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Adaptive Training Diminishes Distractibility in Aging across Species

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SUMMARY

Aging is associated with deficits in the ability to ignore distractions, which has not yet been remediated by any neurotherapeutic approach. Here, in parallel auditory experiments with older rats and humans, we evaluated a targeted cognitive training approach that adaptively manipulated distractor challenge. Training resulted in enhanced discrimination abilities in the setting of irrelevant information in both species that was driven by selectively diminished distraction-related errors. Neural responses to distractors in auditory cortex were selectively reduced in both species mimicking the behavioral effects. Sensory receptive fields in trained rats exhibited improved spectral and spatial selectivity. Frontal theta measures of top-down engagement with distractors were selectively restrained in trained humans. Finally, training gains generalized to group- and individual-level benefits in aspects of working memory and sustained attention. Thus, we demonstrate converging cross-species evidence for training-induced selective plasticity of distractor processing at multiple neural scales, benefitting distractor suppression and cognitive control.

INTRODUCTION

Aging is associated with deficits in cognitive control that span multiple functional domains, including perception, attention, working memory, long-term memory and action (Craik and Salthouse, 2000; Gazzaley, 2013). A common factor underlying these impairments is an age-related deficit in the suppression of task-irrelevant distracting information, which in turn

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degrades achievement of task-relevant goals (Hasher et al., 1999; Gazzaley et al., 2005; Gazzaley, 2013; Wais and Gazzaley, 2014). Distractibility is defined here as the inability to sustain focus on goal-relevant target information due to attending and/or erroneously responding to goal-irrelevant stimuli (distractors) as if they were targets. The detrimental impact of distractibility on cognition in older adults penetrates even basic daily life activities (Strayer and Drews, 2004; Bock, 2008), to the extent that this impairment has become a hallmark of cognitive aging; notably when it occurs in conjunction with other age-related changes, such as diminished processing speed and sensory deficits (Salthouse, 2000; Jackson and Owsley, 2003; Gazzaley et al., 2008; Frisina, 2009).

There have been many cognitive training studies in recent years that have attempted to delay or reverse age-related cognitive decline (Mahncke et al., 2006; Ball et al., 2007; Smith et al., 2009; Anderson et al., 2013; Wolinsky et al., 2013). Reinforcement-driven operant conditioning forms the basis of most of these training approaches and has been shown to engender behavioral improvements as well as remediative neural changes (Berry et al., 2010; Engvig et al., 2012; Gajewski et al., 2012; Anguera et al., 2013). However, despite efforts this training approach has not translated to reduced distractibility in older adults (Berry et al., 2010; Buitenweg et al., 2013) or in any other population that exhibits similar suppression deficits (e.g., children: Stevens et al., 2008). Deficits in distractor suppression also extend to older rats, and a recent operant training study was found to be highly successful in recovering more than twenty age-related cortical processing deficits, yet the distractor suppression deficit remained unaltered (de Villers-Sidani et al., 2010).

We hypothesized that effective neurological remediation of distractibility requires a training approach specifically directed at this deficit. In prior studies that failed to remediate distractibility, individuals were trained to discriminate progressively more challenging task-relevant target stimuli, but not to manage more challenging distractors. These studies, performed both in older humans (Berry et al., 2010, Mishra et al., 2014) and rats (de Villers-Sidani et al., 2010), show robust neural enhancement of relevant information, but find no impact on distractor suppression. This selectivity is expected, as supported by neuroscience evidence showing that neural enhancement and suppression have distinct neural networks (Chadick and Gazzaley, 2011) and are differentially impacted in aging (Gazzaley et al., 2005; 2008; Clapp and Gazzaley, 2012; Chadick et al., 2014).

Motivated by this literature, the current study assessed an adaptive training approach that immersed older trainees in a task that involved progressively more challenging distractors, with the goal of selectively improving neural and behavioral distractor suppression (Adaptive Distractor Training – ADT). The training used auditory tones at various frequencies as targets and distractors, and was evaluated in parallel experiments in older adults of two species, rats and humans. Trainees were presented with three successive tone frequencies on every trial, any one of which could be a target; there was only one unique target frequency in each training block that occurred infrequently (on 20% of trials), while all other stimuli were distractors. Both rats and humans implicitly learned to identify the target tone in each block through reinforcement feedback, and then had to continue to correctly identify that target tone amidst progressively more challenging distractor frequencies (Fig. 1A). Thus, the main feature of the training approach was that task

difficulty was adaptively modified by adjusting the distractor tone frequencies relative to the target based on performance in the preceding trial. Using adaptive algorithms, distractor frequencies were progressively made more similar to the target after correct discriminations or more dissimilar after incorrect discriminations, while the target frequency was kept constant.

The underlying neurophysiological mechanisms of training effects were evaluated in aged rats using single-unit and multi-unit recordings in the auditory cortex and in older humans using high-density electroencephalography (EEG). Recordings in anesthetized trained animals provided a measure of sensory cortex plasticity at single neuron resolution in the absence of cognitive control. Neuronal distractor suppression was evaluated under anesthesia in a classic auditory oddball sequence paradigm in which deviant 'oddball' tones occurred infrequently in a background of fixed frequency distractor tones (de Villers-Sidani et al., 2010). This evaluation complemented EEG-based neural population recordings in awake humans, which probed sensory plasticity in early event related potential (ERP) responses to distractors vs. targets. In humans, we further assessed plasticity of top-down prefrontal neural circuits and prefrontal-sensory communication. Theta frequency band oscillations have been evidenced as a mechanism of top-down cognitive control (Cavanagh and Frank, 2014), which has also been shown to be modulatable in older adults with video game-based cognitive training (Anguera et al., 2013). Hence, we investigated whether theta spectral power, as well as theta phase locking across frontal and sensory electrode sites, was modulated by our distractor training, and importantly whether we observe differential modulation of theta signals elicited to targets vs. distractors. Finally, we assayed generalization of adaptive distractor training benefits in humans using three standard tests of cognitive control to probe working memory span, sustained attention, and impact of interference on delayed-recognition working memory.

We present our findings in comparison to untrained control groups in both species as Experiment 1. In addition, to confirm the specificity of our findings to adaptive distractor training, we subsequently performed Experiment 2 where we introduce adaptive target training (ATT) in humans. The ATT procedure was matched in its range of training stimuli as well as adaptive challenge parameters to ADT, such that these two training groups experienced similar motivation, engagement, challenge and level progressions throughout training. The sole difference was that the adaptive mechanics were focused on progressively more challenging distractors amidst fixed targets in ADT (Experiment 1), and on more challenging targets amidst fixed distractors in ATT (Experiment 2). Thus, in Experiment 2 we investigated whether ATT in comparison to the untrained control group, would confer the same neuroplastic changes to distractor processing as ADT in Experiment 1. Together Experiments 1 and 2 allowed us to understand how adaptive training, customized to each individual's performance capacities and focused on specific neural processes, can be used to achieve selective and corrective tuning of a deficient neural process. Finally, in Experiment 3 we compared behavioral outcomes in older adult rats/humans to single session performance of younger adults to characterize the extent of training-related benefits in aging.

RESULTS

Experiment 1

Behavioral Performance—The ADT program, termed 'Beep Seeker', was identical for both older rats and humans. It involved the presentation of three auditory tone stimuli per trial (Fig. 1A). All presented tones had the same intensity and duration but different frequencies. If the target tone frequency specific for that training block was identified in the presented tone triplet, human participants responded with a 'yes' button-response, while rats made a 'go' reaching-response. Correct responses in human were rewarded with a score increase and unveil of a background image section, while rats obtained a food reward. Training was adaptive to the performance on each trial, with the mean frequency range distance (in octaves) of the distractors relative to the constant target frequency as the adaptive parameter for both rats and humans. ADT was implemented in both older rats (n=10) and humans (n=16) over 36 training block sessions, each block utilizing a distinct target frequency. Humans trained at home and completed their training in 12 30-min sessions (3 training blocks per session) over a 4–6 week duration.

Training resulted in significant improvement in the successful discrimination of targets in the setting of distractors, with a 48% and 33% improvement in rats and humans, respectively (Fig. 1B). This translated to a pre- to post-training improvement in octave resolution (the minimal frequency difference between the target and a distractor tone that can be reliably detected) of 0.8±0.13 (p=0.003, effect size Cohen's d=1.29) in rats and of 0.38±0.1 (p=0.008, d=1.00) in humans. More detailed analyses showed that this improved discrimination ability was driven by a significant decrease in the proportion of incorrect distractor responses, or false positives, which was reduced by 55% and 33% from the onset of training in rats and human, respectively (Fig. 1C, false positive proportion change in rats: 0.27±0.11, p=0.03, d=0.79, in humans: 0.06±0.03, p=0.03, d=0.59). The target hit rate remained constant throughout training at 58% and 40% on average in rats and humans, respectively (Fig. 1D, hit proportion change in rats: 0.06±0.1, p=0.65, in humans: 0.009±0.06, p=0.89).

In older humans we also assessed performance in an untrained control group (UT, n=15). On the 'target amidst distractors' ADT task, octave resolution for UT did not change significantly in repeat assessments performed 4–6 weeks apart, averaging at 1.2±0.08 octaves across T1 & T2 (change p=0.46). The selective improvement in octave resolution in the ADT group was confirmed as a significant group (ADT vs. UT) by session (T1 vs. T2) interaction ($F(1,29)=7.16$, p=0.01, Fig. S1A). Further in the UT group, there was no significant change in distractor false positives across sessions (p=0.12), while this metric showed selective reduction in the ADT group (group x session: $F(1,29)=6.64$, p=0.02, Fig. S1B). Finally, target hits significantly declined at T2 relative to T1 in the UT group (p=0.005); while this metric did not change in the ADT group, again yielding a group x session interaction ($F(1,29)=5.14$, p=0.03, Fig. S1C). Overall the behavioral evidence suggests that diminished distractibility, as reflected by selectively reduced false positives post-training in the ADT group, was the basis of the improved target resolution amidst distractors. We next assessed the neural basis of this effect in both species.

Recurrent distractor suppression in A1 neurons of aged rats—We used a classic auditory 'oddball' sequence paradigm to assess the effect of training on suppression of distracting sounds in trained rat auditory cortex A1 compared to the cortex of untrained rats. While A1 neurons of healthy anesthetized younger rats exhibit significant response suppression to repetitive distractions, resulting in increased contrast for novel deviant stimuli (Ulanovsky et al., 2003; 2004), this bottom-up process has been shown to be consistently deficient in aged rats (de Villers-Sidani et al., 2010). Given this evidence, the 'oddball' paradigm was chosen over other sensory discrimination tasks. To evaluate if ADT altered distractor response characteristics, anesthetized older rats were presented a sequence of high probability recurring pure tone distractors with a deviant 'oddball' tone occurring randomly with a 10% probability. These stimuli sequences were identical to those previously used to document age-related A1 distractor processing impairments in rats (de Villers-Sidani et al., 2010; de Villers-Sidani and Merzenich, 2011; Kamal et al. 2013).

The primary difference in A1 neuronal responses in trained older animals (ADT), as compared to the same recordings in untrained older animals (UT), was significantly greater suppression of background distractors (Fig. 2, mean normalized response asymptote to distracting tones, UT vs. ADT: 0.30±0.009 vs. 0.19±0.008, $p<0.001$). Training had no significant impact on the average magnitude of the responses to the 'oddballs' ($p=0.4$), paralleling the selective behavioral effect of training on distractor performance. Overall, this stronger and selective neural suppression resulted in a 45% increase in the average cell-by-cell 'oddball'-to-distractor response difference in trained vs. untrained older rats (Fig. 2B, UT vs. ADT: $p=0.002$, $d=0.78$). Training also selectively reduced the response variability of A1 neurons to recurring distracting tones (mean coefficient of variation of normalized spike rate, UT vs. T: 0.21±0.02 vs. 0.18±0.04, $p=0.02$), but not to oddballs ($p=0.7$).

Training-induced changes in A1 response selectivity of aged rats—In older rats, in addition to deficits in distractor suppression, A1 tuning curves are broader (i.e., less frequency selective) and the normally smooth A1 frequency representation gradient, also known as the tonotopic axis, becomes disorganized (Mendelson and Ricketts, 2001; Turner et al., 2005; de Villers-Sidani et al., 2010). Broader tuning curves lead to wider stimulus-induced cortical activation, making sensory discrimination purely based on spatial activation of the cortex less reliable (Recanzone et al., 1993; 1999). We examined the impact of training on A1 response selectivity by measuring A1 neuronal tuning bandwidth at the sound intensity of the training (60 dB) and at 20 dB above threshold (BW20), and the degree of receptive field overlap (RF overlap index, RFOI) between closer and more distant neurons on the A1 map (Fig. 3). The RFOI computes the degree of overlap between two receptive fields (RFs) for all frequency-intensity combinations used to build each frequency-intensity tuning curve. It thus provides additional insight on the extent to which A1 neuron pairs might be differently tuned to the range of presented frequency-intensity combinations. A lower RFOI implies less overlap. Bandwidth measurements and RFOI were obtained from a sample of the entire A1 field in both trained (n=10) and untrained (n=10) animals.

Adaptive distractor training resulted in a 37% decrease in bandwidth at training sound intensity and 31% decrease in BW20 ($p=0.002$ and $p=0.004$ respectively), which was uniform across the range of A1 neuronal characteristic frequencies (CF bins of 2.5, 5, 10, 20

kHz, p=0.3, Fig. 3B–C). Training also globally reduced the RFOI for A1 neuron pairs (Fig. 3A bottom row). While this effect was significant for pairs separated by relatively short distances (<0.75mm, p=0.02), training-induced RFOI reduction was significantly more pronounced for longer inter-neuronal distances in trained relative to untrained animals (>0.75mm, p=0.0002). These results indicate that not only did A1 neurons in trained older rats have narrower more specific receptive fields, but they also had improved spatial resolution compared to A1 neurons in untrained animals.

Attenuated distractor processing in human auditory ERP responses—A neural assessment version of the ADT was used to record ERPs elicited by the distractor and target tone stimuli at time points, T1 and T2, preceding and following training in older humans. Participants in the UT control group underwent repeat testing to evaluate practice effects on this assessment. The distractor frequency range proximity to target stimuli was adaptively modulated at the T1 neural assessment, same as in ADT. The T1 assessment consisted of 5 blocks of 150 trials each with a distinct frequency target tone in each block, set at 0.6 kHz, 2 kHz, 0.89 kHz, 1.34 kHz and 0.4 kHz for all participants. These specific tone targets during assessment were never assigned as targets within training. At T1, task difficulty was adaptively modified on each trial by moving the distractor frequency range, spanning 0.2–4 kHz, closer to (or further from) the target within a ±2.0 to ±0.1 octaves range based on the participant's discrimination performance. Similar to the training, stimuli were presented as tone triplets in each trial with 20% target occurrence probability across all trials. Notably at T2, stimuli progressions were yoked to T1 to measure neural response modulations for the same set of physical stimuli at T1 and T2 in each participant. Overall, the large variety of constantly changing distractor frequencies employed in this paradigm provided a much more engaging and challenging assessment in awake humans, in contrast to the 'oddball' assessment in anesthetized rats that measured target responses amidst a background of repetitive distractors.

Early auditory processing in the ADT group showed a significant reduction in the neural response to distractors at 150–160 ms latencies (Fig. 4A). A group (ADT vs. UT) x session (T1 vs. T2) x stimulus type (distractor vs. target) ANOVA revealed a significant 3-way interaction ($F(1,29)=5.06$, $p=0.03$). This interaction was further parsed in separate 2-way session x stimulus type ANOVAs in the ADT and UT groups, revealing significance only in the ADT group ($F(1,15)=7.79$, $p=0.01$, UT: $p=0.36$). Post-hoc t-tests showed the exclusivity of this result to distractor processing in the ADT group (T1 vs. T2: distractors: $p=0.03$, $d=0.46$, targets: $p=0.85$). As a cross-check, a 2-way group x session interaction comparing distractor stimuli in the ADT and UT group also yielded a significant interaction ($F(1,29)=4.10$, $p=0.05$). The group x session interaction for target stimuli was not significant ($p=0.74$).

Further, this reduction in distractor early ERP processing in the neural assessment in the ADT group significantly correlated with their improved octave resolution during training ($r(14)= 0.5$, $p=0.048$, Fig. 4B); smaller distractor ERP responses at T2 correlated with smaller target vs. distractor octave differences that could be resolved post-training.

The neural generators of the distractor elicited neural response at 150–160 ms localized to temporal cortex in the vicinity of the superior temporal gyrus and auditory pitch processing area BA 22 (MNI coordinates of the source cluster peak: +55, −29, +3 mm). These results suggest similar sensory loci of neural modulation, around auditory cortex for both humans and rats. Furthermore, these results demonstrate the same plasticity mechanism of selectively reduced responses to distractors observed at multiple scales–the level of single neurons in rats and population neural activity in humans.

Training-induced changes in top-down distractor processing in humans— Frontal theta (4–8Hz) oscillations have been evidenced as an EEG marker of cognitive control and associated with interference resolution (Cavanagh and Frank, 2014; Anguera et al., 2013). We evaluated early event-related frontal theta (50–150 ms post-stimulus onset) in the neural assessment version of the ADT task in a group (ADT vs. UT) x session (T1 vs. T2) x stimulus type (distractor vs. target) ANOVA. A significant 3-way interaction was observed ($F(1,29)=8.82$, $p=0.006$), which was further parsed in separate 2-way session x stimulus type ANOVAs in the ADT and UT groups. The 2-way interaction was only significant in the ADT group, suggesting differential modulation of target vs. distractor processing in this group but not in the UT group (ADT: $F(1,15)=15.22$, $p=0.001$, UT: $p=0.24$). Post-hoc t-tests showed that ADT individuals selectively increased their target-related frontal theta post-training ($p=0.007$, $d=0.56$) but not distractor theta ($p=0.28$) (Fig. 5A).

Although the ADT group did not elicit a significant mean change in frontal theta to distractors, we investigated if the individual differences in this measure may relate to the change in auditory event-related distractor processing at 150–160 ms. We found a positive correlation between these measures such that ADT individuals who restrained frontal theta more also showed more reduced sensory distractor ERPs post-training ($r(14)=0.66$, $p=0.005$, Fig. 5B).

The neural generators of the early frontal theta power signal were analyzed by distributed minimum-norm source localization. The peak source cluster localized in the middle frontal gyrus (Fig. 5C, MNI coordinates: +46, −1, +44 mm), in close proximity to the inferior frontal junction, which is a known prefrontal site involved in cognitive control and suppression of distracting information (Gazzaley et al., 2007; Wildenberg et al., 2010; Zanto et al., 2010; 2011). The localization of the theta signal to a prefrontal site further showed that it was a unique signal source amidst auditory event-related activity, which often exhibits frontal voltage topography but with dipole sources in temporal auditory cortices (Woods, 1995).

Finally, we analyzed frontal-sensory phase coherence in the theta range between peak frontal theta site (FCz) and peak temporo-lateral site at which auditory distractor ERP processing showed maximal modulation (P6). At 50–150 ms latencies in the upper theta range (6–8 Hz), T2 vs. T1 frontal-sensory phase coherence was selectively attenuated for distractors vs. targets in the ADT group but not in UT group (Fig. 5D–E, group (T vs. UT) x session (T1 vs. T2) x stimulus type (distractor vs. target) ANOVA 3-way interaction $F(1,29)=7.02$, $p=0.01$). Separate 2-way session x stimulus type ANOVAs in either group

confirmed this results (ADT: F(1,15)=14.25, p=0.002, UT: p=0.71). This modulation in distractor phase coherence suggested a training-related change in the interaction between the neural processing at sensory and frontal cognitive control sites. The reduced frontal-sensory phase coherence for distractors post-ADT may be interpreted as reduced distractor encoding in the functional network that represents task-relevant targets. This is in line with recent research showing that sensory cortices encoding task-relevant vs. irrelevant (distracting) information preferentially connect with the fronto-parietal and the default mode networks, respectively (Chadick and Gazzaley, 2011).

Overall, these frontal theta modulations revealed that distractor training-driven neuroplasticity was not simply confined to sensory cortices, but in addition, emerged in frontal activations and inter-regional functional connectivity modulations. Notably, these frontal modulations occurred in the similarly early time ranges post-stimulus onset as the auditory sensory cortex localized changes.

Transfer of training benefits to other measures of cognitive control—The benefits of distractor training on other cognitive control abilities in humans were assessed in the auditory domain in three tests: sustained attention, working memory with secondary task interference, and working memory span. A repeated measures ANOVA on test accuracy, with factors of group (ADT vs. UT), session (T1 vs. T2) and test type (three cognitive assessments), showed a significant 3-way interaction (F(2,58)=4.34, p=0.02). This interaction was driven by a significant group x session interaction on the working memory span test (F(1,29)=6.12, p=0.02), but not for the sustained attention test (p=0.27) nor the working memory with interference test (p=0.20). Post-hoc t-tests showed that only the ADT group significantly improved on working memory span (p=0.02, d=1.3, UT: p=0.4, Fig. 6A). Notably, these working memory span improvements suggest far transfer of the benefits of training to working memory for complex letter/number stimuli from distractor training on elementary tones.

Further, we found neurobehavioral correlations between the auditory ERP distractor processing modulation and the change in working memory span (r(14)=−0.53, p=0.04); i.e., individuals with more diminished distractor neural processing post-training showed greater working memory span improvement (Fig. 6B). Although group mean differences were not observed for the sustained attention test, neurobehavioral correlations also emerged for this test. Individuals with more diminished auditory distractor ERP processing post-training showed greater reductions in reaction time variability on the sustained attention test (r(14)=0.60, p=0.01, Fig. 6C).

Experiment 2

Effect of adaptive target training (ATT) on distractor processing—To further explore the specificity of our behavioral, neural and cognitive transfer results, we enrolled a group of healthy older human adults in adaptive target training (ATT, n=15). This training was similar to the reinforcement training previously applied in older rats (de Villers-Sidani et al., 2010). Individuals were presented a sequence of six tones on every trial, 50% of trials contained a deviant tone of a different frequency (at any position in the sequence) relative to

the other five same-frequency tones. The training task was to respond 'yes' when the deviant target was detected, or else respond 'no'. Importantly, this training was adaptive to performance, such that the deviant target frequency moved closer to the frequency of the background distractor sequence with accurate performance, and moved further away with poor performance. Thus, the ADT and ATT training both included target vs. distractor discriminations, with the sole exception that the adaptive mechanics were either focused on progressively more challenging distractors in ADT (Experiment 1), or more challenging targets in ATT (Experiment 2). After 36 sessions on a similar training schedule and duration as the ADT group, the ATT group significantly improved their training task performance ($p=0.05$, $d=0.94$).

Changes in octave resolution resulting from ATT were evaluated using the same 'target amidst distractors' assessment as used in Experiment 1 to compare ADT and UT groups. Results indicated that the ATT group improved significantly from T1 to T2 ($p=0.02$), and the group (ATT vs. UT) x session (T1 vs. T2) interaction was significant ($F(1,28)=4.20$, $p=0.05$, Fig. S2A). However, a deeper inspection of the target and distractor responses driving this change in octave resolution revealed that this effect was driven by the ATT group significantly shifting their response bias towards more 'No' responses, while there was no significant change in bias in the UT, or ADT group from Experiment 1 (T1 vs. T2 change in total proportion of No responses; ATT: $p=0.03$, UT: $p=0.56$, ADT: $p=0.1$; also confirmed by an assessment of T2 vs. T1 response criterion (c); ATT: $p=0.01$, UT: $p=0.15$, ADT: $p=0.1$). As a result of this bias shift, the ATT group showed a significant reduction in distractor false positives ($p=0.05$, less 'yes' responses to distractors, UT $p=0.12$, Fig. S2B), but also a significant reduction in target hits ($p=0.02$, less 'yes' responses to targets, UT $p=0.005$, Fig. S2C). Overall, the behavioral data showed that although the ATT group appeared to perform better after training, this was the result of a change in response bias and not the result of a true improvement in discrimination. Based on these behavioral findings, we did not expect to find the same signatures of distractor processing related neural plasticity in the ATT group that were found in the ADT group in Experiment 1.

The neural data were evaluated in 3-way ANOVAs with between-subject factor of group (ATT vs. UT) and within-subject factors of session (T1 vs. T2) and stimulus type (distractor vs. target). Auditory ERP processing (150–160 ms) showed no differential ATT vs. UT group effects (group: $p=0.61$, group x session: $p=0.25$, group x session x stimulus type: $p=0.22$, Fig. S3A). Frontal theta power modulation (50–150 ms) was also not different between ATT and UT groups (group: $p=0.35$, group x session: $p=0.35$, group x session x stimulus type: $p=0.38$, Fig. S3B) and frontal-sensory theta phase coherence also showed null interactions (group: $p=0.08$, group x session: $p=0.99$, group x session x stimulus type: $p=0.88$, Fig. S3C). Finally, cognitive transfer measured in a 3-way ANOVA of group (ATT vs. UT) x session (T1 vs. T2) x test type (three cognitive assessments) showed no significant interaction ($p=0.45$).

Overall, these comparisons showed that ATT was not associated with the same neural changes in distractor vs. target related neural processing as observed for ADT vs. UT comparisons in Experiment 1. Further, ATT did not result in significant cognitive transfer

even though it was implemented in a nearly identical training environment and with an equivalent training schedule/duration as ADT.

Experiment 3

Comparison with performance in younger adults—Younger (6–12 months old, n=6) rats were assessed on the 'target amidst distractor' task to assess their octave resolution relative to older rats. On average, younger rats had approximately 25% better octave resolution than older rats (p=0.03). With adaptive distractor training, older rats surpassed younger rats to reach target amidst distractor resolution 33% finer than the younger group (p = 0.02) (Fig. S4).

A healthy younger human adult cohort (n=15) was recruited to perform a single session (T1) behavioral assessment of 'target amidst distractors' octave resolution. Younger adult octave resolution at T1 was compared to performance of all older adults using bootstrap statistics with 10000 iterations of random sampling to account for unequal sample sizes. At T1, younger adults had significantly superior octave resolution, by approximately 14% (p=0.0004). We also compared young performance at T1 to performance of older adults at T2 in a one-way ANOVA with group (young vs. ADT vs. UT vs. ATT) as a factor. A significant effect of group was observed ($F(3,57)=7.75$, p=0.0002) and post-hoc t-tests showed that only the ADT group exhibited significantly better octave resolution at T2, which was 31% finer than the resolution of younger adults (p=0.006, d=1.13); this comparison was not significant for UT (p=0.16) or ATT (p=0.42) groups. Thus, with training, only the ADT older adults surpassed performance of younger adults on the 'target amidst distractors' task (Fig. S4).

Single visit young adult performance was also assayed on the three-test cognitive battery: sustained attention, working memory span, and working memory with interference. Young performance relative to all older adults at T1 was evaluated with an age (younger vs. older) x test type (three tests) ANOVA, which showed a significant interaction ($F(2,118)=4.47$, p=0.01). Post hoc t-tests showed that young and older adults did not differ on the sustained attention test accuracy (p=0.49), or on the working memory span test (p=0.11). But young adults were significantly superior compared to older adults on the working memory with interference test ($F(1,59)=8.01$, p=0.006, d=0.86); for this test we also compared young adult performance separately to each of the older adult training groups at T1 and found significant or near significant differences for each group (YA vs. ADT p=0.04, YA vs. ATT p=0.006, YA vs. UT p=0.06).

Older adult cognitive performance at T2 did not significantly differ from young adult performance at T1 (group (young vs. ADT vs. UT vs. ATT) x test type (three tests) interaction: p=0.38). Specifically, for the working memory with interference test that showed differences at T1, age differences at T2 did not reach significance (YA vs. ADT p=0.07, YA vs. ATT p=0.11, YA vs. UT p=0.35). Note, that while there was a trend towards age-normalization for older adults at T2 for the working memory with interference assessment, the older adult groups did not have significant T2 vs. T1 session differences on this test (all p values > 0.1). In general, these results suggested that our healthy older adults

cohort was a high functioning group, yet ADT improved octave resolution beyond that of young adults.

DISCUSSION

In the present study, we demonstrate that poor signal-to-noise resolution in aging brains stemming from inappropriately heightened neural representations of distractors can be remediated using a simple reinforcement training approach. Selective neural plasticity of distractor representations was observed across aging rats and humans using an adaptive distractor training procedure whose mechanics specifically challenge the trainee to make tone discriminations amidst progressively more interfering distractors (i.e., with frequencies approaching the target tone frequency). In both rats and humans, discrimination of targets amidst distractors was significantly improved via training. Neural impacts were observed at multiple scales: (1) diminished neuronal firing to distractors in rat auditory cortex, (2) concomitantly, enhanced spatial and spectral sensitivity of auditory cortex tonotopic maps in rats, (3) diminished early event-related auditory processing of distractors in humans, and (4) selectively restrained prefrontal engagement and frontal-sensory connectivity to distractors relative to targets in humans. Additionally, behavioral impacts of training include transfer of benefits to improved working memory span at the group level, and reduced variability in sustained attention at the individual level. Importantly, the current training approach provided critical insight that deficient neural processes, here distractor processing, can be selectively targeted by focusing the adaptive mechanics of cognitive training to challenge that specific deficient neural process and behavior. It thus shows principal evidence for an effective means of achieving selective neural tuning via an adaptive cognitive training approach.

Distractibility is a significant problem in aging, and is reflected in neurophysiological signatures at multiple levels. Aging auditory cortex neurons exhibit weakly inhibited firing patterns, indicating degradation of the GABA-ergic inputs (Krukowski and Miller, 2001; Bao et al., 2004; de Villers-Sidani, 2010). This in turn leads to more overlap in spatial and spectral input representations of neuronal assemblies and ‘detuned’ (larger than normal) receptive fields. Detuned RFs generate degraded tonotopy leading to impaired sensory perceptual discriminations (Betts et al., 2007). Cognitive neuroimaging has shown that insufficient distractor suppression in sensory cortices is further associated with abnormally elevated prefrontal-sensory cortical connectivity for distractors, as well as consequent negative impacts on cognitive control behavior during attention, working memory and long-term memory (Gazzaley et al., 2005; 2008, Clapp et al., 2011; Clapp and Gazzaley, 2012; Wais and Gazzaley, 2014, Chadick et al., 2014).

Here we show that distractor suppression can be ameliorated at multiple neural levels. Frequency-invariant distracting tones were effectively suppressed in early (within 50 ms) A1 neuronal responses of older rats, providing evidence for bottom-up sensory plasticity in the absence of cognitive control in the anesthetized animal. Such pure bottom-up modulations revealed under anesthesia i.e., in the absence of influences of top-down goals, can be rarely investigated in humans, and demonstrate a clear benefit of our two-species approach. Further, the observed improvements in A1 spatial and spectral sensory RFs are likely a

direct outcome of the improved neuronal distractor response inhibition (Zheng and Knudsen, 1999). Parallel reduction of distractor processing in humans, primarily localized to superior temporal gyrus and auditory pitch processing cortex, peaked at 150–160 ms, and notably correlated with improved target-distractor discriminations in a dynamic frequency challenge. The relatively later sensory plasticity observed in humans compared to rats may be driven by the dynamic distractor stimuli (varying tone frequencies) used for assessment in humans, and was most likely enabled by early top-down frontal communication that updates goal-relevant target vs. distractor information. Indeed, we additionally found evidence for plasticity of prefrontal processing in early (50–150 ms) frontal theta oscillations in humans, although we did not have an opportunity to measure frontal signals in anesthetized rats.

In humans, the top-down neural signal evaluations were performed in a ‘target amidst distractors’ assessment version of the adaptive distractor training task. This provided a much more challenging assay of distractibility in contrast to the oddball paradigm in anesthetized rats that had no top-down engagement. Thus, while it is true that different neural assessments were performed in the two species, the matched training across rats and humans afforded the opportunity to evaluate pure bottom-up changes in the anesthetized animal, and also inform bottom-up and top-down interactions in awake humans. The stimulus-evoked frontal theta signals recorded in humans were localized to the middle frontal gyrus. Theta responses were selectively enhanced for targets but not distractors in trained humans. Further, individuals who showed greater restraint in early frontal theta responses to distractors also showed reduced processing of sensory distractor ERPs with training. Finally, early frontal-sensory theta phase coherence between the peak frontal theta site and the peak sensory modulation site was significantly reduced for distractors relative to targets. As the frontal theta response localized to cognitive control sites in the vicinity of the inferior frontal junction (IFJ), a region associated with task-relevance (Brass et al., 2005; Zanto et al., 2011), we speculate that the diminished frontal-sensory coherence exclusively for trained distractors is evidence of reduced distractor representations in this task-relevant network (Chadick and Gazzaley, 2011). Overall, these results show that distractor training leads to selective and refined plasticity of early top-down neural processing of distractions. Of note, the time scales of these dynamics match those of attentional modulation in sensory cortices (Hillyard and Anllo-Vento, 1998), which have been shown to be vulnerable in aging (Gazzaley et al., 2008, 2013).

Despite the use of elementary tonal stimuli, we found significant transfer of training benefits to working memory span of letters and numbers at the group level. Working memory span improvements directly correlated with the auditory distractor processing neural changes. Further, the reduced distractor ERP processing with training also correlated with reduced response variability in the sustained attention test, suggesting a general neural mechanism for these transfer effects. That few hours of adaptive distractor training can engender some transfer of benefits aligns with recent understanding that global cognitive improvements are stimulated by fundamental sensory perception and discrimination training (Berry et al., 2010; Vinogradov et al., 2012; Anderson et al., 2013; Wolinsky et al., 2013), which improves signal to noise contrasts at multiple neural scales as evidenced here.

Overall, we provide multiple scales of neurophysiological evidence that distractor processing can be selectively improved by specifically focusing the adaptive mechanics of cognitive training to challenge this deficient process. We demonstrate these results relative to an untrained control group. Subsequently, we also tested an adaptive target training group that engaged in an identical training environment and training schedule as the adaptive distractor training group, with the sole difference in training being the focus of the adaptive mechanics, on targets in ATT vs. distractors in ADT. This adaptive target training group did not differ in comparison with the untrained control group, i.e. did not show the same neural, behavioral, and cognitive benefits as the adaptive distractor training group. These results build on prior findings in older rats that adaptive target challenge amidst fixed distractors does not improve distractor processing (de Villers-Sidani et al., 2010).

It has been recently postulated that none of the documented age-related neural changes are truly random degeneration, but are the result of tightly orchestrated and potentially reversible adjustments of cortical machinery in response to noisy peripheral sensory inputs (de Villers-Sidani and Merzenich, 2011). The functional and structural state of the aging cortex is noted to be similar to the state of the immature or noise-exposed cortex, and thus, intensive training regimens that are designed to specifically drive positive plasticity in neural systems should reverse the aging neuropathology. Indeed aligned with these hypotheses, we observe that with adaptive distractor training older adults can achieve and significantly surpass young adult discrimination performance. It is further hypothesized that a hallmark of successful learning is the widespread and coordinated neural representation of relevant inputs and outputs, distributed and interacting across multiple levels of processing and throughout multiple brain regions (Vinogradov et al., 2012). We provide evidence for this hypothesized large scale coordinated neuroplastic process. By demonstrating these changes in aging, we further emphasize that mechanisms of learning-induced plasticity are active and thriving throughout the adult lifespan (Dahlin et al., 2008; Anguera et al., 2013). Finally, the complementary evidence for neuroplasticity from a parallel animal and human experiment of reinforcement training highlights the usefulness of such an approach in the mechanistic evaluation and refined design of future neuro-cognitive therapeutic interventions for diverse neuropsychiatric populations.

EXPERIMENTAL PROCEDURES

Methods in Rats

All procedures were approved under University of California San Francisco Animal Care Facility protocols. Twenty male aged (26–32 months old) and six young adult (6–12 months) Brown-Norway rats obtained from the National Institute on Aging colony were used for this study. Ten aged rats were trained, ten aged rats were untrained controls.

Training—Lightly food deprived aging rats were rewarded with a food pellet for making a ‘go’ response less than 3 seconds after the presentation of a target stimulus. The target stimulus consisted of a train of three tone stimuli containing a target frequency and two random distractor tones. The intensity and duration of the distractors was identical to that of the target tone. The frequency of the distractors was chosen randomly from a range of

possible values above or below the frequency of the target. The task difficulty was increased by reducing the gap between the target frequency and the range of possible distractor values according to the animal's performance. Training started at level 1 on each day. At level 1 the closest a distractor could be from the target was 1.5 octaves. At level 10, the hardest level, the closest a distractor could be from the target was 0.1 octaves. The minimal distance in frequency between distractor and target was reduced linearly by 0.14 octaves with each increase in level. The level was increased after 3 consecutive correct target identifications and decreased after a response to a non-target (false positive) or miss as a 3up-1down staircase. The tones were presented at 60 dB SPL. Training was performed in an acoustically transparent operant training chamber contained within a sound-attenuated chamber. Psychometric functions and target stimulus recognition thresholds were calculated for each training session by plotting the percentage of go responses as a function of the total number of target stimuli (hit ratio) and the percentage of false positives as a function of the total number of distractors (false positive ratio).

Auditory Cortex Mapping—Acute surgeries and A1 mapping were conducted as previously described (de Villers-Sidani et al., 2007, supplemental experimental procedures). Frequency-intensity receptive fields (RF) were reconstructed by presenting pure tones of 50 frequencies (1–30 kHz; 0.1 octave increments; 25 ms duration; 5 ms ramps) at eight sound intensities (0–70 dB SPL in 10 dB increments) to the contralateral ear at a rate of one stimulus per second.

To assess cortical responses to deviant 'oddball' tones, five minute-long trains of tone pips consisting of 25 ms duration pips, were presented at 5 pulses per second at a sound intensity of 70 dB SPL. Each train had a frequently occurring frequency (standard) with a probability of occurrence of 90% and a pseudo-randomly distributed oddball frequency presented 10% of the time with no repetition. The two frequencies in the train had a constant separation of 1 octave and were chosen so they would be contained within the RF of the recorded neuron and elicit strong reliable spiking responses. Supplemental experimental procedures provide details on electrophysiological data analyses.

Data Statistics—Statistical significance for trained vs. untrained animal data was assessed using unpaired two-tailed t-tests with Bonferroni correction for multiple comparisons. Data are presented as mean ± standard error to the mean (s.e.m) and effect sizes were calculated as the Cohen's d (Cohen, 1988).

Methods in Humans

Participants—Forty-seven healthy older adults (mean age 69 years, 32 females) participated in the study. All participants gave written informed consent in accordance with the guidelines set by the Committee on Human Research at the University of California, San Francisco, and were monetarily compensated for participation. All participants had normal or corrected-to-normal vision, were screened for normal hearing, and underwent neuropsychological testing to ensure healthy executive and memory function (supplemental experimental procedures). Additionally, participants reported no history of stroke, traumatic

brain injury, psychiatric illness, and none used any medication known to affect cognitive state.

Fifteen healthy young adults (mean age 24 years, 8 females) were also recruited from the UCSF community to investigate single session behavioral and cognitive performance relative to the older adult cohort. All young adults had normal or corrected to normal vision, normal hearing and gave written informed consent in accordance with the guidelines set by the Committee on Human Research at the University of California, San Francisco. Young adults were also monetarily compensated at the same rate as older adults to participate in the study.

Training and Assessment Procedures—Post-neuropsychological testing, participants were randomly assigned to the adaptive distractor training group (ADT, n=17) or a no-contact control group (untrained: UT, n=15). Subsequently, an adaptive target training group (ATT, n=15) was also tested. The ADT, ATT and UT groups did not differ in age, hearing level or any test in the neuropsychological battery ($p>0.06$ for all comparisons). No group was aware of the existence of the other groups. Physical contact with the research environment and research team was equivalent in all groups as ADT and ATT group participants performed the training at-home on an internet platform. Training group compliance and performance data were monitored remotely on secure online servers. The UT group controlled for practice effects due to repeat assessments as well as placebo effects to some extent as they were informed that the study was investigating outcomes of repeat testing. One participant in the ADT group was removed due to non-compliance with the training regimen.

The ADT approach in humans, termed ‘Beep Seeker’, was similar to the rat training protocol. Participants heard stimuli at an individually-adjusted comfortable hearing level, through Koss UR29 headphones provided to them. Stimuli were presented in sets of three tone pips of 0.1 sec duration each and 0.3 sec inter-tone interval, followed by Yes/No response prompts. Target stimuli occurred at 20% probability and consisted of a target frequency tone pip and two random distractor tones; the target frequency tone pip could occur at any position in the triplet tone stimulus sequence. The rest 80% stimuli were distractor stimuli containing three random distractor tone pips. Correct target and distractor stimuli identifications were ‘Yes’ and ‘No’ responses, respectively. All correct responses were rewarded by unveil of a jigsaw piece covering part of a background scene. To note, the target frequency for each block was not pre-cued as it was difficult to teach rats such cueing and we wanted to emphasize exactly equivalent training protocols in the two species. So humans, like animals, learned to identify the target over the first few trials within each block. This learning usually occurred within the first 20–30% of trials, and the researcher could easily identify the point at which the target had been ascertained by the participant from the daily learning curves; the octave resolution steadily rose to worse values prior to target identification, but then steadily declined and later plateaued after target identification (example daily learning curve in one participant, Fig. S5). Overall, on a trial-by-trial basis, the trainee’s experience was that of a frequency discrimination task, responding ‘yes’ when they detected a target in the trial tone sequence, and if not they responded ‘no’. Yet this was not simple discrimination as all three tones presented per trial always had different

frequencies; the task required discriminating a specific target tone frequency amidst progressively more challenging distractor frequencies.

The intensity and duration of the distractors was identical to that of the target tone. The frequency of the distractors was chosen randomly from a range of possible values above or below the frequency of the target in the 0.2–4 kHz frequency range. The closest a distractor could be from the target was ±2.0 octaves at the easiest level and ±0.1 octaves at the hardest level. The task difficulty was adaptively increased using a Zest procedure (King-Smith et al., 1994) by reducing the gap between the target frequency and the range of possible distractor values based on trial performance. The Zest adjusted octave step size varied in each trial to maintain overall 85% performance.

New training target frequencies between 0.4–2 kHz were introduced after every 120-trial block. Training was accessed at-home via a secure online interface and participants were encouraged to train in a quiet environment with headphones supplied to them. Participants completed 36 blocks of ‘Beep Seeker’ ADT training over 12 30-minute training sessions in 4–6 weeks. Training compliance and performance data were received over a secure cloud data server after each training session. Target stimulus recognition thresholds in each training block were a function of correct target identifications (hits) and incorrect identification of distractors as targets (false positives). The distractor from target resolution in octaves for each training block was calculated as the gap between the target frequency and the range of possible distractors achieved on average over the last 40 of 120 trials, at which the learning curve for any given target was consistently observed to reach an asymptote.

The ATT training in humans presented stimuli similar to the ADT training, and was identical to the training employed in older rats by de Villers-Sidani et al. (2010). Each trial presented stimuli in sets of six tone pips of 0.1 sec duration each, all of the same intensity and 0.3 sec inter-tone interval, followed by Yes/No response prompts. Participants responded ‘yes’ if a deviant target frequency was present at any position in the six-tone sequence, else no if all stimuli were perceived to be of the same frequency. 50% of trials contained the deviant target (lower target percentages were not implemented as they simply made the task too boring). All correct responses were rewarded by unveil of a jigsaw piece covering part of a background scene. In ATT, the frequency of the deviant target tone was chosen randomly from a range of possible values above or below the frequency of the background distractors in the 0.2–4 kHz frequency range. The background distractor frequency was also randomly picked in the 0.2–4 kHz range on every trial. So on any given trial, the closest a target could be from the distractors was ±2.0 octaves at the easiest level and ±0.1 octaves at the hardest level. The task difficulty was adaptively increased using a Zest procedure (King-Smith et al., 1994), by reducing the gap between the range of deviant target frequencies and the background distractor fixed frequency based on the trial performance. The Zest adjusted octave step size varied in each trial to maintain overall 85% performance. Similar to ADT, ATT training was performed at-home on secure online servers; 120 trials were presented per session for 36 sessions in a training schedule of 12 three-block sessions of 30-minutes each per training day over 4–6 weeks.

The neural and cognitive impacts of training were assessed in the lab in two sessions, T1 and T2. Session T1 occurred within a few days of the neuropsychological assessment, while T2 was performed at completion of training by the ADT and ATT groups or after a 4–6 week no-contact period for the UT group. Effect sizes were calculated as the Cohen's d (Cohen, 1988). The cognitive assessments tested (1) sustained attention using the Test of Variables of Attention, Auditory Version (TOVA-A: Greenberg and Waldman, 1993) with a modified inter-stimulus interval of 1.5 s instead of 2 s, (2) working memory span using Letter Number Sequencing (LNS: Weschler, 2008) and (3) working memory (at 9 and 18 s) with secondary task interference using Auditory Consonant Trigrams (ACT: Stuss et al., 1987).

For the neural assessment at T1, all participants took part in a lab-version of the Beep Seeker 'target amidst distractors' ADT task while their EEG was simultaneously recorded. For the T2 neural assessment, auditory stimuli were yoked to those presented at T1. A non-yoked adaptive behavioral assessment was also performed at T2 to ascertain change in octave resolution. The neural assessment, electrophysiological recordings and analyses are detailed in supplemental experimental procedures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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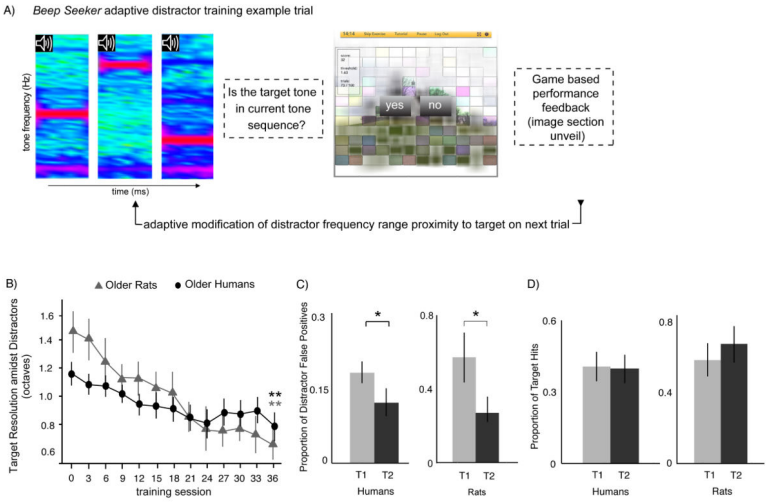

Figure 1.

A) Overview of an example adaptive distractor training trial. Humans and rats were rewarded to discriminate a single target tone amidst distractors in a sequence of three tones. Humans obtained a game-based reward on each trial, unveil of a section of background image, while rats received a food reward. The task was performance adaptive as the distractor frequency range moved closer to the target frequency on successful discriminations. (B) Average distractor-target frequency difference as a function of training session number. The '0' time point in humans corresponds to their T1 assessment. (C) Average proportion of distractor false positives (incorrect discrimination of distractors as targets over the total number of distractors) at first assessment (T1) and at end of training (T2). (D) Average proportion of target hits (correct discrimination of targets over the total number of targets) at T1 and T2. Error shown is s.e.m.

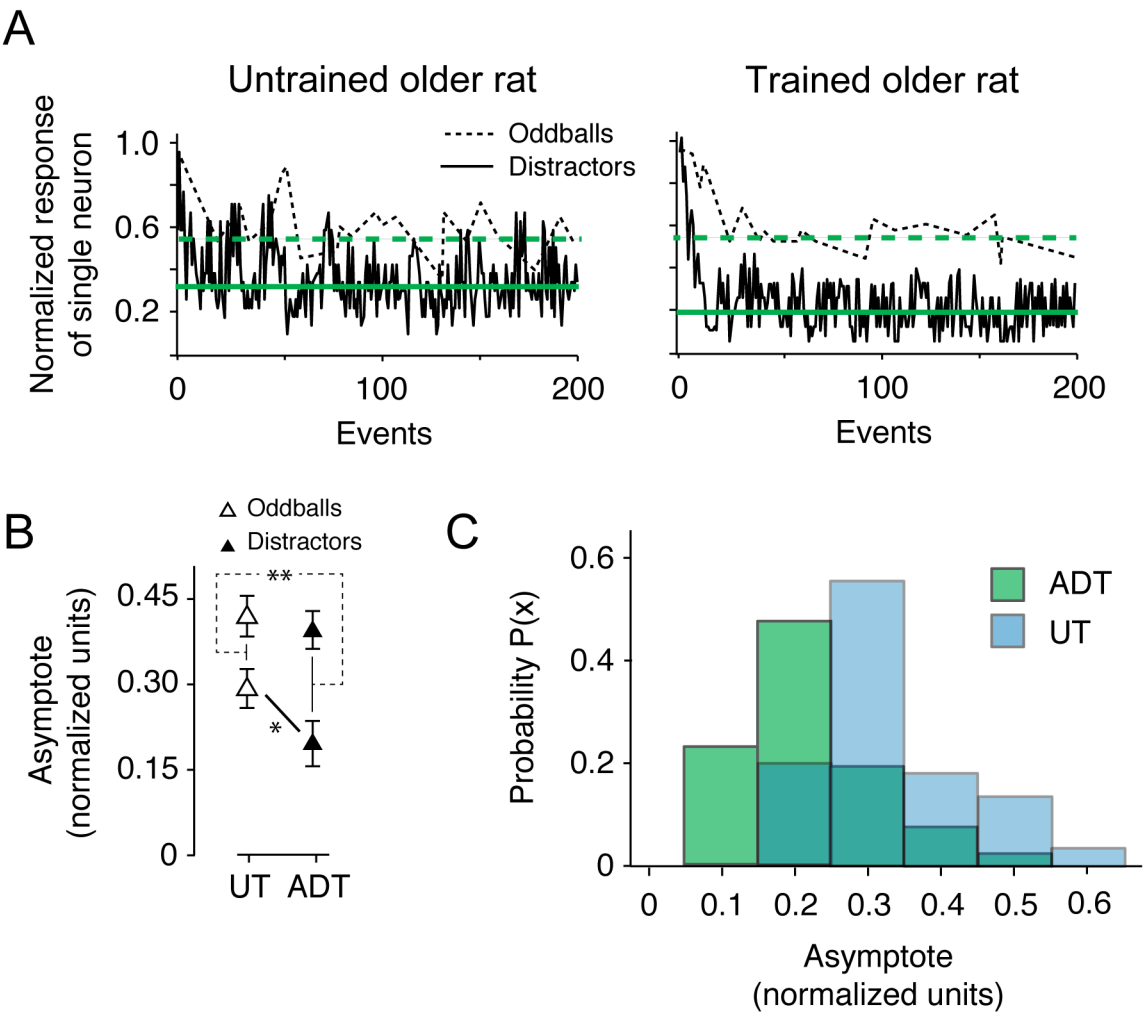

Figure 2.

Distractor suppression in the rat A1 cortex after training. (A) Representative normalized responses of one individual A1 neuron to classic 'oddball' tone sequences in untrained and trained rats relative to tone position in the sequence. Note how responses are progressively suppressed as the sequence progresses. The green horizontal lines represent the response asymptote of the sample neuron to the oddball and repeating distractor tones. (B) Average values of the asymptotes to oddball and distractor tones in the UT and ADT groups. (C) Probability histograms for the values of the asymptotes to distractor tones in the UT and ADT groups. UT neurons recorded: 198; T neurons recorded: 111. Error bars are s.e.m. *: $p<0.05$. **: $p<0.01$.

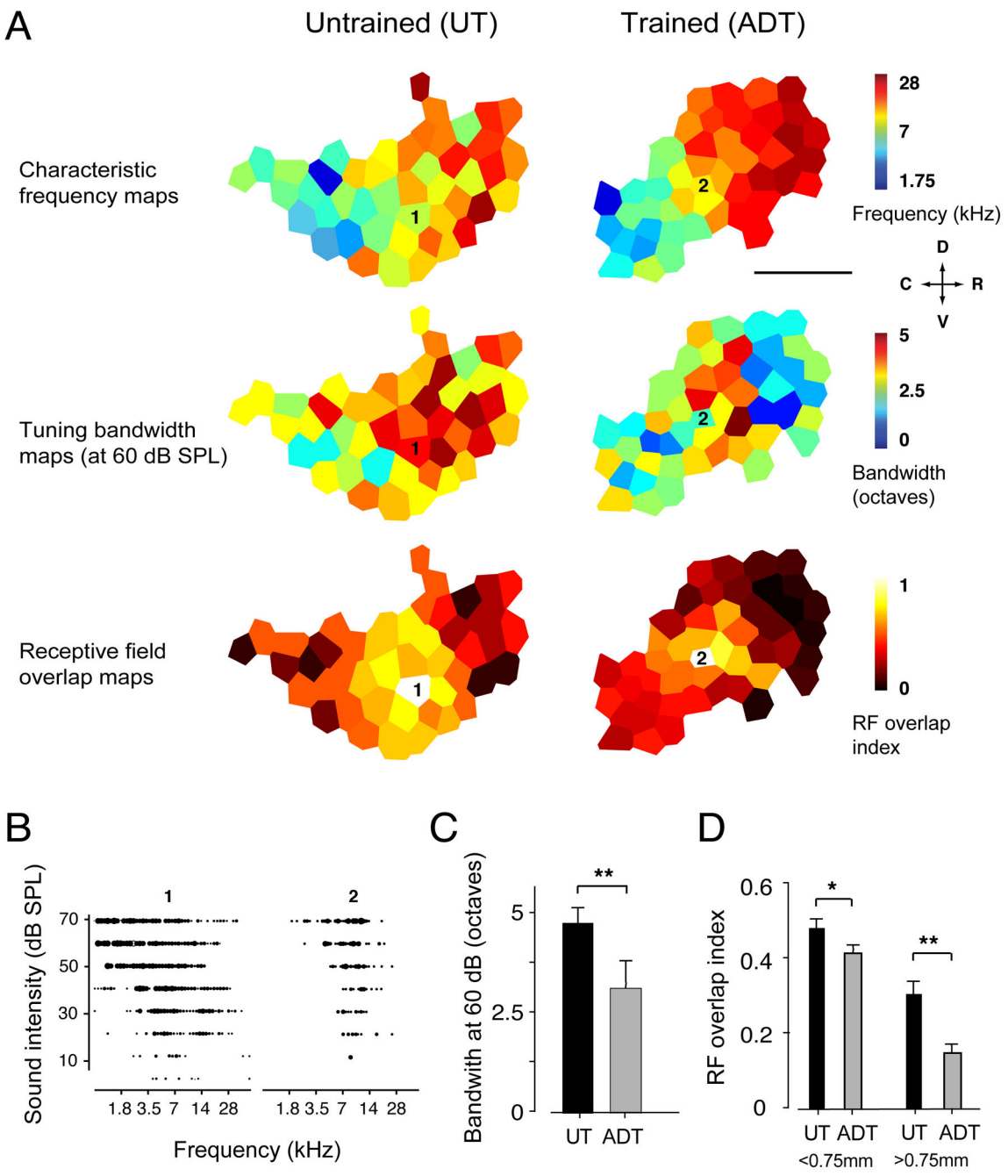

Figure 3.

Training induced changes in rat A1 frequency representation. (A) Top row, representative A1 characteristic-frequency (CF) maps from the UT and ADT groups. The numbers “1” and “2” indicate the location of the neural receptive fields shown in panel (B) and used as reference to reconstruct the receptive field overlap maps (third row of A1 maps). Middle, A1 maps from the same animals showing the representation of tuning curve width at 60 dB SPL (training sound intensity level) and bottom, receptive field (RF) overlap relative to the recording site shown by the star. (B) Representative cortical receptive fields from the CF

maps shown in (A). (C) Average tuning bandwidth at 60 dB (SPL) values for the entire neuron population recorded in each group. Scale bar 1 mm; D, dorsal; C, caudal; R, rostral; V, ventral. UT neurons recorded: 345; ADT neurons recorded: 321. Error bars are s.e.m. **: $p<0.01$: t-test.

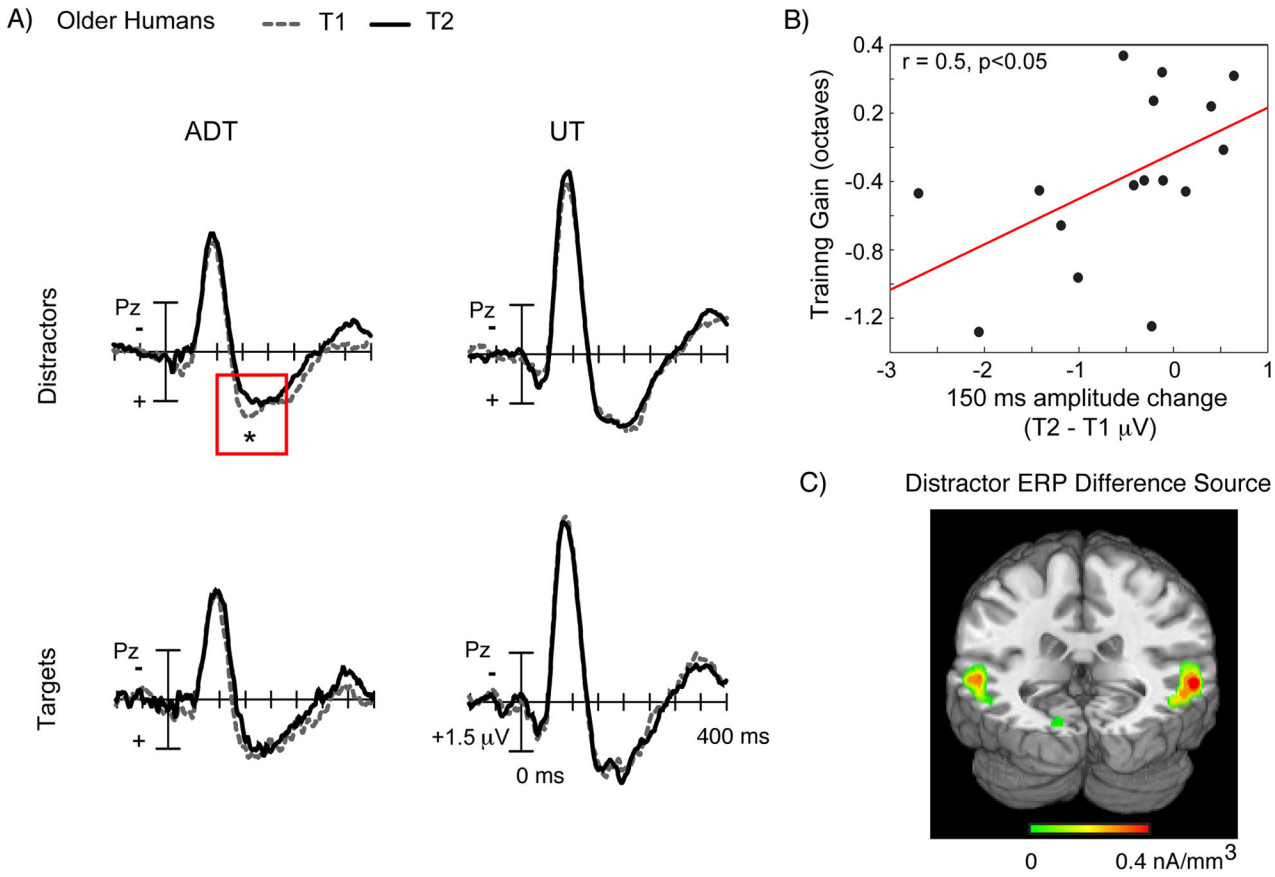

Figure 4.

Training induced changes in human distractor neural processing. (A) Processing at 150–160 ms was significantly reduced at assessment T2 vs. T1 for distractors in the ADT group. Positive deflections plotted below horizontal axis. (B) The change in 150–160 ms distractor neural processing correlated with the octave resolution improvement observed through training. (C) Current source estimates for the 150–160 ms modulation localized to auditory processing cortices. *: $p<0.05$: t-test.

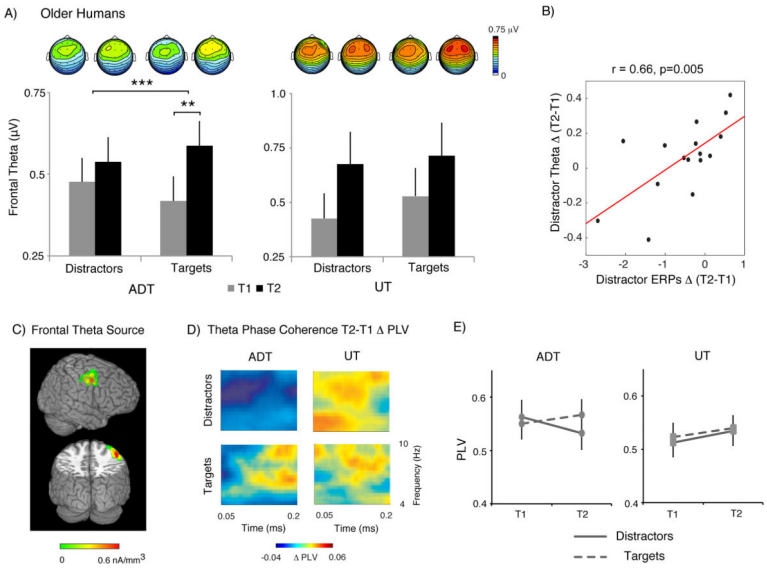

Figure 5.

Training induced changed in frontal theta modulations. (A) At T2 relative to T1, spectral amplitudes of post-stimulus frontal theta bursts were selectively enhanced for task-relevant targets but not distractors in the ADT group, while this selectivity was absent in the UT group. (B) Individual differences in (T2-T1) distractor theta modulation in the ADT group positively correlated with their sensory 150–160 ms ERP modulation. (C) The peak frontal theta source was estimated in the middle frontal gyrus in the vicinity of the inferior frontal junction. (D) Time-frequency plots of the frontal-sensory phase coherence difference (T2-T1) showed selectively reduced theta phase coherence for distractors in the ADT group. (E) Line plots of theta phase coherence modulations shown in (D). Error bars are s.e.m. ***: $p<0.005$, **:$p<0.01$.

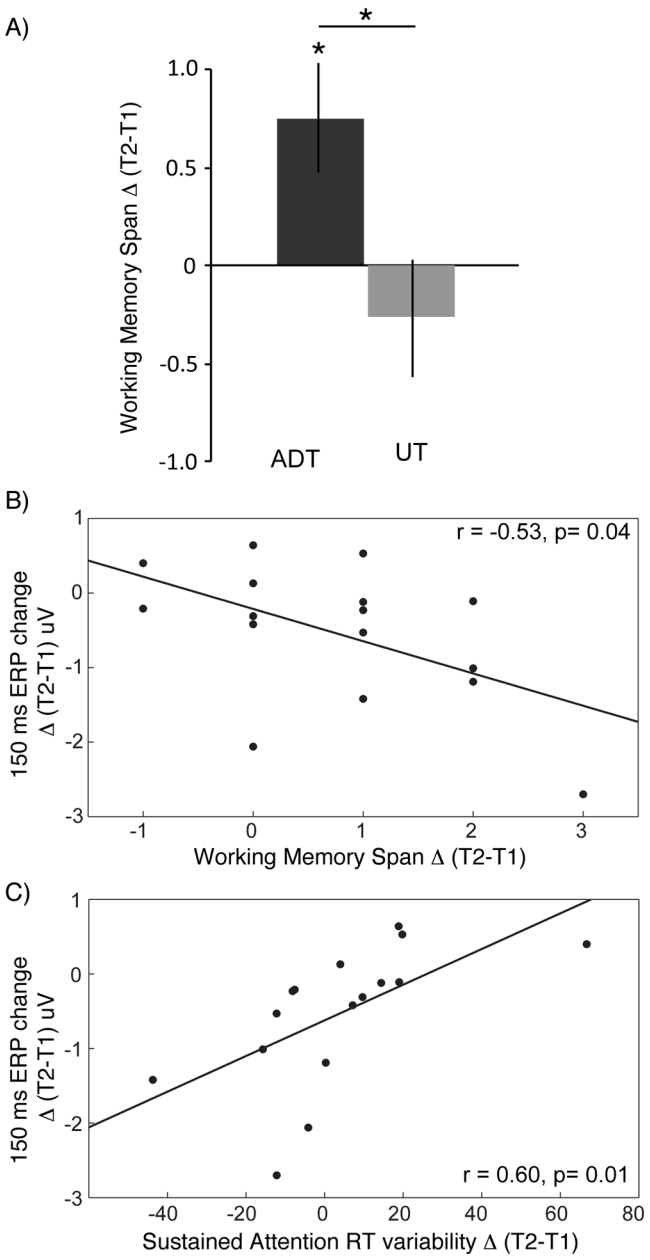

Figure 6.

Training transfer to untrained cognitive control functions. (A) Trained individuals significantly improved their working memory span for letter and number stimuli combinations. (B) In the ADT group, individual improvements in working memory span were correlated with the change in 150–160 ms distractor ERP neural processing. (C) Reduction in sustained attention response time variability in the ADT also yielded a positive neurobehavioral correlation with the 150–160 ms change in distractor ERP processing.