Long-term modification of cortical synapses improves sensory perception

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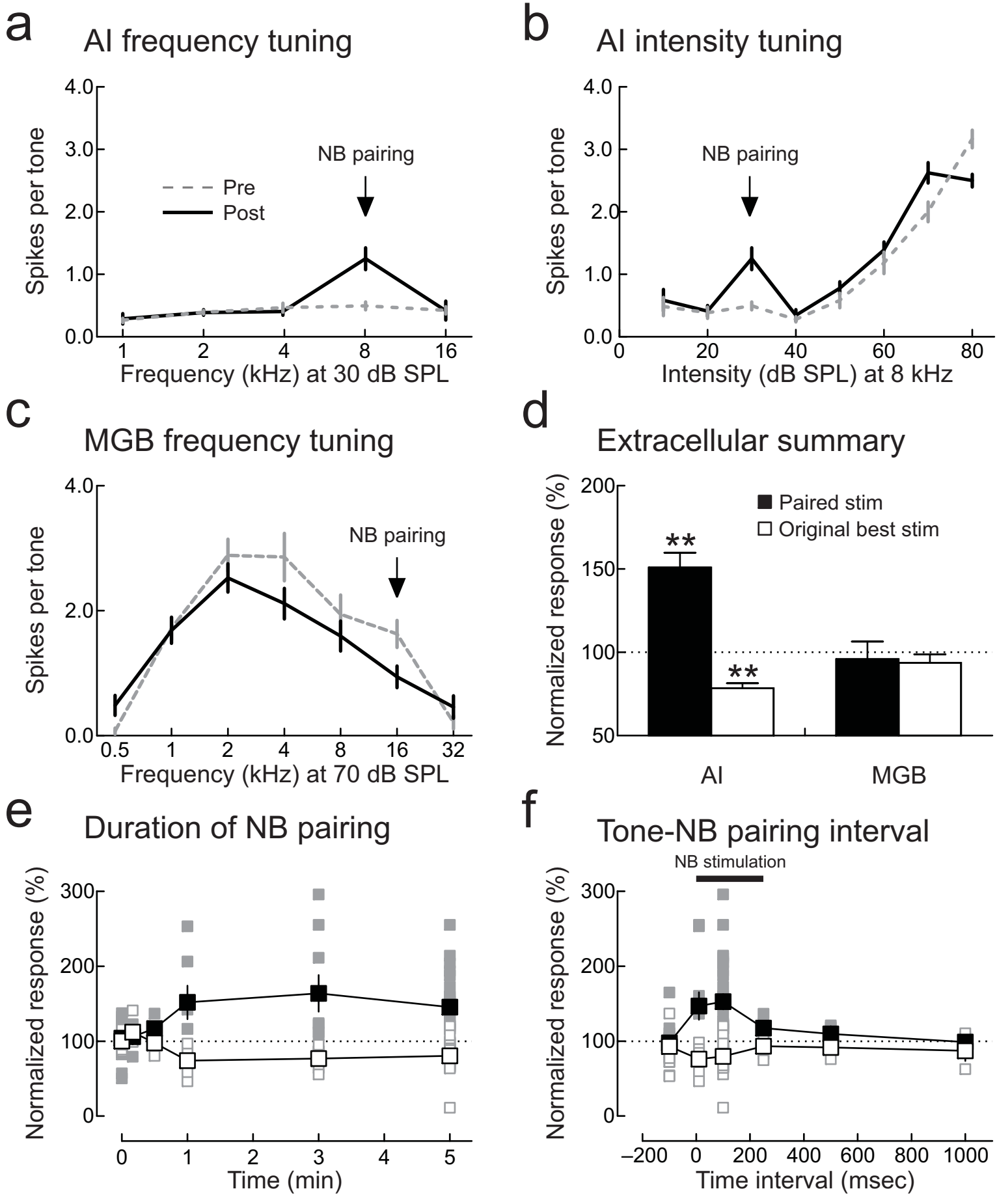
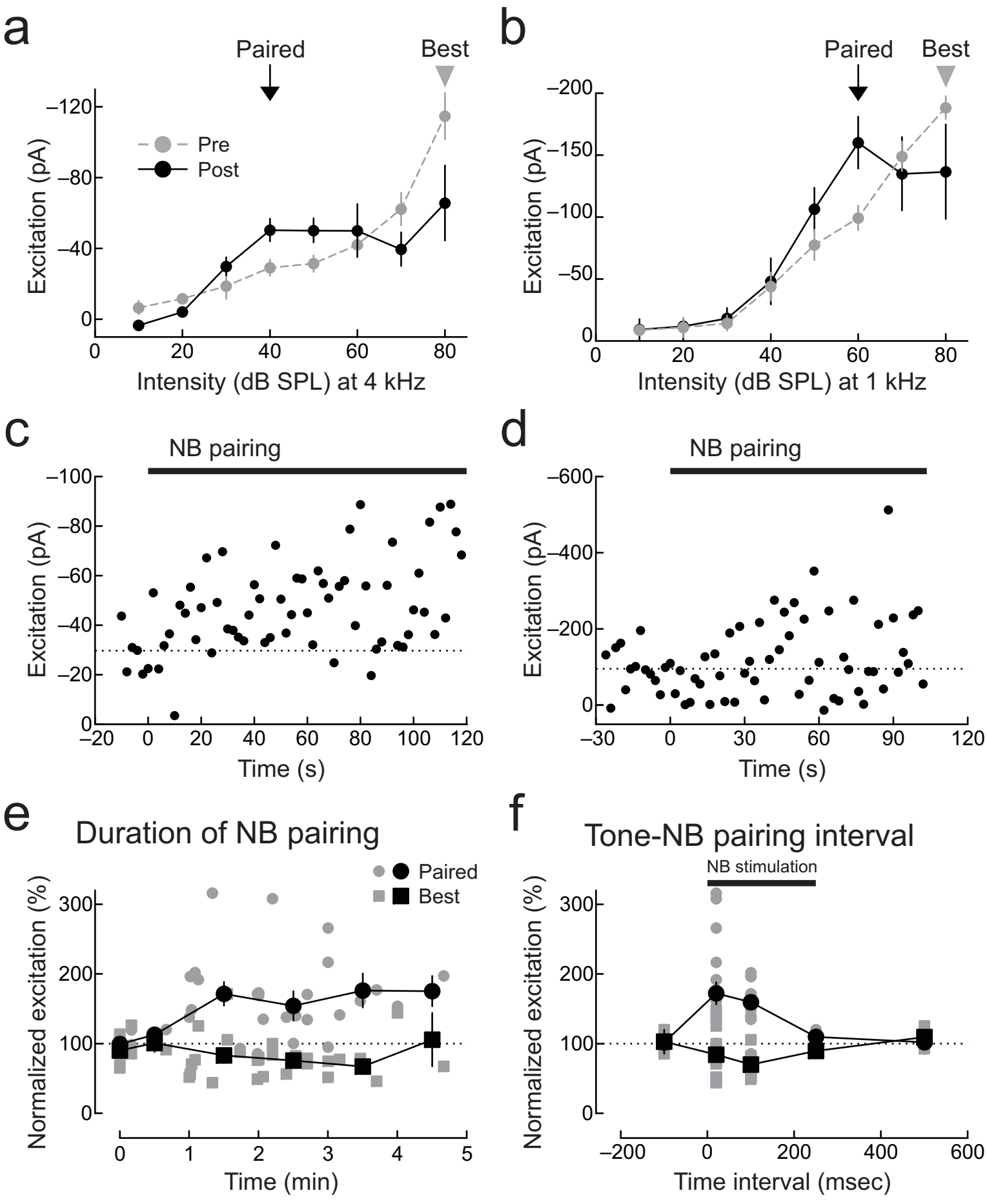
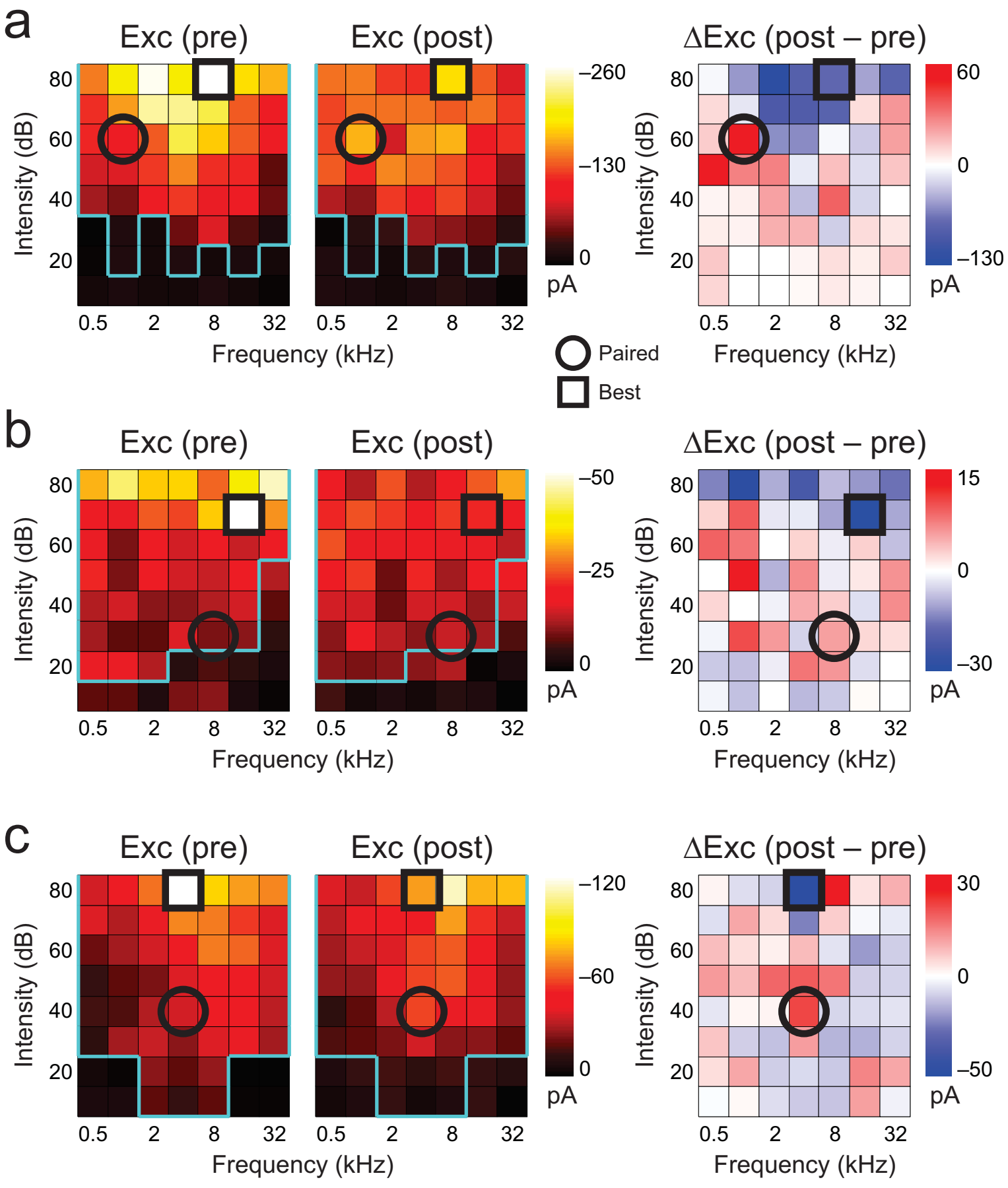
Supplementary Figures 1-10


a
AI frequency tuning
Spikes per tone
4.0
3.0
2.0
1.0
0.0
NB pairing
Pre
Post
1
2
4
8
16
Frequency (kHz) at 30 dB SPL
b
AI intensity tuning
Spikes per tone
NB pairing
0
20
40
60
80
Intensity (dB SPL) at 8 kHz
c
MGB frequency tuning
Spikes per tone
NB pairing
0.5
1
2
4
8
16
32
Frequency (kHz) at 70 dB SPL
d
Extracellular summary
Normalized response (%)
200
150
100
50
Paired stim
Original best stim
**
**
AI
MGB
e
Duration of NB pairing
Normalized response (%)
300
200
100
0
0
1
2
3
4
5
Time (min)
f
Tone-NB pairing interval
NB stimulation
Normalized response (%)
300
200
100
0
–200
0
200
400
600
800
1000
Time interval (msec)

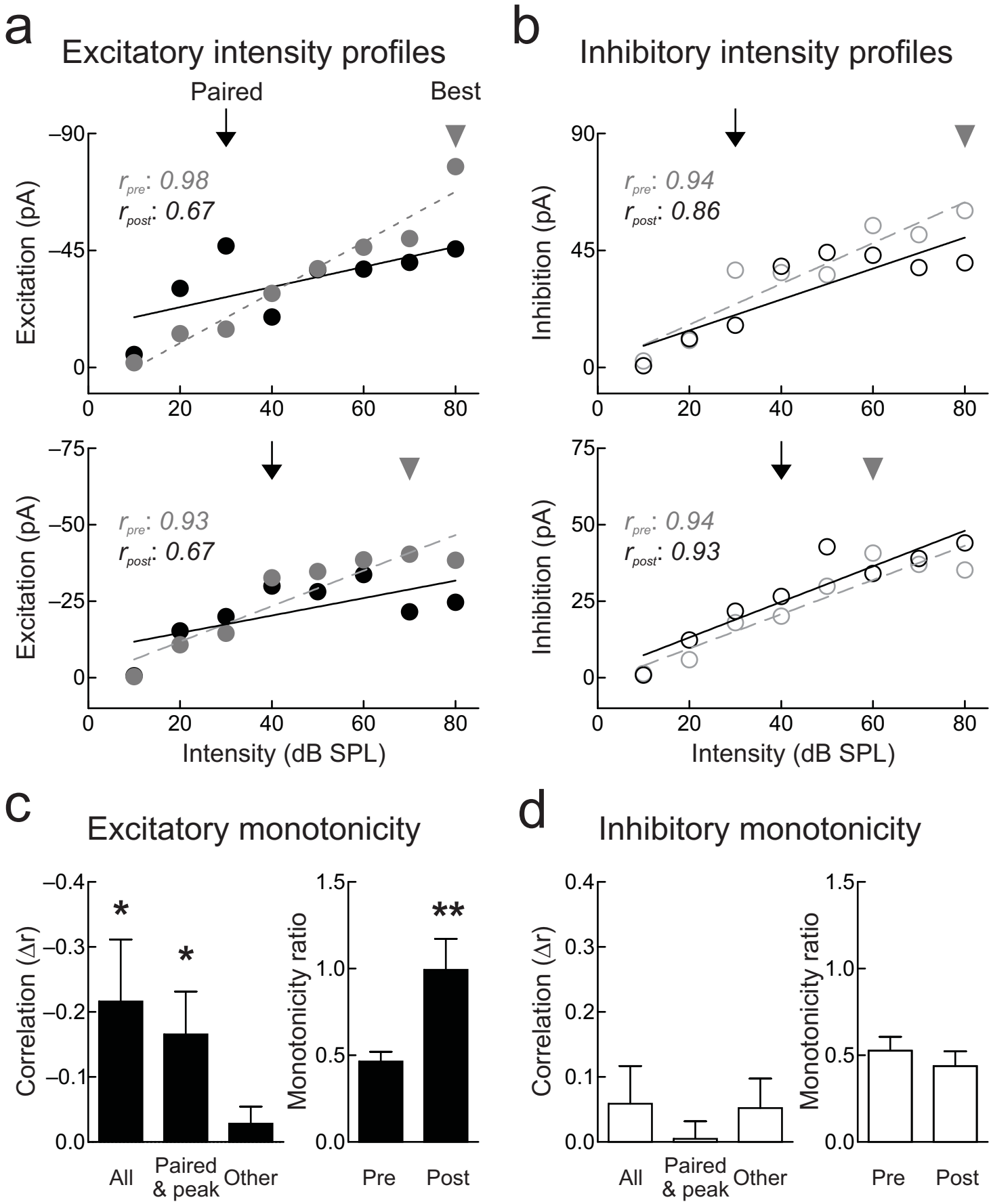
Supplementary Figure 1. Extracellular recordings from AI and MGB were used to determine parameters for nucleus basalis pairing. **a**, Example multiunit recording from adult rat AI before (gray dashed line) and 10-20 minutes after (black solid line) pairing nucleus basalis ('NB') stimulation with 30 dB SPL 8 kHz tones (arrow). Shown are frequency tuning curves for 30 dB SPL tones. Spikes evoked by the paired tone increased from 0.49 ± 0.06 spikes/trial to 1.25 ± 0.17 spikes/trial. **b**, Same recording as in **a**, but showing intensity tuning at 8 kHz before and after pairing. Note decrease of response at 80 dB SPL (from 3.17 ± 0.14 spikes/trial to 2.50 ± 0.10 spikes/trial). **c**, Example recording from MGB before and 10-20 minutes after pairing; thalamic responses were not enhanced (decrease at paired stimulus: 1.6 ± 0.2 spikes/trial to 0.9 ± 0.2 spikes/trial; decrease at original best stimulus: 2.9 ± 0.3 spikes/trial to 2.5 ± 0.2 spikes/trial). **d**, Summary of long-term changes to spiking evoked by paired stimuli (filled bars) and original best stimuli (open bars), measured with multiunit recordings in cortex (AI; increase of spiking at paired stimulus: 49.3 ± 8.5%, $n = 38$, $p < 10^{-5}$, Student's paired two-tailed t-test; decrease of spiking at original best stimulus: –21.5 ± 3.0%, $p < 10^{-6}$) and thalamus (MGB; decrease at paired stimulus: –4.1 ± 10.6%, $n = 7$, $p > 0.7$; decrease at original best stimulus: –6.4 ± 5.2%, $p > 0.2$). Duration of pairing was 1-5 minutes, each pairing trial repeated at 0.5 or 1 Hz, interval between tone onset and start of nucleus basalis stimulation was 10-100 msec, nucleus basalis stimulation frequency was 100 Hz, nucleus basalis stimulation duration was 250 msec, and tone duration was 50 msec. **e**, Long-term changes in tone-evoked spiking at paired (filled squares) and original best stimuli (open squares), as a function of duration of pairing. Gray squares, individual recordings ($n = 63$); black squares and lines, mean changes. **f**, Long-term changes in tone-evoked spiking at paired and original best stimuli ($n = 59$), as a function of the timing of tone onset relative to the start of nucleus basalis stimulation at time 0. Error bars show s.e.m.


a
Paired
Best
Pre
Post
Excitation (pA)
Intensity (dB SPL) at 4 kHz
b
Paired
Best
Excitation (pA)
Intensity (dB SPL) at 1 kHz
c
NB pairing
Excitation (pA)
Time (s)
d
NB pairing
Excitation (pA)
Time (s)
e
Duration of NB pairing
Paired
Best
Normalized excitation (%)
Time (min)
f
Tone-NB pairing interval
NB stimulation
Normalized excitation (%)
Time interval (msec)

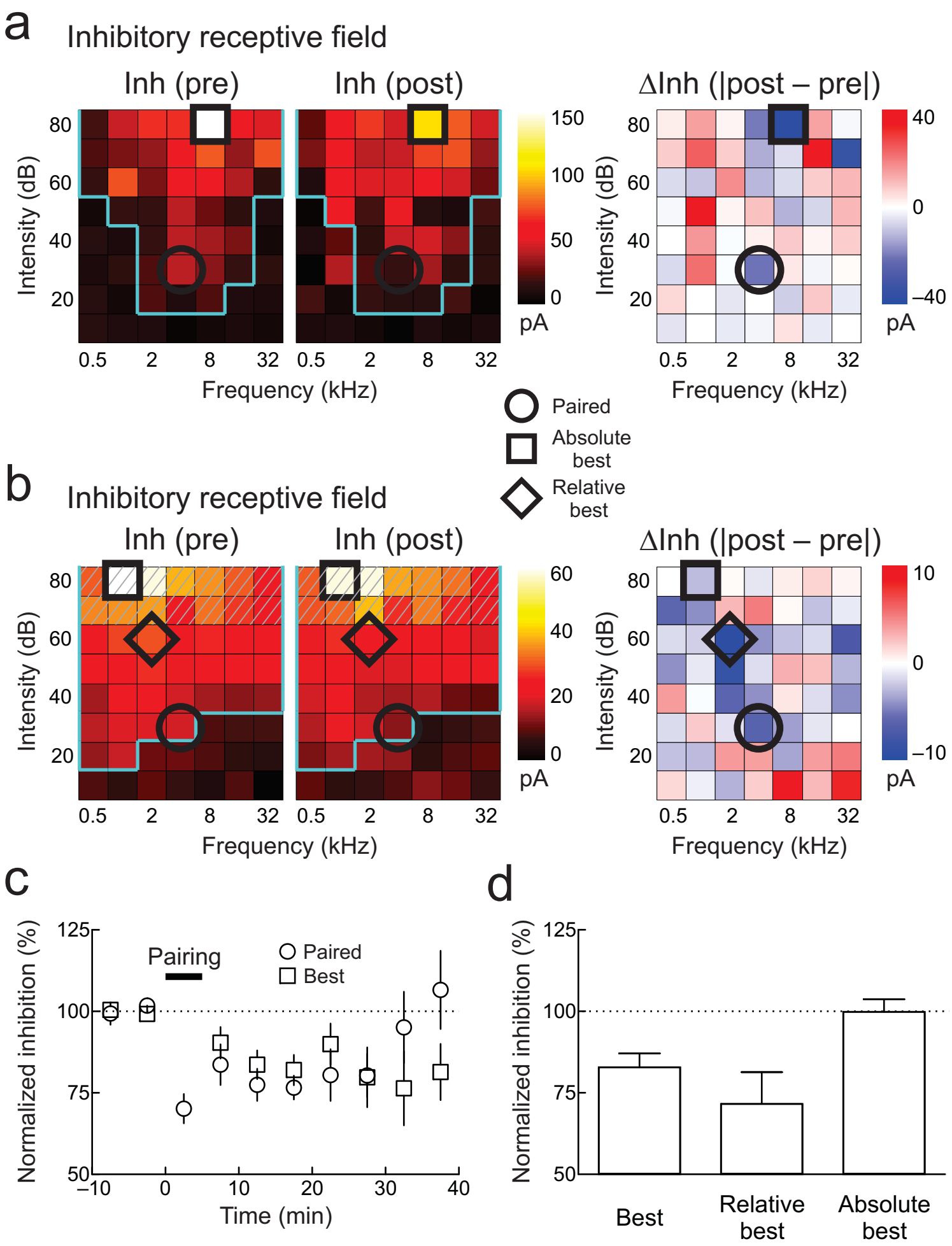
Supplementary Figure 2. *In vivo* whole-cell recordings from AI neurons. **a**, Example intensity tuning curve for synaptic excitation at 4 kHz, before (gray) and 10-20 minutes after (black) nucleus basalis pairing. 40 dB SPL 4 kHz tones (arrow) were presented during pairing; pairing lasted for 120 seconds and tone onset began 20 msec after start of nucleus basalis stimulation. Excitatory strength at the paired stimulus increased from –29.1 ± 4.7 pA to –50.4 ± 6.4 pA, while excitation at the original best level (80 dB SPL; gray arrowhead) decreased from –114.7 ± 13.1 pA to –65.6 ± 21.2 pA. **b**, Example intensity tuning curve for synaptic excitation at 1 kHz for a different neuron than that shown in **a**; pairing lasted for 104 seconds and tone onset began 20 msec after start of nucleus basalis stimulation. Excitatory strength at the paired stimulus (60 dB SPL tones of 1 kHz) increased from –99.2 ± 10.0 pA to –160.0 ± 21.0 pA, while excitation at the original best level (80 dB SPL) decreased from –188.3 ± 9.3 pA to –136.6 ± 38.2 pA. **c**, Time course of changes to tone-evoked EPSCs during nucleus basalis pairing for the recording shown in **a**. Dashed line indicates baseline excitatory strength before pairing. Solid bar indicates duration of pairing procedure. **d**, Time course of changes to tone-evoked EPSCs during pairing for the recording shown in **b**. **e**, Long-term changes in tone-evoked EPSCs at the paired (circles) and original best stimuli (squares), as a function of duration of nucleus basalis pairing. Gray symbols, individual recordings (n = 37); black symbols and lines, mean changes. **f**, Long-term changes in tone-evoked EPSCs at the paired and original best stimuli, as a function of the time interval between tone onset and start of nucleus basalis stimulation (n = 36). Error bars show s.e.m.


a
Exc (pre)
Exc (post)
ΔExc (post – pre)
Intensity (dB)
80
60
40
20
0.5
2
8
32
Frequency (kHz)
–260
–130
0
pA
60
0
–130
Paired
Best
b
–50
–25
15
–30
c
–120
–60
30
–50

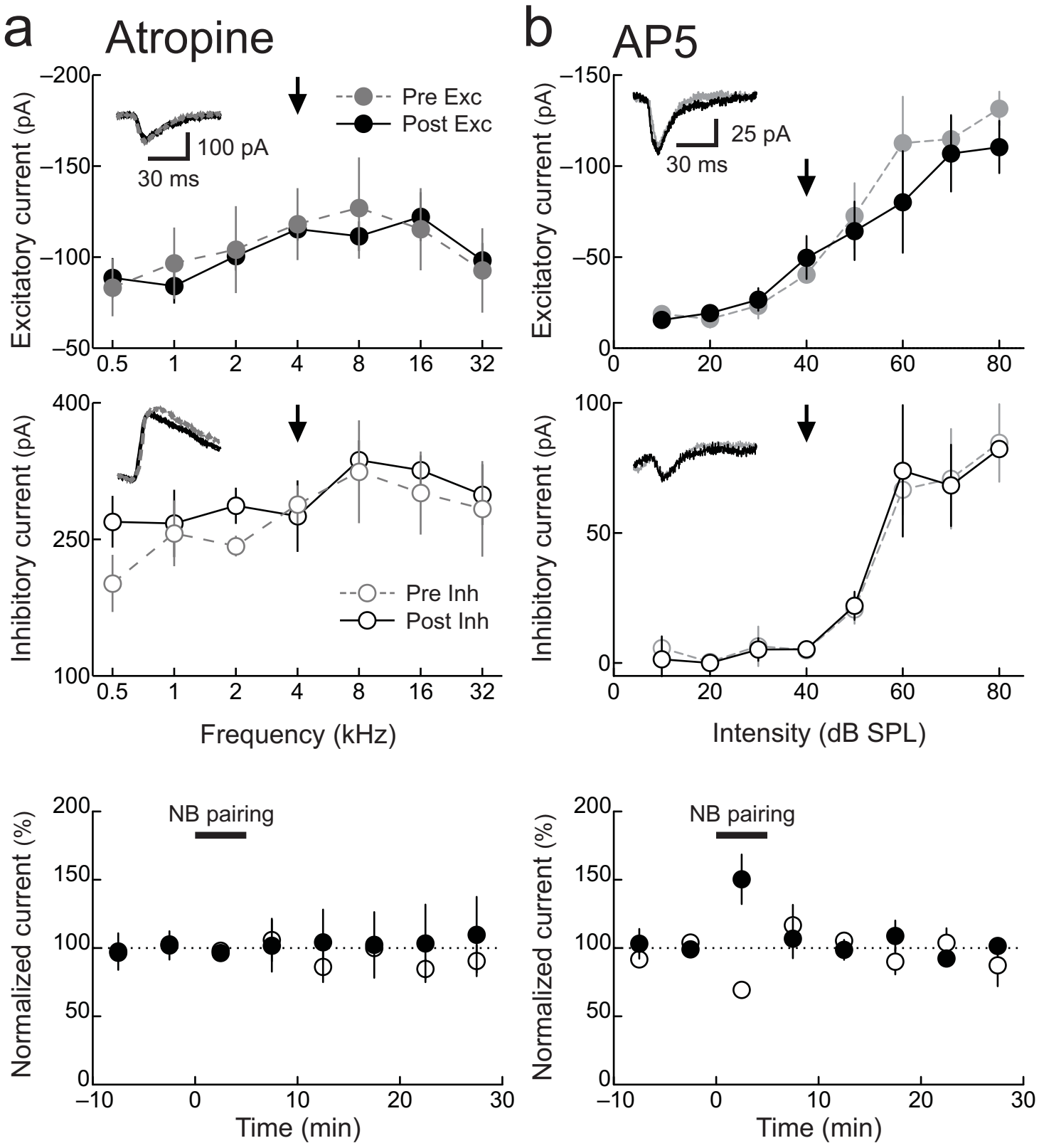
Supplementary Figure 3. Nucleus basalis pairing modifies excitatory synaptic frequency-intensity receptive fields. **a**, Example cell from 8 kHz region of AI; same cell as in **Supplementary Figure 2b**. Left and middle, excitation before (left) and after (middle) pairing. Color indicates EPSC peak amplitude. Right, change in tone-evoked EPSCs (post-pairing – pre-pairing). Color indicates magnitude of change in EPSC amplitude. Excitation at the paired tone (60 dB SPL, 1 kHz; black circle) increased from –99.2 pA to –160.0 pA, while excitation at the original best stimulus (80 dB SPL, 8 kHz, black square) decreased from –253.9 pA to –176.6 pA. **b**, Excitatory receptive field for another cell. Excitation at the paired tone (30 dB SPL, 8 kHz) increased from –9.7 pA to –14.3 pA, while excitation at the original best stimulus (70 dB SPL, 16 kHz) decreased from –48.5 pA to –20.9 pA. **c**, Excitatory receptive field for a third cell. Excitation at the paired tone (40 dB SPL, 4 kHz) increased from –29.1 pA to –50.4 pA, while excitation at the original best stimulus (80 dB SPL, 4 kHz) decreased from –114.7 pA to –65.6 pA.


a
Excitatory intensity profiles
Paired
Best
Excitation (pA)
r_{pre}: 0.98
r_{post}: 0.67
r_{pre}: 0.93
r_{post}: 0.67
Intensity (dB SPL)
b
Inhibitory intensity profiles
Inhibition (pA)
r_{pre}: 0.94
r_{post}: 0.86
r_{pre}: 0.94
r_{post}: 0.93
Intensity (dB SPL)
c
Excitatory monotonicity
Correlation (Δr)
Monotonicity ratio
All
Paired & peak
Other
Pre
Post
d
Inhibitory monotonicity
Correlation (Δr)
Monotonicity ratio
All
Paired & peak
Other
Pre
Post

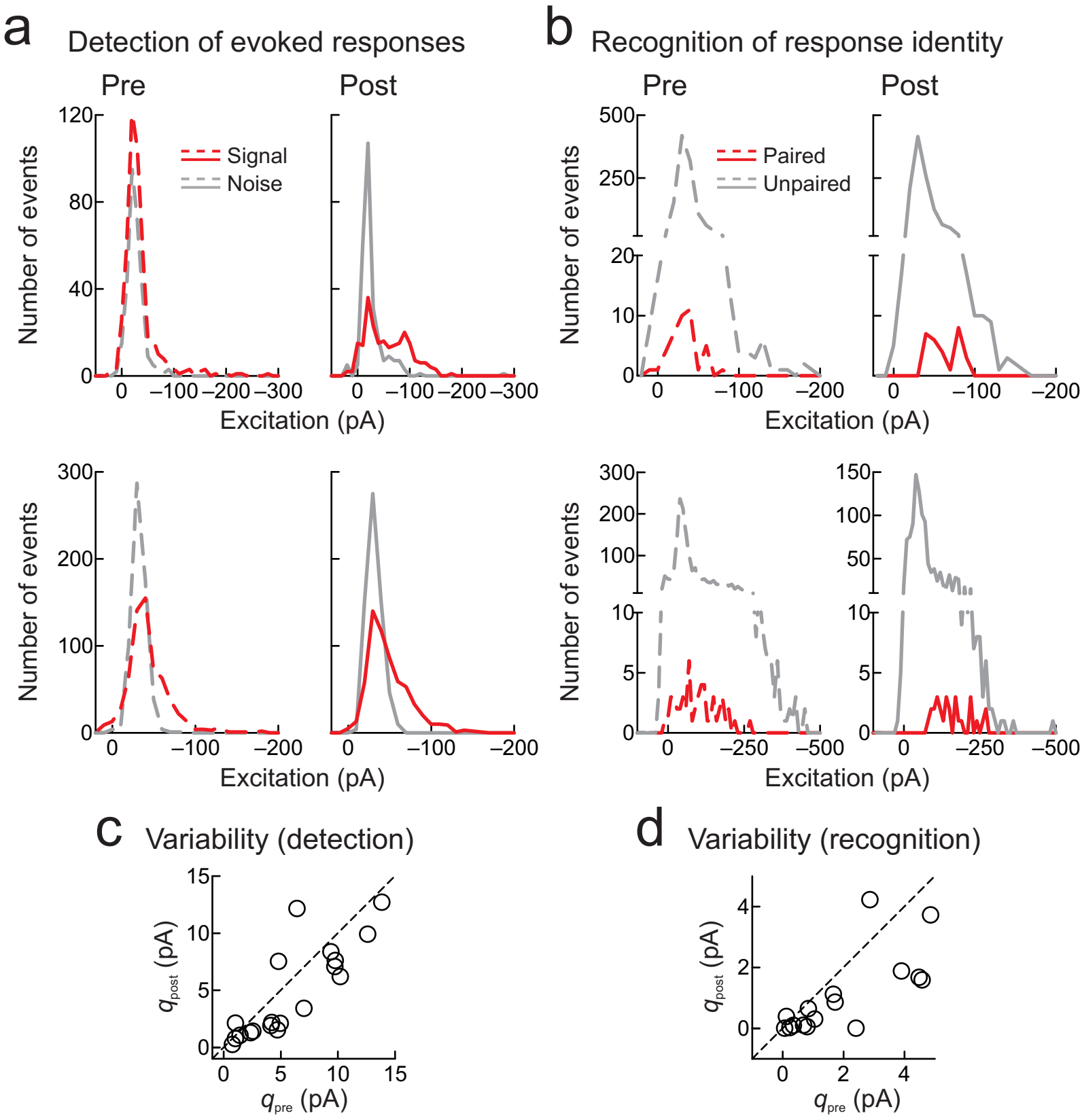
Supplementary Figure 4. Nucleus basalis pairing reduces monotonicity of excitatory synaptic intensity response profiles. **a**, Example recordings in which paired intensity was substantially lower than peak response level. Top, same cell as **Figure 1b,c**. Before pairing, intensity sensitivity was a monotonic function of sound level (linear correlation coefficient r_{pre}: 0.98). After pairing (30 dB SPL), correlation was reduced (r_{post}: 0.67, Δr: –0.31). Bottom, different recording showing that pairing reduced monotonicity of excitatory intensity sensitivity when paired stimulus was relatively low (r_{pre}: 0.93, r_{post}: 0.67, Δr: –0.26). **b**, Same recordings as **a**, showing IPSCs before and after pairing. Top, pairing only modestly reduced correlation (r_{pre}: 0.94, r_{post}: 0.86, Δr: –0.08). Bottom, correlation was unaffected by pairing (r_{pre}: 0.94, r_{post}: 0.93, Δr: –0.01). **c**, Reduction in correlation (left) and monotonicity ratio (right) of excitation was due to changes at paired and best stimuli, as opposed to non-specific changes to other intensities. Left, considered collectively ('All'), post-pairing changes in intensity profiles reduced linear correlation between sound level and EPSC amplitude (Δr: –0.22 ± 0.10; n = 12, $p < 0.05$). Considered separately, this reduction was due to changes to original peak intensity response, paired intensity, and responses–10 dB from paired ('Paired & peak'; Δr: –0.17 ± 0.07; $p < 0.03$). Non-specific changes to the other five stimuli did not contribute significantly to changes in correlation ('Other'; Δr: –0.03 ± 0.03; $p > 0.3$). Right, the ratio between responses to the paired intensity and the highest intensity was 0.50 ± 0.06 before pairing and significantly increased to 1.04 ± 0.18 after pairing ($p < 0.004$). *, $p < 0.05$; **, $p < 0.01$. **d**, As in **c**, except for inhibitory responses. Left, pairing did not significantly affect linear correlation between intensity and response size ('All', Δr: 0.06 ± 0.06; n = 12, $p > 0.3$; 'Paired & peak'; Δr: 0.00 ± 0.03; $p > 0.8$; 'Other'; Δr: 0.05 ± 0.05; $p > 0.2$). Right, pairing did not affect ratio between paired and highest intensity responses (before: 0.53 ± 0.08, after: 0.44 ± 0.09, $p > 0.05$). Error bars show s.e.m.


a
Inhibitory receptive field
Inh (pre)
Inh (post)
ΔInh (|post – pre|)
Intensity (dB)
80
60
40
20
0.5
2
8
32
Frequency (kHz)
150
100
50
0
pA
40
0
–40
Paired
Absolute best
Relative best
b
Inhibitory receptive field
Inh (pre)
Inh (post)
ΔInh (|post – pre|)
60
40
20
10
–10
c
Normalized inhibition (%)
125
100
75
50
Pairing
Paired
Best
–10
0
10
20
30
40
Time (min)
d
Best
Relative best
Absolute best

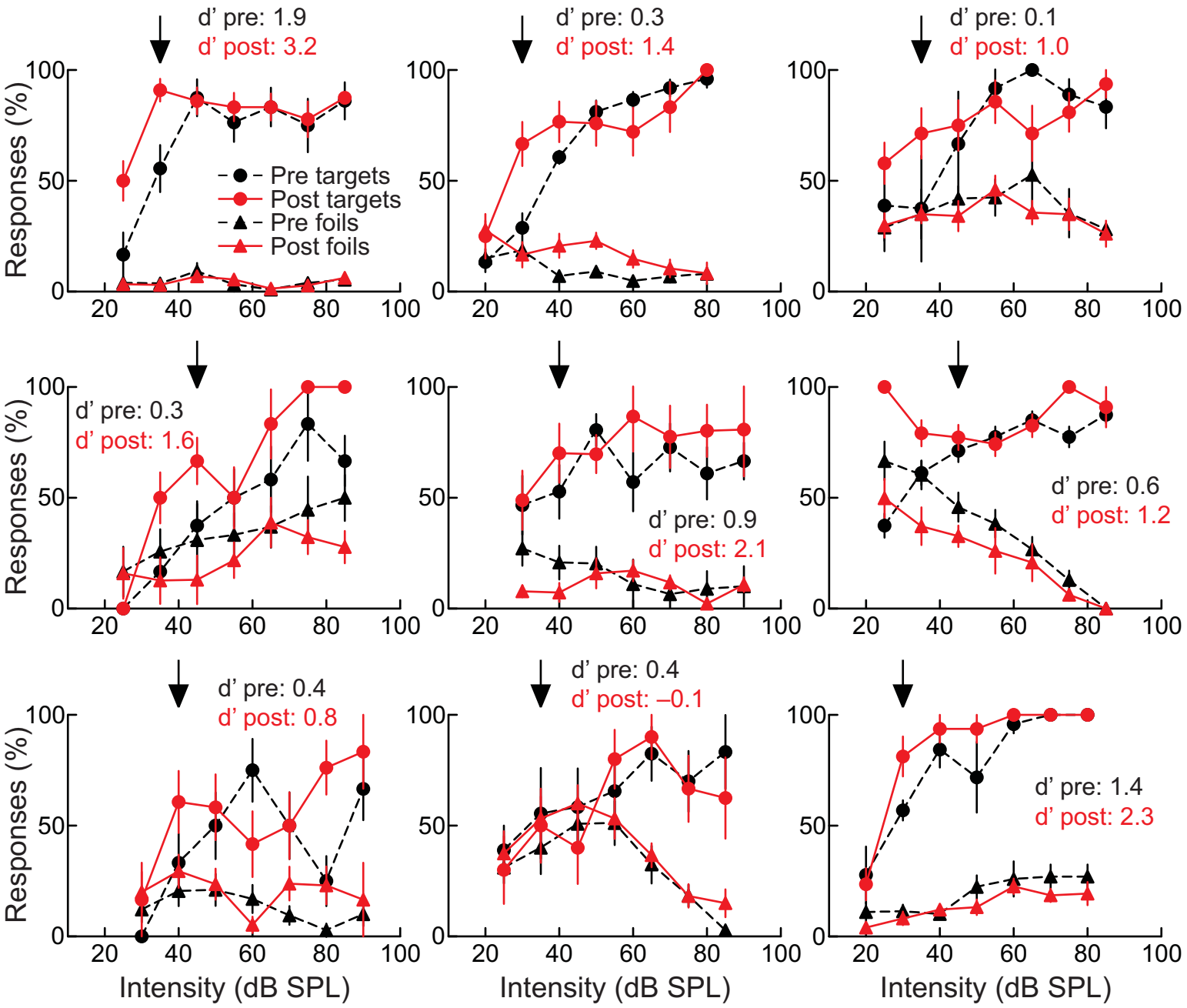
Supplementary Figure 5. Nucleus basalis pairing modifies inhibitory receptive fields. **a**, Inhibitory receptive field for the cell in **Figure 1c**. Top, inhibition before (left) and after (middle) pairing. Color indicates IPSC peak amplitude. Right, change in tone-evoked IPSCs (post-pairing – pre-pairing). Color indicates magnitude of change in IPSC amplitude. Inhibition at the paired tone (30 dB SPL, 4 kHz; black circle) decreased from 37.5 pA to 16.3 pA (decrease of –51.3%); inhibition at the original best stimulus (80 dB SPL, 8 kHz, black square) also decreased from 142.1 pA to 95.9 pA (decrease of –32.5%). **b**, Inhibitory receptive field for the cell in **Figure 3a**; the original best stimulus for inhibition was 80 dB SPL and 1 kHz. During pairing, tones at 30 dB SPL, 4 kHz were presented. For ten minutes after pairing, no stimuli above 60 dB SPL were played (excluded stimuli at 70-80 dB SPL indicated by hatched lines). Afterward, the full stimulus set was played. Inhibitory responses to the paired tone decreased (before pairing: 11.7 pA, after pairing: 6.1 pA, decrease of –47.9%; circles), responses to the absolute best stimulus were unchanged (before pairing: 56.7 pA, after pairing: 54.4 pA, decrease of –4.1%; squares), and responses to relative best stimuli (60 dB SPL, 2 kHz tones) were depressed (before pairing: 23.7 pA, after pairing: 14.7 pA, decrease of –38.0%; diamonds). **c**, Time course of changes to IPSCs evoked by paired (open circles) and absolute best stimuli (open squares). Responses to both stimuli were reduced after pairing, with inhibition at best stimuli significantly depressed after 10+ minutes. Bar indicates time and duration of pairing. Same experiments as **Figure 2c** (n = 29). **d**, Summary of experiments to determine input specificity of best stimuli inhibitory depression. IPSCs evoked by relative best stimuli were depressed to comparable levels as in the experiments summarized in **c**, while responses to absolute best stimuli at higher intensity were unchanged when those stimuli were not presented. Left bar from experiments in **c** (n = 29); middle and right bars from experiments in **Figure 3b**, left (n = 13). Error bars show s.e.m.


a
Atropine
b
AP5
Excitatory current (pA)
Pre Exc
Post Exc
100 pA
30 ms
25 pA
Inhibitory current (pA)
Pre Inh
Post Inh
Frequency (kHz)
Intensity (dB SPL)
NB pairing
Normalized current (%)
Time (min)

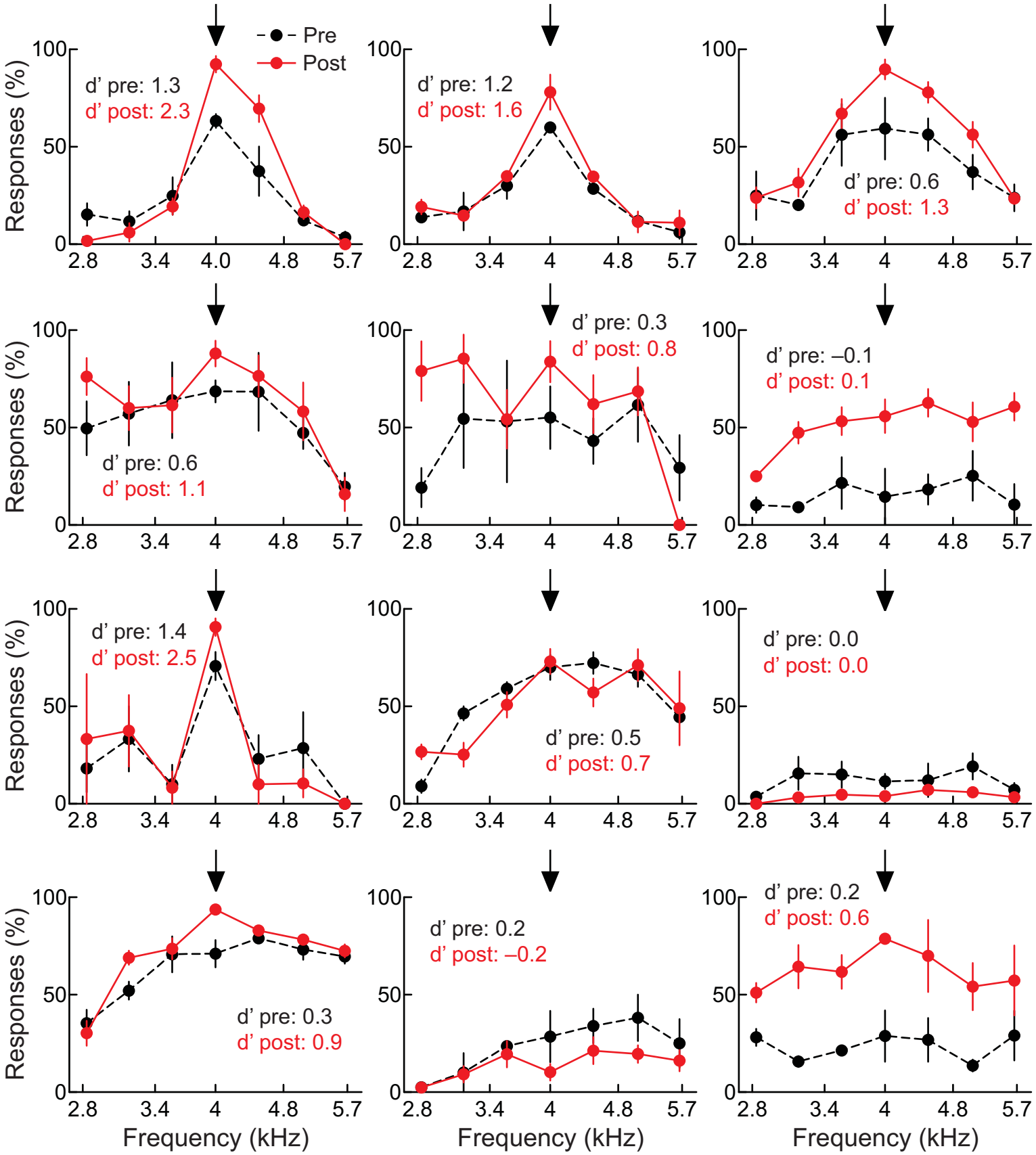
Supplementary Figure 6. Long-term synaptic receptive field changes induced by nucleus basalis pairing require AI muscarinic and NMDA receptors. **a**, Atropine, a muscarinic receptor antagonist, prevents short- and long-term changes in AI synaptic tuning curves. Atropine (1 mM) was applied topically to AI. Top and middle, example cell showing that excitatory (top; filled symbols) and inhibitory (middle; open symbols) tuning curves are similar before (gray symbols and dashed line) and 10-20 minutes after (black symbols and line) nucleus basalis pairing. Bottom, time course of excitatory and inhibitory synaptic strength before and after nucleus basalis pairing in the presence of atropine (n = 5 neurons). Synaptic strength was unchanged during (decrease in excitation: –3.6 ± 5.8%, $p > 0.3$, Student's paired two-tailed t-test; decrease in inhibition: –2.0 ± 5.1%, $p > 0.4$) and 10-20 minutes after pairing (increase in excitation: 2.9 ± 24.9%, $p > 0.4$; decrease in inhibition: –7.6 ± 6.7%, $p > 0.2$) after application of atropine to AI. Duration of pairing is indicated by the horizontal bar. **b**, AP5, an NMDA receptor antagonist, prevents long-term but not immediate changes to AI synaptic strength during and after nucleus basalis pairing. AP5 (1 mM) was applied topically to AI. Top and middle, example cell showing that in the presence of AP5, excitatory and inhibitory tuning curves are similar before and 10-20 minutes after pairing. Bottom, time course of synaptic strength before and after nucleus basalis pairing in the presence of AP5 (n = 6 neurons). Synaptic strength was modified during (increase in excitation: 50.4 ± 18.2%, $p < 0.04$; decrease in inhibition: –30.6 ± 5.0%, $p < 0.03$) but not 10-20 minutes post-pairing (increase in excitation: 0.7 ± 7.1%, $p > 0.9$; decrease in inhibition: –0.5 ± 4.3%, $p > 0.9$) after application of AP5 to AI. Error bars show s.e.m.


a
Detection of evoked responses
Pre
Post
Signal
Noise
Number of events
Excitation (pA)
b
Recognition of response identity
Paired
Unpaired
c
Variability (detection)
d
Variability (recognition)
q_{post} (pA)
q_{pre} (pA)

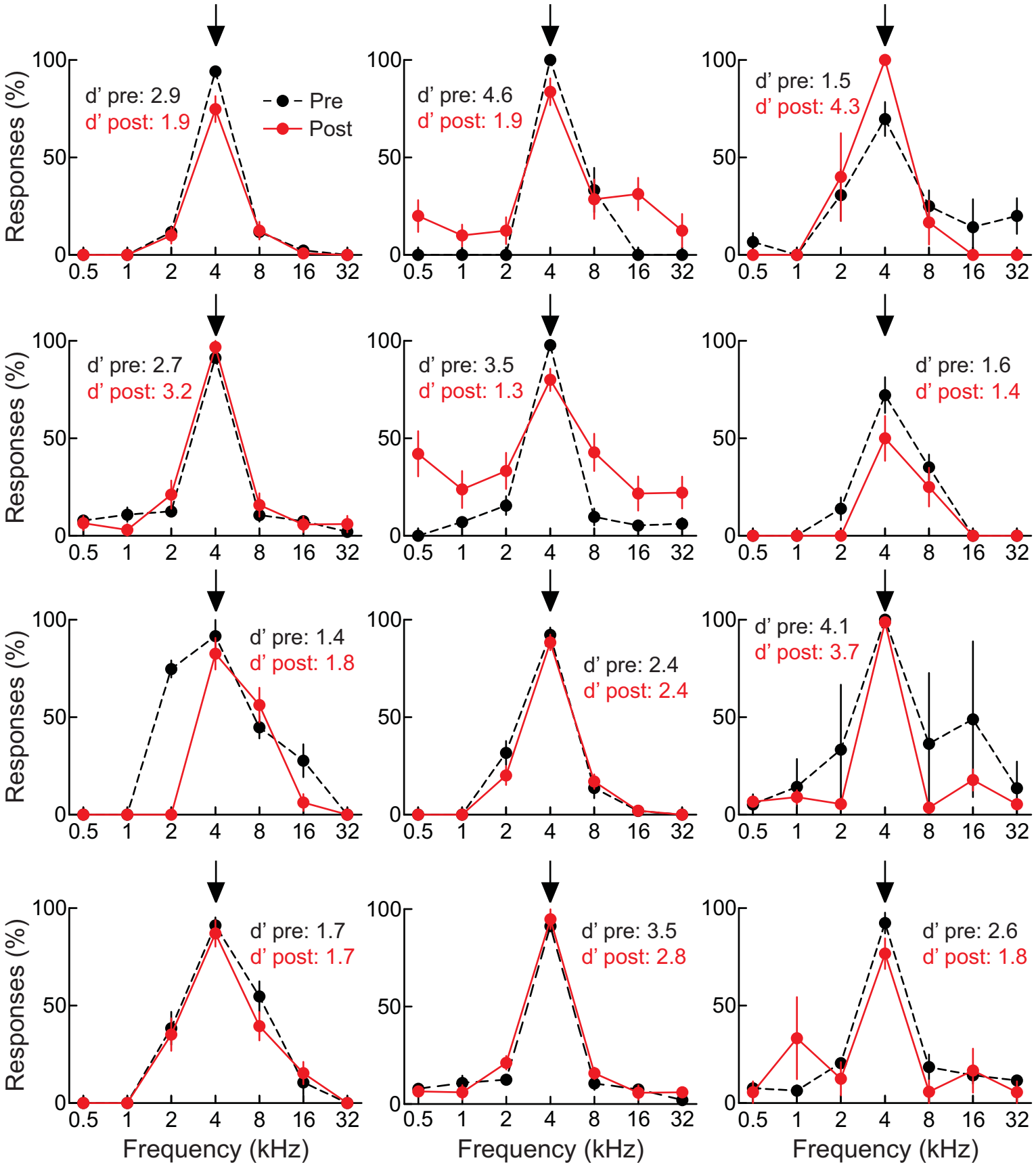
Supplementary Figure 7. Nucleus basalis pairing modifies statistics of synaptic distributions to enhance responses to paired stimuli. **a**, Two examples of 'signal' (tone-evoked, red lines) and 'noise' (spontaneously-occurring, gray lines) synaptic distributions, before (dashed lines) and after nucleus basalis pairing (solid lines). Mutual information between signal and noise increased after pairing. Top, mutual information increased from 0.13 bits to 0.23 bits after pairing. Bottom, mutual information increased from 0.17 bits to 0.20 bits after pairing. **b**, Two examples of 'paired' (red lines) and 'unpaired' (gray lines) distributions. Mutual information between paired and unpaired events also increased after pairing. Top, mutual information increased from 0.01 bits to 0.04 bits after pairing. Bottom, mutual information increased from 0.03 bits to 0.07 bits after pairing. **c**, Same as in **Figure 4c**, top right, except that the x- and y-axes have been reduced in scale to emphasize the reduction of variability in the 'signal' distributions after pairing, even for low *q* values. **d**, Same as in **Figure 4d**, top right, except that the x- and y-axes have been reduced in scale to emphasize the reduction of variability in the 'paired' distributions after pairing, even for low *q* values.


d' pre: 1.9
d' post: 3.2
d' pre: 0.3
d' post: 1.4
d' pre: 0.1
d' post: 1.0
Pre targets
Post targets
Pre foils
Post foils
d' pre: 0.3
d' post: 1.6
d' pre: 0.9
d' post: 2.1
d' pre: 0.6
d' post: 1.2
d' pre: 0.4
d' post: 0.8
d' pre: 0.4
d' post: –0.1
d' pre: 1.4
d' post: 2.3
Responses (%)
Intensity (dB SPL)
0
50
100
20
40
60
80
100

Supplementary Figure 8. Psychophysical curves of each animal included in this study on the detection task. Each panel shows data from a different animal. Black symbols and dashed line, baseline performance; red symbols and line, performance 1-2 hours after nucleus basalis pairing. Arrow indicates paired intensity. Circles, responses to target 4 kHz tones. Triangles, responses to non-target foils averaged across all foil stimuli at a given intensity. Error bars show s.e.m.


Pre
Post
Responses (%)
Frequency (kHz)
d' pre: 1.3
d' post: 2.3
d' pre: 1.2
d' post: 1.6
d' pre: 0.6
d' post: 1.3
d' pre: 0.6
d' post: 1.1
d' pre: 0.3
d' post: 0.8
d' pre: –0.1
d' post: 0.1
d' pre: 1.4
d' post: 2.5
d' pre: 0.5
d' post: 0.7
d' pre: 0.0
d' post: 0.0
d' pre: 0.3
d' post: 0.9
d' pre: 0.2
d' post: –0.2
d' pre: 0.2
d' post: 0.6

Supplementary Figure 9. Psychophysical curves of each animal included in this study on the narrowband recognition task. Each panel shows data from a different animal. Black symbols and dashed line, baseline performance; red symbols and line, performance 1-2 hours after nucleus basalis pairing. Arrow indicates paired frequency, which was always the target 4 kHz tone. Error bars show s.e.m.


Responses (%)
100
50
0
0.5
1
2
4
8
16
32
Frequency (kHz)
Pre
Post
d' pre: 2.9
d' post: 1.9
d' pre: 4.6
d' post: 1.9
d' pre: 1.5
d' post: 4.3
d' pre: 2.7
d' post: 3.2
d' pre: 3.5
d' post: 1.3
d' pre: 1.6
d' post: 1.4
d' pre: 1.4
d' post: 1.8
d' pre: 2.4
d' post: 2.4
d' pre: 4.1
d' post: 3.7
d' pre: 1.7
d' post: 1.7
d' pre: 3.5
d' post: 2.8
d' pre: 2.6
d' post: 1.8

Supplementary Figure 10. Psychophysical curves of each animal included in this study on the wideband recognition task. Each panel shows data from a different animal. Black symbols and dashed line, baseline performance; red symbols and line, performance 1-2 hours after nucleus basalis pairing. Arrow indicates paired frequency, which was always the target 4 kHz tone. Error bars show s.e.m.