memory over time (Recanzone et al. 1993; Shang et al. 2019). Subcortical neurons in the lemniscal auditory nuclei also exhibit changes in tuning properties to represent behaviorally relevant sound frequencies across the lifespan (Suga 2012; Terreros and Delano 2015). Furthermore, the profound auditory cortical modulation of subcortical sound processing (Luo et al. 2008; Xiong et al. 2009; Suga 2012) suggests that auditory system plasticity interacts at multiple levels to serve high-order functions beyond simple feature coding of acoustic frequency. As such, noninvasive auditory brainstem neurophysiological responses (ABR) in humans that capture system-wide processing of sound can predict individual high-order auditory skills that involve listening-in-noise and language intelligibility (Thompson et al. 2017; White-Schwoch et al. 2017).

Importantly, adult learning-induced cortical plasticity is not merely a reflection of encoded sound-stimulus statistics; instead it reflects task-related rules that support adaptive behavior (Polley et al. 2006; Bieszczad and Weinberger 2010b). Furthermore, and perhaps the strongest reason for extending research to the individual, is that individual subjects seldom form identical memory, even within a group that has undergone the same sound-frequency training with *identical* task rules (Bieszczad and Weinberger 2010b;

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Bieszczad et al. 2013; Weinberger et al. 2013). Therefore, other genetic or experiential factors must explain variable outcomes. However, such individual differences create an opportunity to discover neural plasticity that can account for behavioral functions. For example, a neural change in individual subjects that matches the specific sensory content of the individual subject's memory can validate the candidate as a neural substrate of those specific contents. Thus, the auditory system may provide a substrate for the specificity of acoustic content of memory, albeit only one part of the complete memory, which is likely distributed in other modalities of the brain and in various forms.

Here, the auditory content of memory is defined in the highly tractable acoustic frequency domain, where animals may remember a sound cue *specifically* as the particular frequency heard during training with reward. A precise memory for acoustic frequency is *specific* to the acoustic frequency of the training signal. This is in contrast to memory for sound that is *generalized* across acoustic frequency, in which animals do not remember acoustic frequency per se, as the mere presence of a sound signal will effectively cue behavior. Indeed, previous studies have shown that auditory memory spans a continuum from signal-specific to general (Dunsmoor et al. 2017, Stegman et al. 2019), with potential substrates of these individual differences in both auditory cortical (Wigestrand et al. 2016), and nonauditory circuits (Ghosh and Chattarji 2015; Reznik and Paz 2015). To detect individual differences in memory along the frequency-*specific* to *general* continuum, this study used a simple appetitive auditory operant task in which reward is contingent on the presence of a single sound frequency cue called the "signal tone". However, the task can be solved without attending to frequency per se. Animals could use one of two strategies: (a) to learn and remember to respond only to the training sound frequency (i.e., a frequency-*specific* strategy), or (b) to learn and remember that a response to an auditory stimulus delivers reward (i.e., a frequency-*general* strategy). This approach has been used to successfully determine brain-behavior relationships that explain individual variability despite identical training (Bieszczad et al. 2010c; Bieszczad et al. 2015). Given that learning experiences with sound can alter the frequency-tuning properties of both cortical and subcortical auditory neurons, this study is the first to determine whether learning-induced auditory system plasticity in cortical and subcortical areas are neural substrates for the frequency-specificity of memory. We predicted that a form of frequency-specific neurophysiological plasticity would emerge at a group-level analysis, which could be promoted by manipulating a molecular epigenetic control, and that individual differences would validate this form of plasticity's behavioral function for frequency-specific memory.

Results

Early auditory system plasticity predicts individual differences in memory precision

To determine the function of auditory system plasticity for memory, auditory brainstem responses (ABRs) were recorded from a group of six adult, male rats before and after they learned a simple single-tone auditory operant task (tone-reward training; see Materials and Methods). Rats were trained with a 5.0 kHz signal tone that predicted availability of a water reward after an operant response (bar-press), but were otherwise untreated (Fig. 1A). After reaching asymptotic performance, animals were given a memory test (Fig. 1B). In this test, rats were randomly presented with the 5.0 kHz signal tone and four novel tones that differed in acoustic frequency to determine which individuals responded selectively only to the trained sound frequency (specific memory) versus which individuals that responded broadly across acoustic frequency (general memory) (see the section "Behavioral procedures and analysis" for the determination of specific vs. general memory). Despite being trained identically in this single-tone task, animals varied in the distribution of responses among test tone frequencies. To identify a potential candidate form of early auditory system plasticity for memory, the change in response amplitude of the first peak (PW1) in the signal tone-evoked ABR was calculated for each individual from a recording session outside of the training context, which was made once before training, and again after reaching high levels of performance in training (Fig. 1C). One animal that responded selectively to the trained sound at Memory Test, was characterized to have remembered the signal tone (5.0 kHz) *specifically*. This animal showed the largest PW1 peak amplitude increase (M = 71.64%), while other animals showed less specificity and variably smaller changes in PW1 amplitude (M = −1.01, SE = 13.52). Importantly, comparing individual PW1 amplitude changes against an animal's own proportion of bar presses made to the signal tone (vs. novel tones) during the Memory Test revealed a significant positive correlation: the greater the increase in peak amplitude, the greater the specificity of behavioral responses to the signal tone at memory test ($r = 0.842$, $P = 0.035$) (Fig. 1D). These findings support a function of this form of ABR plasticity is to underlie long-term sound-specific memory. A subsequent experiment capitalized on a known molecular mechanism of long-term memory formation (McQuown and Wood 2011; Bieszczad et al. 2015) that we hypothesized would drive interacting forms of plasticity across the auditory system toward memory substrates for more frequency specific and selective behavior.

Inhibition of an epigenetic regulator drives neural substrates toward frequency-specific memory

Epigenetic mechanisms, such as histone deacetylase 3 (HDAC3), have been recently studied for their strong influence on the formation, strength, and persistence of long-term memory (Campbell and Wood 2019), including for sensory cues (Phan and Bieszczad 2016). Inhibition of class I HDACs like HDAC3, which releases HDAC-mediated constraints on gene expression, has been found to enhance the specificity of auditory memory across species (McQuown and Wood 2011; Phan et al. 2017; Shang et al. 2019) including humans (Gervain et al. 2013). Therefore, HDAC3 inhibitors may be useful tools to determine substrates of precise memory. Here, we confirm that HDAC3 inhibition enhances the frequency-specificity of auditory memory (Fig. 2). Individual curves (Supplemental Fig. S1) were analyzed in order to categorize animals as exhibiting specific or general memory. Frequency-specific memory was analyzed and validated in three ways: (1) *Behavioral contrast scores:* To determine memory specificity for the signal tone, contrast measures of relative to response to the signal tone, versus novel tones, were calculated as follows: (a) Percent of responses to signal tone—(average percent of response to distant tones) and (b) Percent of responses to signal tone—(average percent of responses to nearby tones). Positive values indicate greater responding to the signal tone than novel tones. Only individuals with *positive* contrast values for both distant and nearby tones (relative to the signal tone) were labeled as those with frequency-specific memory (see Supplemental Fig. S6 for individual behavioral contrast scores). We find a significant positive correlation between contrast scores for distant and nearby tones, which indicates that individuals had similar contrast scores for both distant and nearby tones to show memory was highly specific for the signal frequency ($r = 0.799$, $P = 0.00004$; Supplemental Fig. S7) (2) *Similarity to specific memory template*: To validate memory phenotype assignment, the individual behavioral response gradients were correlated with a "template" memory from the rat that exhibited the sharpest behavioral response peak to the signal tone

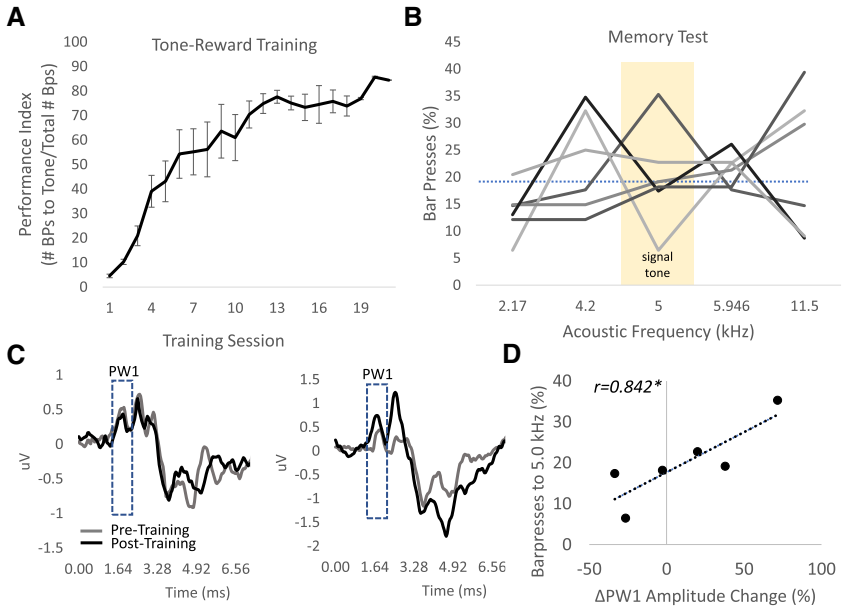

Figure 1. Individual differences in auditory brainstem response plasticity predict sound-specific memory following identical learning experience. (*A*) Rats ($n=6$) learn to associate a 5.0 kHz signal tone with an operant water reward. Individuals are trained to asymptotic performance. Error bars represent ±SEM. (*B*) Despite being trained with a single tone, the Memory Test reveals variability in how selective responses are to the training tone frequency (5.0 kHz). In fact, only one rat responded substantially more the signal tone versus other tone frequencies. Lines represent individual subjects. Solid lines represent individual subjects. The dashed line represents the Memory Test gradient if responses were equally distributed among all tone frequencies, which would indicate a completely generalized memory. (*C*) Tone-evoked auditory brainstem responses recordings were obtained from all subjects ($n=6$) before ("pretraining," gray) and after ("posttraining," black) to determine learning induced changes in signal tone-evoked positive wave 1 (PW1) amplitude. Dashed boxes indicate PW1. Graphs depict data from two of six individuals. (*D*) There is a significant positive correlation between individual differences in PW1 amplitude changes and the percent of responses made to the signal tone during the Memory Test. Greater amplitude increases predict a greater percent of responses allocated to the signal tone frequency. (*) $P<0.05$.

(Supplemental Fig. S4). Supplemental Table S1 shows that this analysis yields the same grouping: animals categorized as exhibiting frequency-specific memory have greater similarity to the template memory ($r>0.06$) than animals categorized as exhibiting frequency-general memory. (3) *Percent responses to signal tone at memory test:* To further validate memory phenotype assignment, individual were ranked according the percent of total responses made to the signal tone at memory test. Supplemental Table S2 shows that this analysis yields the same grouping: animals categorized as exhibiting frequency-specific memory made ≥30% of responses to the signal tone frequency, while animals with frequency-general memory made <30% of responses to the signal tone frequency.

Rats given injections of the HDAC3 inhibitor, RGFP966 (Abcam Inc., 10 mg/kg, $n=6$; vs. vehicle, $n=7$) immediately following early sessions of tone-reward training exhibited a frequency-specific behavioral response distribution at Memory Test weeks later (Fig. 2A), which characterized a "specific" memory phenotype. RGFP966-treated animals responded significantly more to the 5.0 kHz signal frequency tone than to distant tones (M = 20.04, SE = 6.67, one-sample *t*-test: t(5) = 3.00, $P=0.029$), while the difference did not reach significance to nearby tones (M = 19.26, SE = 9.65, one-sample *t*-test: $t_{(5)}=1.99$, $P=0.102$) (Fig. 2B). In contrast, vehicle-treated animals did not behaviorally discriminate the signal tone from nearby tones (M = 0.94, SE = 7.14, one-sample *t*-test: $t_{(6)}=0.132$, $P=0.899$), nor from distant tones (M = −4.82, SE = 8.45, one-sample *t*-test: $t_{(6)}=-0.5711$, $P=0.588$), which characterizes a "general" memory phenotype. Compared to the untreated rats ($n=1$ out of 6 untreated individuals), RGFP966 treatment significantly increased the proportion of individuals in the group with "specific" memory (to $n=4$ out of 6, binomial test vs. untreated: $P=0.009$), while vehicle treatment did not significantly alter the within-group proportion ($n=2$ out of 7, binomial test vs. untreated: $P=0.331$) (Fig. 2C). The small but nonsignificant increase in the proportion of individuals with specific memory in the vehicle group ($n=2$ out of 7) versus untreated group ($n=1$ out of 6) may be attributed to daily postsession injections that can affect arousal, which has been previously shown to affect cue reactivity in auditory memory (Hui et al. 2006). Interestingly, pharmacological treatment condition did not significantly affect other performance measures between groups, including the shape of the acquisition curve and final performance level at asymptote (Supplemental Fig. S2b), or the total number of bar press responses during the Memory Test 2 d later (Supplemental Fig. S2c). There were also no differences between groups in the expected decrease in behavioral responses over the course of the Memory Test that was conducted under *extinction* conditions (i.e., without rewards), except that the extinction of responses to the trained signal frequency, 5.0 kHz, appeared to be delayed in RGFP966 animals compared to vehicle (Supplemental Fig. S3a–c). Furthermore, despite behavioral extinction, the overall shape of the response distribution among test tone frequencies did not differ between the first and second halves of the Memory Test (Supplemental Fig. S3d). Therefore, RGFP966- and vehicle-treated animals maintained their frequency-specific or -general response patterns throughout the session (Supplemental Fig. S3d). Overall, the primary behavioral effect of HDAC3 inhibition was to shift within-group variability toward frequency-specific memory. Furthermore, a direct group comparison of ranked distributions of animals by the specificity of memory just reaches a statistical distinction between RGFP966 and vehicle-treated animals (Mann–Whitney one-tailed $U\text{-test}_{(7,6)}=8.0$; $P=0.050$). This finding supports that HDAC3 is a mechanism that drives memory in one direction toward specificity along a natural continuum of individual variability in memory evident in any animal learning this task. The link between HDAC3 and memory specificity revealed behaviorally is likely due to its role to promote the consolidation of learning experiences via frequency-specific auditory system neuroplasticity (Bieszczad et al. 2015; Shang et al. 2019).

HDAC3 inhibition promotes signal-specific auditory system plasticity

Analyses of untreated animals in Figure 1 identified a putative function of auditory system plasticity for memory specificity. Here, we sought to determine whether under conditions of pharmacological treatment, group differences in memory specificity revealed behaviorally between RGFP66- versus vehicle-treated

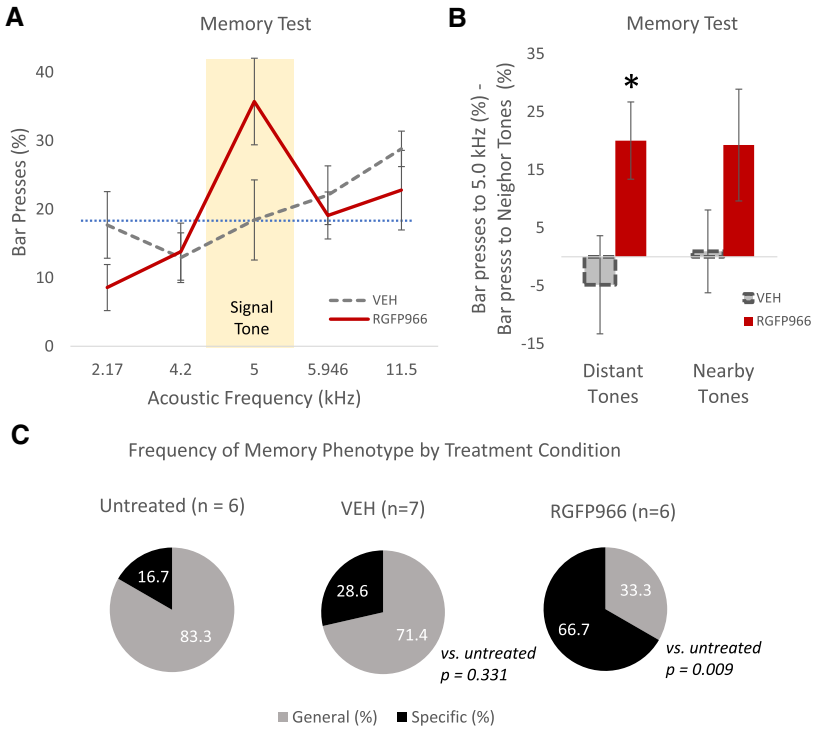

Figure 2. Posttraining treatment with HDAC3 inhibitor RGF966 promotes frequency-specific memory. (*A*) RGFP966-treated rats ($n=6$) exhibit a frequency-specific response distribution peaking at the signal tone frequency, while vehicle-treated rats ($n=7$) exhibit a shallow response gradient. The dashed line represents the Memory Test gradient if responses were equally distributed among all tone frequencies, which would indicate a completely generalized memory. (*B*) Quantifying the shape of the response distribution using relative measures of responding to the signal tone versus other test tone frequencies reveals that RGFP966-treated animals behaviorally discriminate. They respond to the signal tone more than both distant (far) tones (*left*) and nearby tones (*right*). Vehicle-treated rats do not discriminate, responding equally to signal tone versus nearby or distant tones. (*C*) RGFP966 treatment significantly increases the proportion of individuals with frequency-specific memory type, compared with untreated individuals ($n=6$). Vehicle treatment does not alter the distribution of memory phenotype. All error bars represent ±SEM. (*) $P<0.05$.

animals would mimic natural learning-induced individual variability in auditory system plasticity.

HDAC3 inhibition has known sequelae in learning-induced plasticity at the level of the primary auditory cortex (A1) (Bieszczad et al. 2015; Shang et al. 2019). Thus, electrophysiological recordings in A1 were obtained outside of the training context, and following the Memory Test to identify forms of A1 plasticity in the treated groups (RGFP966 vs. vehicle) to compare with a separate group of five naïve rats that did not undergo behavioral training. Electrophysiological data were analyzed according to the characteristic frequency of each site to parallel behavioral analyses by pooling neural data *near* the signal tone frequency (Fig. 3A) separately from sites tuned *far* from the signal tone frequency (Fig. 3B) and sites tuned *very far* from the signal tone (Supplemental Fig. S9a). Cortical receptive fields were analyzed for tuning bandwidth (BW, with respect to the breadth of frequency responsiveness in octaves) and response threshold (with respect to sound-evoked level in decibels). In sites tuned near the signal tone frequency (within one-third of an octave), one-way ANOVA revealed a significant difference in tuning bandwidth between groups at all sound levels tested above threshold (i.e., 10 dBs above threshold, BW10; and so on for BW20, BW30, BW40; Table 1). Post hoc Holm-Bonferroni-corrected *t*-tests showed that RGFP966-treated animals had significantly narrower bandwidth than both naïve and vehicle-treated animals at each sound level tested above threshold, while there were no significant differences between naïve or vehicle-treated animals at any bandwidth (Table 1). Cortical sound-evoked response threshold did not differ among groups (naïve: $n=28$, M = 21.63, SE = 2.036; veh: $n=44$, M = 22.39, SE = 1.794; RGFP966: $n=23$, M = 16.78, SE = 2.543; one-way ANOVA: $F_{(2,92)}=1.6732$, $P=0.193$).

In recording sites tuned far (over an octave away) from the signal tone frequency, there were no significant overall group differences in tuning bandwidth, except BW10 (Table 1; Fig. 3B). At BW10, post hoc Holms-Bonferroni corrected *t*-tests show RGFP966-treated animals had narrower bandwidth than vehicle-treated animals, but not naïve animals, with no other group differences. Again, response threshold did not differ among groups (Naïve: $n=53$, M = 22.01, SE = 1.877; veh: $n=62$, M = 21.65, SE = 1.817; RGFP966: $n=41$, M = 19.59, SE = 2.309; one-way ANOVA: $F_{(2,153)}=0.040$, $P=0.960$). In recording sites tuned very far from (over two octaves away) from the signal tone frequency, there were no significant group differences in tuning bandwidth (Table 1; Supplemental Fig. S9a) and no group differences in cortical response threshold ((naïve: $n=33$, M = 27.26, SE = 1.654; general: $n=60$ M = 21.59, SE = 1.781; specific: $n=40$, M = 23.90, SE = 1.891; one-way ANOVA: $F_{(2,132)}=2.270$, $P=0.107$). These findings again support HDAC3 as a mechanism that drives neural substrates of memory in a direction toward specificity along a natural continuum of individual variability.

To determine whether HDAC3 effects also mimic subcortical neural substrates of frequency-specific memory, ABRs were recorded before and after training in the same groups of treated animals to quantify learning-induced change in PW1 amplitude to: the signal tone (5.0 kHz), a *nearby* tone frequency (5.946 kHz), or a *distant* tone frequency, over an octave away from the signal (11.5 kHz). PW1 is the earliest peak evident in the ABR, thought to be generated as early as the auditory nerve (Starr 1976; Chen and Chen 1991). Among vehicle-treated animals, there was no significant change in PW1 amplitude evoked the 5.0 kHz signal tone (M = −4.4738, SE = 14.336, one sample *t*-test: $t_{(6)}=-0.3314$, $P=0.766$), or by the 5.946 kHz *near* tone (M = 14.848, SE = 11.568, one sample *t*-test: $t_{(6)}=1.283$, $P=0.246$), while there was a small but significant amplitude change in the opposite direction (decrease) in PW1 amplitude evoked by the *far* 11.5 kHz tone (M = -26.738, SE = 10.679, one sample *t*-test: $t_{(6)}=-2.503$, $P=0.046$) (Fig. 3C). Among RGFP966-treated animals however, there was a notable increase in PW1 amplitude evoked by the 5.0 kHz signal tone, though not statistically significant likely due to the small sample size ($n=4$) given attrition in two out of six subjects at the posttraining time point (M = 40.239, SE = 25.809, one sample *t*-test: $t_{(3)}=1.559$, $P=0.218$) (Fig. 3D). RGFP966-treated animals also did not exhibit ABR amplitude changes evoked by either the 5.946 kHz tone (M = −7.056, SE = 6.351, one sample *t*-test: $t_{(3)}=-1.110$, $P=0.346$) or the 11.5 kHz tone in either direction (M = −9.4073, SE = 10.825, one sample *t*-test: $t_{(3)}=-0.869$, $P=0.448$). However,

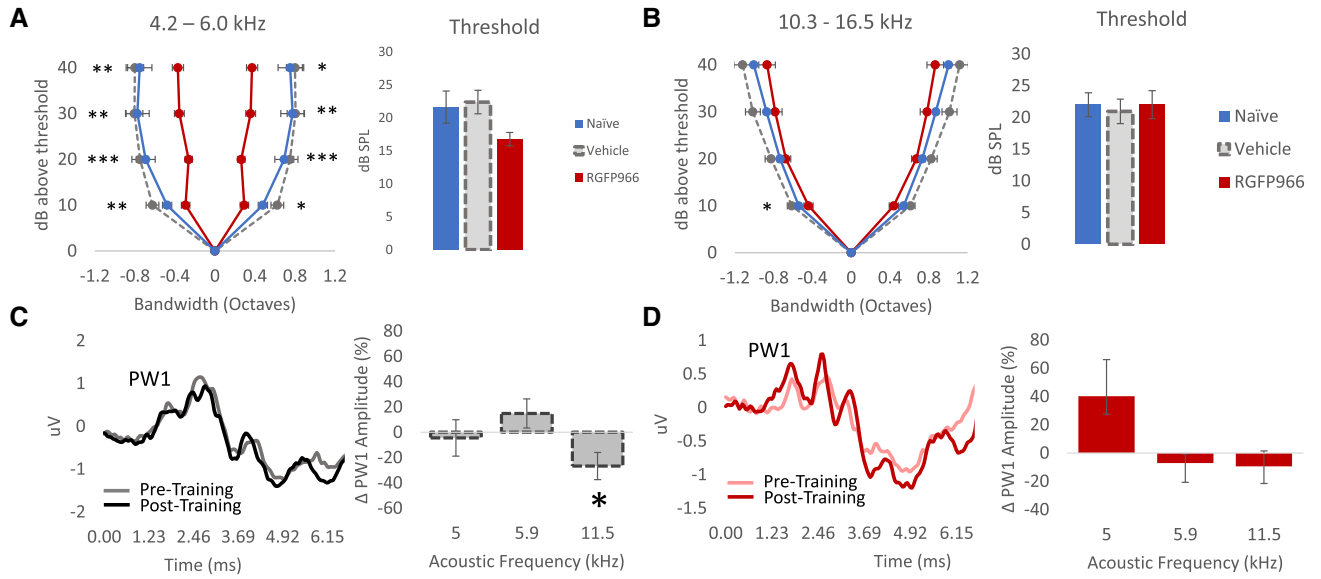

Figure 3. HDAC3 inhibition promotes learning-induced auditory system plasticity that is signal-specific. Panels represent sound-evoked neural responses from the auditory cortical (*A*,*B*) and auditory brainstem response (*C*,*D*) recordings. (*A*) Among auditory cortical sites tuned near the signal tone frequency (±1/3 octave), RGFP966-treated animals ($n=6$ animals; 23 recording sites) showed significantly narrower tuning bandwidth at every sound level than vehicle-treated ($n=6$ animals, out of 7; 44 recordings sites) and naïve animals ($n=5$ animals; 28 recording sites). Bandwidth among vehicle-treated and naïve animals did not differ. There were no group differences in response threshold (dB SPL). (*B*) Tuning bandwidth between-groups was more similar among auditory cortical sites tuned far away from the signal tone frequency (+1.03–1.33 octaves); RGF966-treated rats only had narrower BW10 ($n=6$ animals; 41 recording sites) than vehicle-treated rats ($n=6$ animals; 50 recording sites), but were the same as naïve ($n=5$ animals; 59 recording sites). (C) *Left,* Representative signal-tone evoked ABR traces from a single (out of 7) vehicle-treated subject recorded before ("pretraining," gray) and after ("posttraining," black). *Right,* Quantification of learning-induced PW1 amplitude changes in ABRs evoked by the 5.0 kHz signal tone, as well a near (5.946 kHz) and far (11.5 kHz) neighbor frequency. One-sample *t*-tests reveal no significant amplitude changes in 5.0 or 5.946 kHz evoked PW1, but a significant amplitude decrease in 11.5 kHz evoked PW1. (*D*) *Left,* Representative signal-tone evoked ABR traces from a single RGFP966-treated subject (out of 4) recorded before (pink) and after (red) training. *Right,* Quantification of learning-induced PW1 amplitude changes in ABRs evoked by the 5.0, 5.946, and 11.5 kHz, though none reached statistical significance. All error bars represent ±SEM. (*) $P<0.05$, (**)$P<0.01$, (***) $P<0.001$. In (*A*,*B*), asterisks on the left represent comparisons between vehicle and RGFP966; on the right, naïve versus RGFP966. No significant differences were found between naïve and vehicle groups.

Table 1. Cortical tuning bandwidth for RGFP966- and vehicle-treated animals

Frequency range (kHz)	Group	Tuning Bandwidth			
		BW10	BW20	BW30	BW40
4.2–6.0	naïve ($n=5$ subjects; 26 sites)	0.96 ± 0.009	1.38 ± 0.188	1.55 ± 0.236	1.50 ± 0.242
	vehicle ($n=7$ subjects; 44 sites)	1.24 ± 0.126	1.50 ± 0.162	1.61 ± 0.166	1.60 ± 0.173
	RGFP966 ($n=6$ subjects; 23 sites)	**0.58 ± 0.084*§[a]**	**0.52 ± 0.073***§§§[b]**	**0.71 ± 0.098**§§[c]**	**0.74 ± 0.111**§[d]**
10.3–16.5	naïve ($n=5$ subjects; 50 sites)	1.08 ± 0.082	1.47 ± 0.211	1.74 ± 0.119	2.01 ± 0.155
	vehicle ($n=7$ subjects; 59 sites)	1.22 ± 0.088	1.62 ± 0.119	1.96 ± 0.148	2.18 ± 0.175
	RGFP966 ($n=6$ subjects; 41 sites)	**0.87 ± 0.101*[e]**	1.34 ± 0.109	1.58 ± 0.145	1.72 ± 0.175
20.0–32.0	naïve ($n=5$ subjects; 33 sites)	0.83 ± 0.067	1.27 ± 0.123	1.56 ± 0.195	1.96 ± 0.241
	vehicle ($n=7$ subjects; 60 sites)	0.84 ± 0.063	1.22 ± 0.112	1.76 ± 0.181	2.21 ± 0.220
	RGFP966 ($n=6$ subjects; 40 sites)	0.94 ± 0.096	1.08 ± 0.110	1.68 ± 0.170	1.86 ± 0.178

[a]One-way ANOVA: $F_{(2,90)}=7.602$, $P=0.0008$; Holms-Bonferroni corrected two-tailed independent samples *t*-test: naïve versus veh: $t_{(68)}=-1.612$, $P=0.114$; naïve versus RGFP966:$t_{(47)}=2.9259$, $P=0.014$§; veh versus RGFP966:$t_{(65)}=3.558$, $P=0.0021$*.
[b]One-way ANOVA: $F_{(2,90)}=9.193$, $P=0.0002$; Holms-Bonferroni corrected two-tailed independent samples *t*-test: naïve versus veh: $t_{(68)}=-0.445$, $P=0.657$; naïve versus RGFP966: $t_{(47)}=4.048$, $P=0.0002$§§§; veh versus RGFP966: $t_{(65)}=4.255$, $P=0.00021$***.
[c]One-way ANOVA: $F_{(2,90)}=6.366$, $P=0.0025$; Holms-Bonferroni corrected two-tailed independent samples *t*-test: naïve versus veh: $t_{(68)}=-0.2062$, $P=0.837$; naïve versus RGFP966: $t_{(47)}=3.122$, $P=0.006$l§§; veh versus RGFP966: $t_{(65)}=3.74$, $P=0.0013$**.
[d]One-way ANOVA: $F_{(2,90)}=5.251$, $P=0.0069$. Holms- Bonferroni corrected two-tailed independent samples *t*-test: naïve versus veh: $t_{(68)}=-0.328$, $P=0.743$; naïve versus RGFP966: $t_{(47)}=2.734$, $P=0.0174$§; veh versus RGFP966: $t_{(65)}=3.376$, $P=0.0036$*.
[e]One-way ANOVA: $F_{(2,147)}=3.468$, $P=0.033$; Holms-Bonferroni corrected *t*-test: veh versus RGFP966: $t_{(89)}=2.522$, $P=0.039$).
This tables displays tuning bandwidth (M ± SE) for sites tuned around the signal tone (4.2–6.0 kHz), sites tuned far from the signal tone (10.3–16.5 kHz), and sites tuned very far from the signal tone (20.0–32.0 kHz). Significant differences are in bold. * Indicates a difference between versus vehicle-treated animals, where * $P<0.05$, ** $P<0.01$, and *** $P<0.001$. § Indicates a difference versus naïve animals. § $P<0.05$, §§ $P<0.01$, and §§§ $P<0.001$.

findings of group treatments were based on ignoring the actual frequency-specificity of individual subject memory, which may have masked significant relationships that exist at the level of the individual subjects. Insofar as individualized analyses could be performed without compromising group-based evaluations, the same data were reanalyzed. Regrouping the ABR data from the RGFP966- and vehicle-treated rats by "specific" ($n = 5/13$) versus "general" ($n = 6/13$) memory phenotype (rather than by treatment) revealed greater signal-specific PW1 amplitude increases as individuals exhibit more frequency-specific memory behaviorally (Supplemental Fig. S8c). Interestingly, regrouping the cortical data also by "specific" ($n = 6/13$) versus "general" ($n = 7/13$) memory phenotype (i.e., regardless of treatment condition) revealed the same significant brain-behavior relationship reported above: individuals with frequency-specific memory exhibited a cortical narrowing in tuning bandwidth in sites tuned only near the signal frequency, with no significant differences in threshold (Supplemental Fig. S8a,b; Supplemental Fig. S9b; Supplemental Table S3). Therefore, though HDAC3 inhibition via RGFP966 does promote frequency-specific memory (Fig. 2; Bieszczad et al. 2015; Shang et al. 2019), this functional outcome may depend not just on the intervention alone, but on the ability of that intervention to facilitate the appropriate form, locus, and magnitude of auditory system plasticity that together provide sufficient neural substrates for the specificity of memory to reveal behaviorally. In the present case, memory specificity appears to require both cortical and subcortical substrates.

Individual differences validate cortical and subcortical substrates of specific memory

Thus far, the findings reveal that (1) treatment with HDAC3-inhibitor RGFP966 drives individual differences toward a frequency-specific memory phenotype, and (2) that frequency-specific memory is associated with forms of signal-specific plasticity at multiple levels of the auditory system. As such, intervention with RGFP966 treatment resulted in an opportunity to determine brain-behavior relationships to better understand the function of auditory system plasticity for auditory memory specificity. To capitalize on this opportunity, individual subjects were used to determine whether magnitude of effects in the forms of plasticity identified (both subcortically, as in Fig. 1 and Supplemental Fig. S8c; and cortically, as in Fig. 3) would reflect magnitude effects in the frequency-specificity of learned behavior.

Replicating the relationship observed in untreated animals (Fig. 1D), there was a significant positive correlation between the change in signal-tone evoked PW1 amplitude and the proportion of responses to the signal tone during Memory Test in treated animals ($r = 0.890$, $P = 0.0002$). The greater the amplitude gain, the greater the proportion of bar-presses to the signal frequency (Fig. 4A). Notably, there was no relationship between pretraining PW1 amplitude and subsequent responses at Memory Test ($r = 0.137$, $P = 0.655$), which supports that all other reported relationships are learning-induced (Fig. 4B). To quantify memory specificity at the individual level, two response contrast measures were derived between pairs of neighboring tone frequencies for each subject: (1) for behavioral contrast, as the difference in bar-presses to the signal tone versus near or distant neighboring tone, and (2) for neural contrast, as the difference in PW1 amplitude changes (i.e., before- *minus* after-training) evoked by the signal tone versus neighboring tone. Figure 4C shows a significant positive correlation discovered between subcortical neural and behavioral contrasts for the 5.0 kHz signal tone and the near neighbor tone 5.946 kHz ($r = 0.727$, $P = 0.011$) as well as its distant neighbor tone 11.5 kHz ($r = 0.696$, $P = 0.017$) (Fig. 4D)*:* greater neural contrast predicts greater behavioral contrast. Further, there was a significant cortical correlate of frequency-specific behavioral responding: Cortical tuning bandwidth negatively correlated with the proportion of bar presses to the signal tone during the Memory Test ($r = -0.668$, $P = 0.017$) (Fig. 4E). Thus, narrower signal-specific cortical tuning also predicted greater behavioral signal contrast.

We linked the two analyses together to report here for the first time a putative connection between subcortical and cortical forms of plasticity accompanying the formation of signal-specific memory. There is a significant correlation between the amplitude change of 5.0 kHz-evoked PW1 and signal-specific auditory cortical tuning bandwidth ($r = -0.838$, $P = 0.0024$): as cortical bandwidth decreases, PW1 amplitude increases (Fig. 4F). Thus, individual differences in two identified forms of learning-induced auditory neuroplasticity validated them both as coordinated substrates of memory's acoustic specificity. In sum, these findings confirm and extend a hypothesized relationship between cortical plasticity, subcortical plasticity, and learned behavior. Supplemental Table S4 summarizes all the group correlations, as well as subgroup correlations for treatment condition and memory phenotype, the latter of which reveal the contribution of each phenotype to drive the brain-behavior correlation. Overall, the strongest correlations between brain and behavior exist with specificity, whether induced naturally or with RGFP966 treatment.

Discussion

We report three main findings. (1) Frequency-specific memory, whether *natural* or mediated by a HDAC3 pharmacological intervention, is associated with multiple forms of signal-specific auditory system plasticity that includes cortical and subcortical candidate substrates. (2) Inhibition of HDAC3 during early auditory learning of a single-tone task promotes a lasting frequency-specific memory phenotype. (3) A three-way correlation between auditory cortical plasticity, auditory subcortical plasticity, and sound-specific behavior revealed by within-group individual differences validates the neural candidates as substrates of memory revealed in behavior.

The three-way correlation between sound-specific cortical and subcortical plasticity, and behavior supports that learning can induce coordinated auditory system reorganization at multiple levels. Broadly speaking, this finding supports the idea that memory relies on distributed plasticity. When those forms of plasticity emerge in a signal-specific way for acoustic frequency, the learned behavior emerges with signal-specificity for acoustic frequency. Furthermore, the magnitude of learning-induced cortical changes explains the magnitude of amplitude changes even in the earliest peak of the ABR, thought to be generated as early as the auditory nerve (Starr 1976; Chen and Chen 1991). Thus, coordination appears to span the highest to lowest levels of the auditory system, which is consistent with previous corticofugal interpretations of long-lasting experience-dependent plasticity in the human ABR (Chandrasekaran et al. 2014) and the brainstem's frequency-following response (FFR) (Coffey et al. 2016). Indeed, the interaction between cortical and subcortical sound-evoked responses is not new (Winer and Lee 2007), which includes evidence of cortical reorganization of descending inputs after early auditory system damage (Asokan et al. 2018). The present findings relate these interactions to adult learning-dependent effects. Importantly, ABR plasticity that was detected outside of the training context after achieving high-levels of performance predicted *subsequent* specificity of behavioral performance in a completely novel situation, days later, at Memory Test. Therefore, noninvasive ABR neurophysiology has high translational potential to track and anticipate the effects of learning for sound-specific behavioral functions on an individual subject basis, which is relevant for the successful transfer of training experiences from a clinical setting to real-life

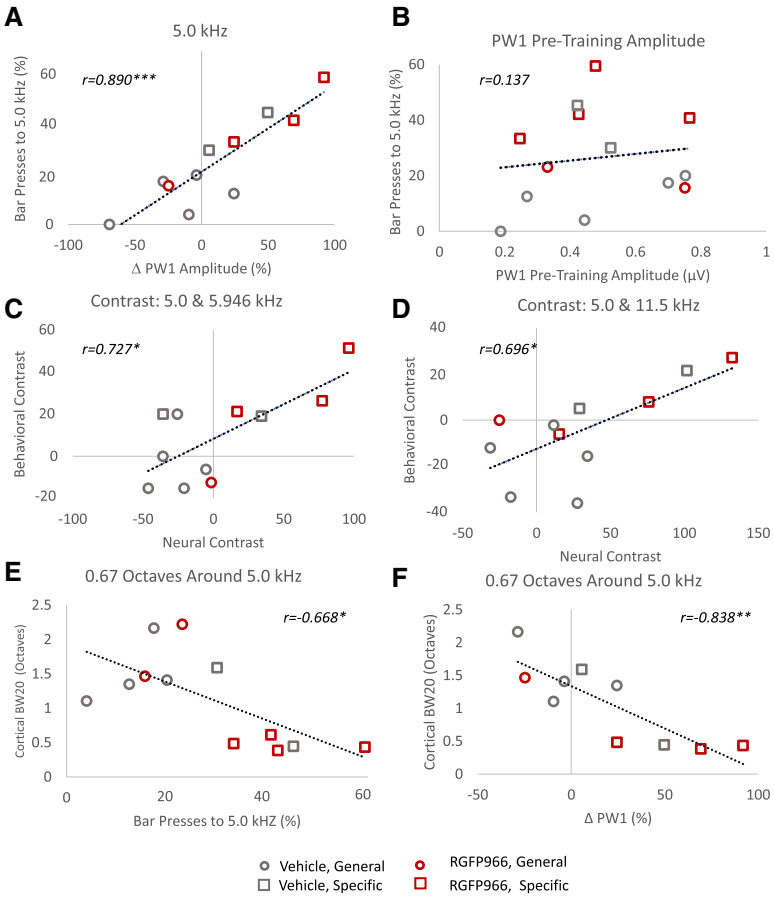

Figure 4. Coordinated forms of auditory system plasticity are correlated with the frequency-specificity of auditory memory. (*A*) Greater amplitude gains in signal-tone evoked PW1 predict a greater percent of total responses to the signal tone frequency at Memory Test ($n=11$). (*B*) Pretraining PW1 amplitude has no relationship with subsequent memory specificity ($n=13$). (*C*) Greater neural contrast between the signal tone and a near neighbor tone (as measured by PW1 amplitude changes) predicts greater behavioral contrast (measured by difference in percent of bar presses) to that same pair of tones ($n=11$). (*D*) Greater neural contrast between the signal tone and a distant neighbor tone also predicts greater behavioral contrast among that pair of tones ($n=11$). (*E*) Narrower auditory cortical tuning bandwidth (BW20) for sites tuned near the signal tone correlates with a greater percentage of responses to the signal tone ($n=12$. (*F*) Narrower auditory cortical tuning bandwidth (BW20) for sites tuned near the signal tone is predicted by greater amplitude gains in signal tone-evoked PW1 ($n=10$). (*)$P<0.05$, (**)$P<0.01$, (***)$P<0.001$.

contexts. Here, we highlight the novel finding of behaviorally relevant plasticity in the *earliest* peak of the ABR (PW1). Future studies will be useful to determine plasticity in additional subsequent components of the ABR to determine likely relationships between plasticity and behavior in other subcortical nuclei.

A significant enhancement in PW1 amplitude appeared in animals with frequency-specific memory, regardless of pharmacological treatment. This supports that the plasticity of PW1 amplitude is a natural form of learning-induced change that is not dependent on RGFP966, the HDAC3-inhibitor. Rather, PW1 amplitude enhancement appears to be a neural feature of frequency-specific behavior, which is supported by evidence in Supplemental Table S4 that animals with frequency-specific memory are likely driving the significant group-level brain-to-behavior relationships. The effect on PW1 was revealed using a binary grouping of the data sets according to memory phenotype, though general and specific memories appear to lie on a natural continuum. Indeed, while strong brain-behavior correlations exist in animals with specific memory, correlations are weak between neuroplasticity and behavior in animals with a general memory, which is consistent with the interpretation that something other than sound frequency per se was driving the latter behavior during the Memory Test. Therefore, other approaches to measure novel forms or loci of plasticity will be required for future studies to explain variability among animals with general memory, while the forms of signal-specific auditory system plasticity reported here are particularly significant substrates of memory specificity. Overall, this interpretation emphasizes that sensory neuroplasticity is driven by individual strategies used to learn tasks rather than the actual sensory statistics of experience, which is in-line with previous work (Polley et al. 2006). Thus, these findings are interpreted to signify that the ability of learning to induce frequency-specific neurophysiological plasticity will dictate the *degree* of memory precision at the individual level.

Similarly, a significant sharpening of auditory cortical tuning bandwidth appeared in animals with frequency-specific memory, regardless of pharmacological treatment. This is in agreement with previous reports in both auditory- and nonauditory sensory systems to support the relationship between signal-specific, sharpened tuning bandwidth in sensory neurons and signal-specific memory (Kass et al. 2013; Recanzone et al. 1993; Bieszczad et al. 2015; Kass and McGann 2017; Shang et al. 2019). It is tempting to assume that reductions in sensory tuning bandwidth necessarily affect perceptual discrimination thresholds between similar stimuli. However, in the cortex, an alternative possible function for the tuning bandwidth is to confer the ability to associate different values or expected outcomes (e.g., go vs. no-go) to different —but similar—sounds. Indeed, Chen et al. (2019) report that psychometric tuning filters for perceptual discrimination can be quite narrow, that is, animals can "hear" differences between highly similar tone frequencies. In contrast, despite being able to *hear* the differences between tones, animals have wider "associative" filters, i.e., it is more difficult for animals to *associate* perceptually similar (but distinct) tones to different outcomes, e.g., go versus no-go. Therefore, significantly sharpening auditory cortical tuning might reduce the tendency to generalize associative outcomes from one tone to nearby tones. As such, narrowed sensory filters have been proposed to have a function to support precise memory (Chen et al. 2019). In support of this, we report for the first time a significant relationship between narrowed auditory cortical tuning bandwidth and memory specificity at the level of individual subjects.

It is important to highlight that highly specific memory is not necessarily *better* than more generalized memory. Which is "better" will depend on the set of behavioral challenges an animal faces in novel tasks or experiences subsequent to the original learning event. In a differential frequency discrimination task, a specific memory may be very valuable (as in Chen et al. 2019; Shang

et al. 2019), but in a simple detection task, generality may actually be better than developing highly precise memory for a single tone. Indeed, there is noted value for generalization in aversive learning situations where behavioral discrimination is reduced (Reznik and Paz 2015). On the other hand, over-generalization is a major component of psychiatric disorders like posttraumatic stress (Lissek 2012; Morey et al. 2015; Castro-Gomes et al. 2016; Kaczkurkin et al. 2016; Lopresto et al. 2016; Sillivan et al. 2017; Pollack et al. 2018), which suggests that different circumstances warrant appropriate balancing between specificity and generalization. Interestingly, the degree of specificity may also vary with different circuit generators at the time of retrieval. While the auditory cortex may drive highly sound-specific responses in an appetitive task, it is possible that fear conditioning relies on a fast, preattentive, amygdala-based system. The responses of amygdalar neurons have broader tuning at retrieval (Ghosh and Chattarji 2015; Reznik and Paz 2015; Wigestrand et al. 2016), despite that the coactivation of the amygdala with auditory cortical evoked responses can drive highly specific frequency retuning in the auditory cortex during memory acquisition (Chavez et al. 2009, 2013). Overall, it may be evolutionarily important to have flexibility in those systems and circuits that dictate the specificity of memory (Manassero et al. 2019). That HDAC3-inhibition plays a role to shift the distribution of individual differences toward specificity is a step toward understanding the neural mechanisms that might confer such flexibility.

In addition to demonstrating a function of signal-specific auditory system plasticity for memory specificity, the findings confirm HDAC3 as a mechanism of long-term memory formation by promoting signal-specific consolidation of auditory system plasticity, which now includes subcortical effects. Future research is necessary to determine whether the effects of systemic delivery of an HDAC3 inhibitor facilitates learning-induced neuroplasticity directly in both sensory subcortical and cortical areas, or whether its effects on the ABR are sequelae of primary effects in the cortex via descending connections. In either case, HDAC3 inhibition appears to confer a significant shift along a natural continuum of individual variability in memory formation toward specificity, maintaining the same characteristic neurophysiological substrates of auditory memory as "naturally"-learning subjects. In addition, animals with precise memory in the present study—regardless of treatment—exhibited frequency-specific increases in PW1 amplitude and frequency-specific decreases in cortical tuning bandwidth. Thus, the effects of HDAC3 inhibition on memory precision likely operate within individual constraints. The efficacy of this intervention may depend on its ability to facilitate the factors that naturally underlie the formation of memory along the general-to-specific continuum, including the appropriate form, locus and magnitude of plasticity. While it is not possible with the current data set to determine what degree of memory precision HDAC3-inhibited rats would have developed in absence of pharmacological intervention, the prediction is that it is *greater* than it would have been without intervention, even if it did not reach the present threshold for frequency-specific memory. This reasoning may also explain why some of the animals treated with the HDAC3-inhibitor showed weaker effects than others in the same treatment group. The rank-order analysis of memory specificity among vehicle- and RGFP966-treated subjects demonstrated overlap between treatment groups to support the conclusion that HDAC3 inhibition results in a bias toward memory precision along a naturally inducible continuum; it does not result in a separate and unique distribution. Previous work further supports the relationship between precise memory for acoustic frequency and sharpened cortical frequency tuning in naturally learning subjects (Recanzone et al. 1993; Keeling et al. 2008; Chen et al. 2019). Therefore, HDAC-targeted manipulations may be useful tools to study the links between neurophysiological and molecular substrates of natural long-term memory in the brain. Used in the auditory and other sensory systems, these tools could provide answers to how multidimensional memories are stored with multifeature specificity with consequence for future behavioral action.

HDAC inhibitors have recently been targeted for their memory enhancing effects (Vecsey et al. 2007; Stefanko et al. 2009; McQuown et al. 2011; Malvaez et al. 2013; Phan et al. 2017). The present study brings to light that these effects may be limited to particular attributes of memory. For example, memory can be defined by many characteristics, including its associativity, specificity, strength, and long-lastingness. Here, we found that HDAC3-inhibition did not affect the acquisition of a simple single-tone detection task, which is consistent with prior studies using a single-tone task, even when daily RGFP966 treatment was extended throughout the 2–3 wk of training (Bieszczad et al. 2015). All subjects learned the task at similar rates and to a similar final level of asymptotic performance, regardless of treatment. Therefore, HDAC effects on associativity, or the extent to which a stimulus event can be linked with an outcome, were not observed, which is also consistent with memory studies using passive (nonassociative) exposure (Phan et al. 2017). Thus, consistent with previous findings (Bieszczad et al. 2015), these data do not support a general improvement in memory performance due to RGFP966. Instead, we discovered a role for the specificity of memory—that is, how precisely memory can form for the sensory features of a training stimulus. While the present study did not explicitly require animals to discriminate among frequencies to successfully solve the auditory operant task to obtain rewards, the findings predict that if animals were presented with a task that challenged the discrimination of two or more stimuli, then effects on learning rates and performance would emerge. This was found in Shang et al. (2019) who used an auditory discrimination task with two training sounds to show that HDAC3 inhibition both accelerated learning rates and promoted a greater degree of memory precision (compared to vehicle treatment). Thus, HDAC3 may control the storage of sensory details in memory, thereby facilitating the use of a behavioral strategy that depends on precise cues (Bieszczad et al. 2015; Phan and Bieszczad 2016). This interpretation for HDAC function is consistent with previous studies in other learning paradigms and in other experimental designs that block HDAC3 function before, during or after training sessions (McQuown et al. 2011; Malvaez et al. 2013). For example, McQuown et al. (2011) used an object recognition task to show that blocking HDAC3 enabled object recognition memory. Interestingly, their findings could be interpreted consistently with an HDAC3-mediated effect on memory precision, which would be required for animals in that task to recognize that one object had been replaced by another distinct object by its distinguishing sensory features. It may be important for future studies to systematically consider HDAC-mediated effects on characteristics of memory separately, such as its strength (which can be defined as resistance to extinction) and long-lastingness (defined as the persistence of memory over time), rather than to interpret effects as a general memory improvement, as well as for effects on the acquisition, consolidation and retrieval phases of memory. Indeed, evidence exists also for "long-lastingness" from Stefanko et al. (2009) to show that HDAC-inhibitors succeed to extend the lastingness of memory beyond a timepoint at which it would normally fail. Evidence for "strength" exists in the present results, since RGFP966-treated animals exhibited a resistance to extinction during the memory test, but only for the training sound frequency. In contrast, extinction defined as the decline in responses made to *all* sounds during the Memory Test did not differ between treatments (see Supplemental Fig. S3c). Thus, the effect on memory strength was dependent on the effect on memory precision. Further, the results are interpreted with respect to effects on the

consolidation of auditory memory since the HDAC3-inhibitor was administered posttraining, which was also useful to avoid within-session performance confounds. Future studies may also benefit from designs that study the covariance among different aspects of long-term memory, perhaps also by investigating individual differences in acquired learning strategies and consequent memory performance. Such studies could lead to informed hypotheses for the underlying neurophysiological mechanisms that link HDACs to their mnemonic and behavioral effects.

A remaining open question is: *Where do individual differences come from?* The answer is beyond the scope of the current studies, but not beyond the scope of behavioral neuroscience, where much work is being done to identify key factors. Here, all animals were the same species, strain, sex, age, and all were experimentally naïve prior to training. Therefore, other putative factors related to the integrity of anatomical circuitry, efficiency of experience to drive neuromodulatory events, or the availability of molecular signaling factors could be examined. Recent evidence in adult and aging subjects points to amygdala (Ghosh and Chattarji 2015; Reznik and Paz 2015) and temporal lobe function and anatomical integrity as a likely locus of effect for the specificity (vs. generalization) of memory (Yassa and Stark 2011), which may prove to interact with sensory cortical substrates. Regardless of the source of individual differences in the brain, or their environmental causes, the lesson learned from this work is that to harness plasticity mechanisms for adaptive goals, we must identify neurophysiological substrates in form and magnitude that match their desired functional outcomes. Indeed, individual differences in auditory specificity in human subjects is well-known (Dunsmoor et al. 2017; Stegman et al. 2019). Since the individual is of prime importance in a clinical setting, these issues remain a critical subject for future behavioral neuroscientific research.

Materials and Methods

Subjects

A total of 24 adult male Sprague-Dawley rats (275–300 g on arrival; Charles River Laboratories) were used ($n = 6$ untreated; $n = 13$ treated; $n = 5$ naïve) in behavioral and electrophysiological procedures. The five naïve adult males were untrained and only used for cortical electrophysiological recordings. In sum, these rats represent four separate groups: (1) untreated: rats trained in the auditory task, but not treated with the HDAC3 inhibitor RGFP966 or vehicle, (2) treated-vehicle: rats that received vehicle injections during training in the auditory task, (3) treated-RGFP966: rats that received RGFP966 injections during training in the auditory task, and (4) naïve: rats that did not receive training in the auditory task nor drug injections so did not generate any behavioral data, and were exclusively used for baseline comparison of cortical electrophysiology. Only rats in the treated groups (RGFP966 and vehicle) were used for analysis of general and specific memory phenotypes (Supplemental Figs. S5, S6b, S8, S9b). All animals were individually housed in a colony room with a 12-h light–dark cycle. Throughout behavioral procedures, rats were water-restricted, with daily supplements provided to maintain at ∼85% free-drinking weight. All procedures were approved and conducted in accordance with guidelines by the Institutional Animal Care and Use Committee at Rutgers, The State University of New Jersey.

Behavioral procedures and analysis

All behavioral sessions were conducted in instrumental conditioning chambers within a sound-attenuated box. All subjects initially learned how to press a lever for water reward in five ∼45-min bar-press shaping sessions. This phase of training assured that all animals could acquire the procedural aspects of the task (i.e., bar-pressing for rewards) before any sounds were introduced. Next, all rats underwent *tone-reward training* in a single tone detection task, in which they could learn to associate a 5.0 kHz signal tone with the operant reward. Because the task is a sound-detection task and does not require animals to perform sound discriminations in order to receive reward it allows for individual differences in the strategies used to learn. Thus, rats could learn and remember the actual training sound frequency, or they could learn and remember to respond to sound per se. Responses in the presence of the signal tone were rewarded, while responses during the intertrial interval (ITI) triggered a visual error signal and a time-out that extended the time until the next tone trial. All rats were trained to performance criteria, where on average 70% of bar presses occurred in the presence of the signal tone for two consecutive days (average training sessions for all subjects: $n = 19$, $M = 12.10 \pm 1.5$). A two-way ANOVA was used to compare group performance on the first two tone-reward training sessions and the final two tone-reward training sessions.

Forty-eight hours following the final tone-reward training session, rats were tested in a Memory Test that would reveal the strategy they had used to learn and remember the task. This Memory Test was used to determine the degree of memory specificity for the signal tone frequency. In the Memory Test session, rats were presented with the 5.0 kHz signal tone, as well as four novel tone frequencies representing "nearby" neighbors (±0.25 octaves) to the signal tone (5.946 and 4.2 kHz) and "distant" neighbors (±1.20 octaves) to the signal tone (11.5 and 2.17 kHz). All novel tones are readily discriminable from the signal tone, as the threshold for discrimination is ∼3%–6% ΔF in rodents (6% ΔF range with respect to 5.0 kHz: 4.7–5.3 kHz) (Heffner and Masterton 1980; Syka et al. 1996; Talwar and Gerstein 1998; Chen et al. 2019). Each tone frequency was presented a total 12 times. The session was divided into four continuous blocks, with three presentations of each tone per block in a pseudorandom order. No responses were reinforced. The distribution of bar presses among the test tone frequencies was used to determine the shape of the frequency generalization gradient. To quantify memory specificity for the signal tone, contrast measures of relative to response to the signal tone, versus novel tones, were calculated as follows: (1) Percent of responses to signal tone—(average percent of response to distant tones) and (2) Percent of responses to signal tone—(average percent of responses to nearby tones). Positive values indicate greater responding to the signal tone than novel tones. Single-sample *t*-tests were used to determine whether contrast scores were significantly different than 0.

To determine memory phenotype, individual behavioral responses gradients were analyzed in three ways: (1) *Behavioral contrast scores:* To determine memory specificity for the signal tone, contrast measures of relative to response to the signal tone, versus novel tones, were calculated as follows: (a) Percent of responses to signal tone—(average percent of response to distant tones) and (b) Percent of responses to signal tone—(average percent of responses to nearby tones). Positive values indicate greater responding to the signal tone than novel tones. Only individuals with *positive* contrast values for both distant and nearby tones (relative to the signal tone) were labeled as those with frequency-specific memory. (2) *Similarity to specific memory template*: To validate memory phenotype assignment, the individual behavioral response gradients were correlated with a "template" memory from the rat that exhibited the sharpest behavioral response peak to the signal tone. Animals with Pearson r values >0.06 were considered to have frequency-specific memory. (3) *Percent responses to signal tone at memory test:* To further validate memory phenotype assignment, individual were ranked according the percent of total responses made to the signal tone at memory test. Animals that made ≥30% of total responses to the signal tone were considered to have frequency-specific memory.

A binomial test was used to determine the categorical frequency of memory phenotype by treatment condition, compared to untreated, trained subjects. A one-tailed Mann–Whitney *U*-test was used to determine differences in rank-order distribution of memory specificity by treatment condition. To assess group differences in extinction dynamics, a two-way mixed-model ANOVA was used with the within-subject factor of *quartile block* of the Memory Test and the between-subject factor of *treatment group*. To determine whether the behavioral response distribution was stable

over the course of the Memory Test, a one-way repeated measures MANOVA was used for each treatment group to assess similarity in the proportion response to the five test tone frequencies in the first half versus the last half of the Memory Test. For Pearson correlative data, behavioral contrast measures were also derived for bar-press responses between the signal tone and a single neighbor to match the sound frequencies used in auditory brainstem response recordings.

Pharmacological inhibition of HDAC3

A pharmacological HDAC3 inhibitor RGFP966 was used alter molecular mechanisms of auditory memory formation induced by learning (Bieszczad et al. 2015). Rats in this treatment experiment were randomly assigned to either the RGFP966 ($n = 6$) or vehicle ($n = 7$) condition prior to tone reward-training. Rats received three consecutive days of postsession injections of RGFP966 (10 mg/kg, s.c.) or vehicle (equated for volume) on training days 2–4 (dose established [Malvaez et al. 2013], and confirmed in auditory system function [Bieszczad et al. 2015]). Posttraining pharmacological treatment confines manipulation to the memory consolidation period, while avoiding potential performance effects based on perception, motivation or within-session learning. For the remainder of training sessions after day 4, all rats received postsession injections of saline (equated for volume) to ensure that any effect of the injection itself remained consistent throughout training until reaching performance asymptote.

Auditory brainstem response recordings and analysis

Auditory brainstem responses (ABRs) were recorded twice in anesthetized rats (sodium pentobarbital, 50 mg/kg, i.p.) to determine learning-induced changes in subcortical sound processing: (1) Twenty-four hours prior to the first tone-reward training session and (2) Twenty-four hours following the final-tone reward training session. All recordings were made in a recording chamber completely separate from the training chamber and while the animal was anesthetized, which is a completely different state and context than that used in training. Stimulus presentation and neural response recordings were carried out using BioSig RZ software (TDT Inc.). Evoked potentials were recorded using a three-electrode configuration, with subdermal needle electrodes (1 kΩ) positioned at the midline along the head (recording), immediately below the left pinna (reference), and the midline on the back of the neck (ground) Sound stimuli were 60 dB SPL, 5 msec pure-tones (2 msec cosine-gated rise/fall time) presented at 21 Hz to the left ear from a speaker positioned 4 cm away. Three tone frequencies (11.5, 5.946, and 5.0 kHz) were presented in a blocked format (512 stimuli per block). The averaged evoked response was used for analysis of the first positive peak (PW1) of the waveform. Custom Matlab scripts were used to identify peaks within the waveform and derive the trough-to-peak amplitude (uV). Learning-induced amplitude changes were calculated as ((Posttraining amplitude – pretraining amplitude)/pretraining amplitude) × 100. Two-tailed single-sample *t*-tests were used to determine significant amplitude changes as a function of learning. For Pearson correlative data, neural contrast scores were calculated as learning-induced amplitude change in ABR evoked by the signal tone—learning-induced amplitude change in ABR evoked by a neighbor tone. We were unable to obtain valid posttraining for two subjects, resulting in the following treatment-group and phenotype-group numbers: vehicle: $n = 7/7$ versus RGFP966: $n = 4/6$; or general memory: $n = 6/7$ versus specific memory: $n = 5/6$.

Auditory cortical recording procedures and analysis

To determine changes in the frequency-specificity of auditory cortical bandwidth tuning, electrophysiological recordings were obtained from anesthetized subjects (total $n = 19$ rats) (sodium pentobarbital, 50mg/kg, i.p.) in an acute, terminal recording session 24–48 h following the Memory Test. All recordings were in the same recording chamber as what was used to obtain ABRs, which was completely separate from the training chamber while the animals were in a completely different state and context than that used in training. Recordings were also obtained from a group of experimentally naïve rats that received no behavioral training ($n = 5/19$). All recordings were performed inside a double-walled, sound attenuated room using a linear array (1 × 4) of parylene-coated microelectrodes (1–2 MΩ, 250 µm apart) targeted to the middle cortical layers (III-IV, 400–600 µm orthogonal to the cortical surface) of the right auditory cortex. Multiple penetrations were performed across the cortical surface (M = 63.55 sites/animal, SE = 3.62). Acoustic stimuli were presented to the left ear from a speaker positioned ~10 cm from the ear. Sounds were 50 msec pure tones (1–9 msec cosine-gated rise/fall time) presented in a pseudorandom order (0.5–54.0 kHz in quarter-octave steps; 0–70 dB SPL in 10 dB steps; 5 repetitions) with a variable inter-stimulus interval an average of 700 ± 100 msec apart. Neural activity was amplified × 1000 and digitized for subsequent off-line spike detection and analysis using custom Matlab scripts. Recordings were band-pass filtered (0.3–3.0 kHz). Multiunit discharges were characterized using previously reported temporal and amplitude criteria (Elias et al. 2015). Acceptable spikes were designated as waveforms with peaks separated by no more than 0.6 msec and with a threshold amplitude greater than 1.5 (for the positive peak) and less than 2.0 (for the negative peak) × RMS of 500 random traces from the same recording on the same microelectrode for each site. For each recording site, tone-evoked spike rate (spikes/s) were calculated by subtracting spontaneous spiking (40 msec window prior to tone onset) from evoked-spiking within a 40 msec response-onset window (6–46 msec after each tone onset). Responses greater than ±1.0 SEM of the spontaneous spike rate were considered true evoked responses. Tone-evoked activity was used to construct frequency-response areas (FRAs) for each recording site, which reveal the mean sound-evoked activity to each frequency/sound level combination. The borders of each FRA were determined based on a threshold firing rate value determined by its spontaneous activity. Only evoked responses greater than the mean of preonset spontaneous activity were considered true sound-evoked responses. The outside border of each FRA was used to determine (1) response threshold, or the lowest sound level (dB SPL) that evokes a response, (2) characteristic frequency (CF), or the frequency to which the site responds most strongly (in spikes/s) at threshold sound level, and (3) tuning bandwidth, or the breadth of frequency responsivity (in octaves) as a function of dB above response threshold. Thus, BW10, BW20, BW30, and BW40 denote bandwidth 10, 20, 30, and 40 dB SPL above threshold sound level, respectively. In order to determine tuning plasticity as a function of acoustic frequency, bandwidth data was sorted by CF to create three frequency bins : (1) sites tuned near (within ±1/3 octave) the 5.0 kHz signal tone frequency (4.2–6.0 kHz), (2) sites tuned far (between 1.04 and 1.70 octaves) away from the 5.0 kHz signal tone frequency (10.3–16.5 kHz), and sites tuned very far (between 2–2.67 octaves) away from the 5.0 kHz signal tone frequency (20.0–32.0 kHz). For group analysis of bandwidth, individual recording sites were treated as individual observations (naïve: $n = 5$ subjects/26 recordings sites near 5.0 kHz/50 recording sites far from 5.0 kHz/33 sites very far from 5.0 kHz; vehicle: $n = 7$ subjects/44 sites near 5.0 kHz/59 sites far from 5.0 kHz/60 sites very far from 5.0 kHz; RGFP966: $n = 6$ subjects/23 sites near 5.0 kHz/41 sites far from 5.0 kHz/40 sites very far from 5.0 kHz). Differences in tuning bandwidth within a frequency bin was compared among conditions (vehicle, RGFP966, and naïve) using one-way ANOVA. Pairwise comparisons were made with Holm-Bonferroni corrected two-tailed *t*-tests. Corrected *P*-values are reported. For Pearson correlative data, an average bandwidth score for BW20 was computed for each individual. One outlier belonging to the vehicle/frequency-general memory groups was excluded from analysis justified by >3 times the mean Cook's distance.

Data availability

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

Competing interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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