nature neuroscience

Change detection by thalamic reticular neurons

Xiong-Jie Yu[1,2], Xin-Xiu Xu[1], Shigang He[1] & Jufang He[1,2]

The thalamic reticular nucleus (TRN) is thought to function in the attentional searchlight. We analyzed the detection of deviant acoustic stimuli by TRN neurons and the consequences of deviance detection on the TRN target, the medial geniculate body (MGB) of the rat. TRN neurons responded more strongly to pure-tone stimuli presented as deviant stimuli (low appearance probability) than those presented as standard stimuli (high probability) (deviance-detection index = 0.321). MGB neurons also showed deviance detection in this procedure, albeit to a smaller extent (deviance-detection index = 0.154). TRN neuron deviance detection either enhanced (14 neurons) or suppressed (27 neurons) MGB neuronal responses to a probe stimulus. Both effects were neutralized by inactivation of the auditory TRN. Deviance modulation effects were cross-modal. Deviance detection probably causes TRN neurons to transiently deactivate surrounding TRN neurons in response to a fresh stimulus, altering auditory thalamus responses and inducing attention shift.

The dorsal thalamus relays sensory and motor information to the cerebral cortex and receives strong modulatory input back from the cortex. Both thalamocortical and corticothalamic projections send collaterals to the TRN of the ventral thalamus[1,2]. The TRN consists of GABA-containing (GABAergic) neurons, which only project back to the dorsal thalamus[2–4]. These neurons exhibit burst firing that, under different conditions, occurs in synchrony with several frequencies of rhythmic oscillations in the corticothalamic networks[5–8]. The location of the TRN, along with its firing patterns and unique connections, has led to the proposal that the TRN is important in the internal attentional searchlight[9] and for coordinating multiple neuronal processes by linking specific and nonspecific pathways[10]. In the auditory sector of the TRN, neurons show various response patterns to acoustic stimuli, including the burst response, phasic ON response and OFF response[11,12]. TRN neurons are tuned to a broad range of frequencies[12].

Novel stimuli attract our attention as a result of deviant stimulus preference (DSP), a phenomenon in which neurons show increased responsiveness to deviant stimuli. Such neurons have been identified in several brain regions, including the visual and auditory cortex and the inferior colliculus[13,14]. Compared with thalamocortical neurons in the MGB, TRN neurons in the auditory sector show greater adaptation to repeated stimuli[15]. Considering the potential role of the TRN in the internal attentional searchlight or attention shift, fast-adapting TRN neurons are likely to exhibit DSP. We used *in vivo* extracellular recording and an oddball procedure to analyze DSP (that is, deviance detection) in TRN neurons. We then investigated the functional implications of TRN neuron DSP by examining how the DSP affects the responses of thalamocortical neurons (a TRN output target) to auditory stimuli. Inter-modality interaction was investigated by examining how a preceding light stimulus affects the auditory responses of the MGB neurons.

RESULTS

Deviance detection by TRN neurons

To determine whether the fast adaptation of TRN neurons is stimulus specific, we used an oddball procedure with a combination of two pure-tone stimuli (with a standard frequency f_1 of 14 kHz and a deviant frequency f_2 of 8 kHz). A block of pure-tone stimuli consisting of f_1, f_1, f_1, f_1, f_1, f_1 and f_2 was repeated 30 times. The f_1 stimuli with an interstimulus interval (ISI) of 200 ms elicited strong responses in both the first and second trials of block 1; however, adaptation was apparent in subsequent trials of this block (trials 3–6; **Fig. 1a**). Introduction of the f_2 stimulus at trial 7 evoked a strong response (block 1; **Fig. 1a**). Reintroduction of the f_1 stimuli in blocks 2–5 resulted in weak or absent responses. However, f_2 stimuli elicited strong responses in all blocks (**Fig. 1a**). As shown by the raster displays of all 30 blocks (**Fig. 1a**), the f_2 stimulus elicited much stronger responses than the standard frequency.

Next, the standard and deviant frequencies were swapped. The new standard frequency stimulus (f_2, 8 kHz) elicited strong responses in the first trial, weak responses in trials 2–4 and no response in trials 5 and 6 (block 1; **Fig. 1b**). However, the new deviant stimulus (f_1, 14 kHz) elicited a strong response (block 1; **Fig. 1b**). The f_2 stimulus evoked a strong response at trial 1 in block 2, but evoked a weak or absent response in trials 2–6 (**Fig. 1b**). Reintroduction of the oddball stimulus at block 2 was associated with only a weak response. The neurons showed good responses to the first trials of the standard stimuli in the blocks and weak responses to the following trials of the standard stimuli (**Fig. 1b**). Responses to deviant f_1 stimuli (**Fig. 1b**) were much stronger than those to standard f_1 stimuli of the same frequency (**Fig. 1a**). The same was true of deviant (**Fig. 1a**) and standard f_2 stimuli (**Fig. 1b**). A comparison of average responses to f_2 (**Fig. 1c**) and f_1 (**Fig. 1d**) as either standard or deviant stimuli clearly showed that the TRN neurons preferred deviant stimuli. Analysis of the TRN neuron exposed to pure

[1]CAS-Hong Kong Joint Research Laboratory for Visuo-Auditory Integration, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China. [2]Laboratory of Applied Neuroscience, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong. Correspondence should be addressed to J.H. (rsjufang@polyu.edu.hk) or S.H. (shiganghe@moon.ibp.ac.cn).

Received 10 February; accepted 19 June; published online 16 August 2009; doi:10.1038/nn.2373

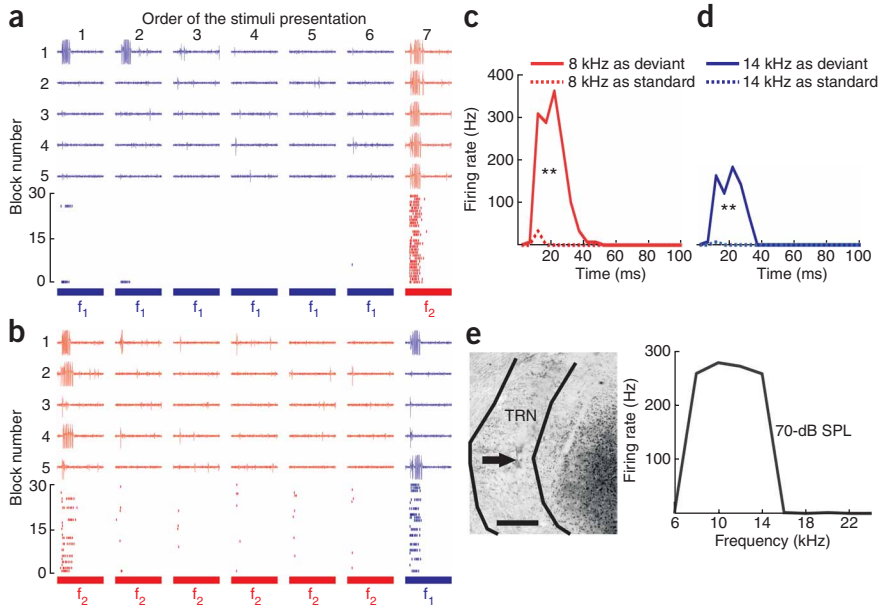

Figure 1 Responses of a TRN neuron to pure-tone stimuli of two frequencies presented in an oddball procedure. (**a**) Responses to 14-kHz frequency tones (f_1) when presented as the standard tone and to 8-kHz frequency tones (f_2) when presented as the deviant tone. Neuronal responses to the first 5 of 30 blocks are presented in the upper part. Tracings from the five blocks are read from left to right and top to bottom. The order of presentation was block 1 (f_1, f_1, …, f_1, f_2), block 2 (f_1, f_1, …, f_1, f_2), … block 30 (f_1, …, f_1, f_2). Blocks were contiguous in time. The lower part of the figure shows the raster displays of 30 blocks of seven sequential tones. Only the first 100 ms of the responses are shown in the traces and raster display, although the ISI was 200 ms. (**b**) Responses on reversal of the standard and deviant tones. (**c**,**d**) Peristimulus time histograms showing responses (that is, firing rate) to standard and deviant stimuli. ** $P < 0.01$ (ANOVA). (**e**) Track of recording electrode, as shown by Nissl stain (left, the arrow indicates the recording site) and responses as a function of stimulus frequency at 70-dB SPL (right). Scale bar represents 200 μm. Pure tones of varying frequencies (6–24 kHz), separated by a 2-kHz interval, were randomly presented, with each frequency being presented in 20 trials.

tones at a 70-dB sound pressure level (SPL) revealed that the responses ranged from 8 to 15 kHz (**Fig. 1e**).

Increasing the ISI to 1 s and altering the appearance ratio to 9:1 of the standard to deviant stimuli yielded similar results (see example of another neuron in **Fig. 2a**,**b**, where $f_1 = 19.02$ kHz and $f_2 = 21.02$ kHz, and mean data from 19 neurons in **Fig. 2c**). That is, the neuron had a stronger response to pure-tone stimuli when they were presented as the deviant stimulus than when they were presented as the standard stimulus.

Deviance detection by MGB neurons

Using the same stimulus procedure and parameters, we found that MGB neurons showed less difference in responses to pure-tone stimuli with different presentation probabilities (standard versus deviant). In one MGB neuron (**Fig. 3a**), we observed comparable responses to f_1 (17.12 kHz) stimuli as standard (90% frequency of presentation) and as deviant (10%) as well as to f_2 (18.92 kHz) stimuli as standard and as deviant. In contrast, another MGB neuron (**Fig. 3b**) showed obvious differences in responses to f_1 (11.42 kHz) stimuli as standard and as deviant as well as to f_2 (12.61 kHz) stimuli as standard and as deviant. Analysis of the mean responses of 41 MGB neurons using the same procedure and parameters revealed a trend toward greater responses to deviant stimuli than standard stimuli ($P = 0.08$; **Fig. 3c**).

We adopted the stimulus-specific adaptation index for each frequency as frequency-specific index $SI(f_i)$, which was calculated using the equation $SI(f_i) = \frac{d(f_i)-s(f_i)}{d(f_i)+s(f_i)}$, where $d(f_i)$ and $s(f_i)$ were responses to the deviant and standard frequency, respectively[16]. In $SI(f_2)$ versus $SI(f_1)$ scatter plots, the points of TRN neurons deviated from the diagonal more than those of MGB neurons (**Fig. 4**). The greater the deviation of the point from the diagonal, the greater the stimulus-specific adaptation/deviance detection that the neuron showed. A normalized deviance-detection index SI, defined as $\frac{d(f_1)+d(f_2)-s(f_1)-s(f_2)}{d(f_1)+s(f_1)+d(f_2)+s(f_2)}$, was approximately 208% greater in TRN neurons ($n = 19$) than in MGB neurons ($n = 41$) (0.321 ± 0.051 versus 0.154 ± 0.020, mean ± s.e.m., $P < 0.01$).

The deviance procedure alters MGB responses

To investigate the functional implication of DSP in TRN neurons, we examined neuronal responses in the MGB using a deviance procedure with an added probe stimulus. The objective was to

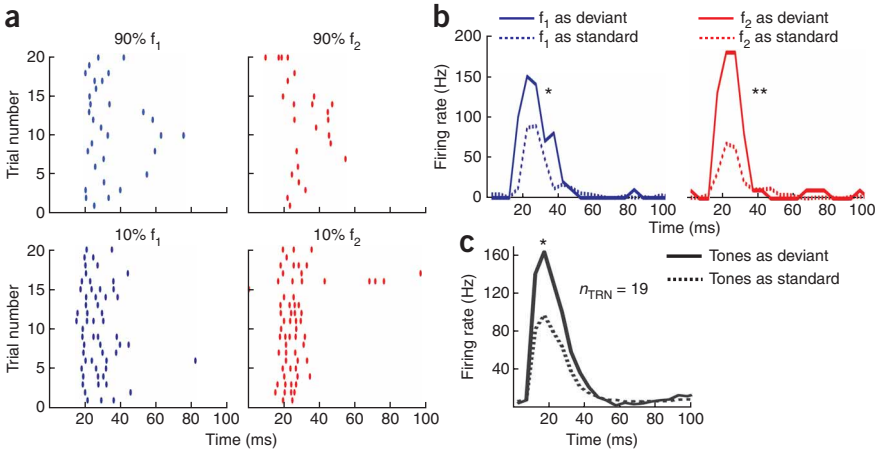

Figure 2 Differential responses of TRN neurons to pure-tone stimuli of two frequencies presented in an oddball procedure. (**a**) Raster displays showing responses to tones of two frequencies (f_1, 19.02 kHz; f_2, 21.02 kHz) when presented as f_1 standard (90% appearing probability) and f_2 deviant (10% appearing probability) or f_1 deviant and f_2 standard. The ISI was 1 s. We sampled responses to the standard frequency from trial numbers 81 to 100 (20 trials), whereas we sampled all of the responses to the deviant frequency (20 trials,: numbers 1 to 20). (**b**) Peristimulus time histograms (PSTHs) of responses shown in **a**. (**c**) PSTHs showing the mean responses of 19 TRN neurons. * $P < 0.05$ and ** $P < 0.01$ (ANOVA). The ISI was 1 s.

activate the TRN neurons that exerted inhibition/disinhibition on the recording MGB neuron and to investigate whether the deviance procedure modulated MGB neuronal responses to the probe stimulus. The deviance procedure consisted of a sequence of pure-tone f_1 stimuli (standard), pure-tone f_2 stimuli (deviant), and a probe stimulus (p), f_1, f_1, f_1, f_1, f_1, f_1, f_1, f_1, f_1, f_2 and p (probe stimulus: noise-burst or pure tone of the best frequency, f_3). In the control procedure, the f_2 in the deviance procedure was replaced by f_1. When an MGB neuron was selected, a preliminary screening was performed to ensure that the MGB neuron responded to the probe stimulus of either noise-burst or a pure-tone of f_3 and failed to respond to a pure-tone f_1 or f_2 stimulus.

Two of the MGB neurons that we examined (**Fig. 5**) responded to the probe stimuli under both control and deviance procedures, but they failed to respond to pure tones of f_1 (30.44 kHz) and f_2 (33.64 kHz) (another two examples of MGB neurons are shown in **Supplementary Fig. 1**). One neuron (**Fig. 5a**) showed weaker responses to the probe stimulus (p: f_3 = 8-kHz tones) under the deviance procedure than under the control procedure. We named this MGB neuron a deviance-suppressed neuron. Conversely, another neuron (**Fig. 5b**) had a stronger response to the probe stimulus (p: noise) in the deviance procedure and was referred to as a deviance-enhanced neuron. We used an index to measure the modulatory effect of the deviance procedure on MGB neuronal response (IDC), defined as $\frac{R_D - R_C}{R_D + R_C}$, where R_D and R_C are the responses to the probe stimulus in the deviance and control procedures, respectively). A total of 77 MGB neurons were examined using the deviance procedure. Of these, 27 were deviance-suppressed neurons and 14 were deviance-enhanced neurons (**Fig. 5c**). Accordingly, the average amplitude of the suppression (IDC = –0.263 ± 0.047, n = 27) showed a trend of being greater than the amplitude of enhancement (IDC = 0.144 ± 0.037, n = 14) (P = 0.098).

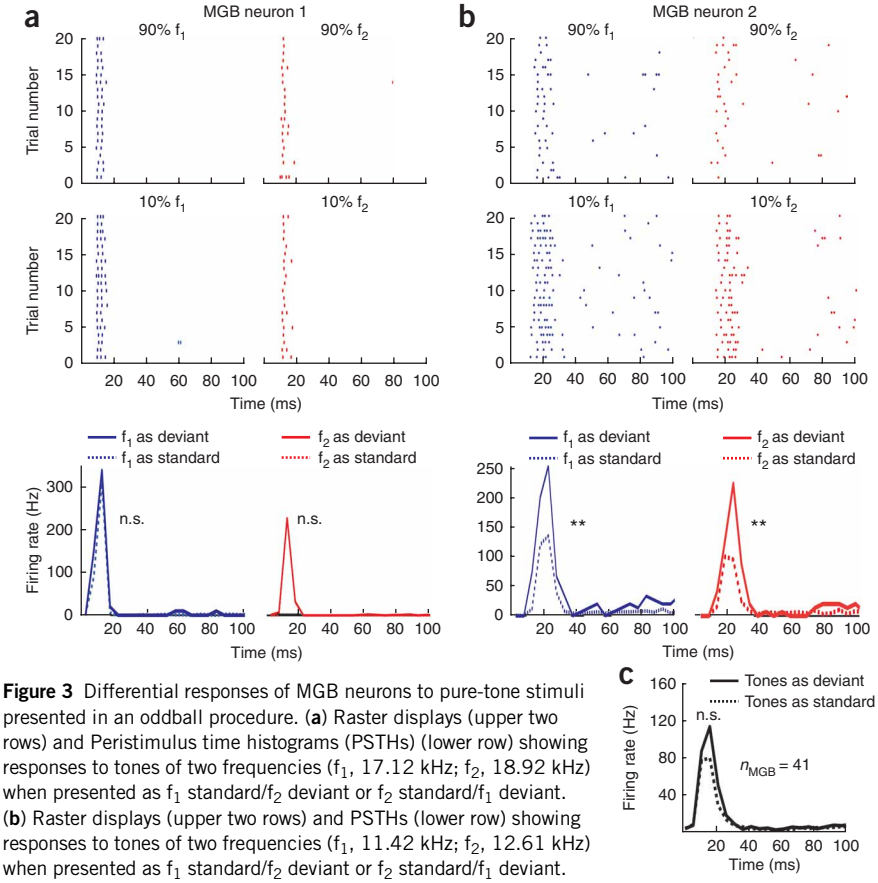

Figure 3 Differential responses of MGB neurons to pure-tone stimuli presented in an oddball procedure. (**a**) Raster displays (upper two rows) and Peristimulus time histograms (PSTHs) (lower row) showing responses to tones of two frequencies (f_1, 17.12 kHz; f_2, 18.92 kHz) when presented as f_1 standard/f_2 deviant or f_2 standard/f_1 deviant. (**b**) Raster displays (upper two rows) and PSTHs (lower row) showing responses to tones of two frequencies (f_1, 11.42 kHz; f_2, 12.61 kHz) when presented as f_1 standard/f_2 deviant or f_2 standard/f_1 deviant. (**c**) PSTHs showing the mean responses of 41 MGB neurons. The ISI was 1 s. ** $P < 0.01$; n.s., not significant ($P = 0.088$).

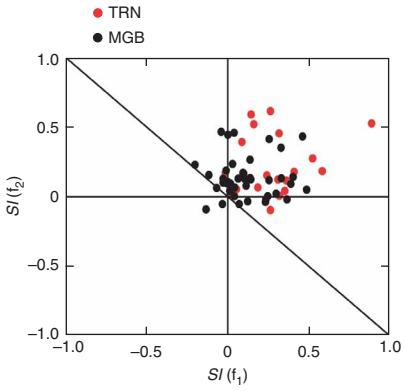

Figure 4 Deviance preferences of TRN and MGB neurons. Scatter plot of $SI(f_2)$ versus $SI(f_1)$ in all TRN (red) and MGB neurons (black).

TRN inactivation suppresses deviance modulation of MGB

To determine whether the changes in MBG neuron responses to the probe stimulus of the deviance procedure were caused by the DSP of TRN neurons, we investigated the effect of lidocaine-induced TRN inactivation on MGB neuronal responses to the probe stimulus (**Supplementary Fig. 2**). Before TRN inactivation, one MGB neuron (**Fig. 6a**,**b**) exhibited responses to the probe stimulus (noise burst), but not to the pure tone of f_1 (30.44 kHz) or f_2 (33.64 kHz) (**Fig. 6a**). Responses to the probe stimulus were significantly weaker ($P < 0.01$) under the deviance procedure than under the control procedure (**Fig. 6c**).

After TRN inactivation, the neuron responded to the pure-tone stimulus f_2, but not f_1. In addition, responses to the probe stimuli were significantly increased under both control (182%, $P < 0.05$; **Fig. 6a–c**) and deviance procedures (305%, $P < 0.01$; **Fig. 6a–c**), implying that the TRN strongly inhibited the MGB. However, responses to the probe stimuli did not differ between the control and deviance procedures after TRN inactivation ($P = 0.27$; **Fig. 6b**,**c**). This result indicates that the deviance modulation of the MGB was primarily attributable to the TRN.

MGB Responses are modulated by a preceding light stimulus

The above experiments were designed to investigate deviance modulation in the same modality. We next investigated whether MGB neuronal responses could be modulated in a cross-modal manner. To do this, we introduced a light stimulus before the probe sound stimulus (light-sound, light-sound procedure). One of the MGB neurons that we examined (**Fig. 7a**,**b**) had significantly stronger

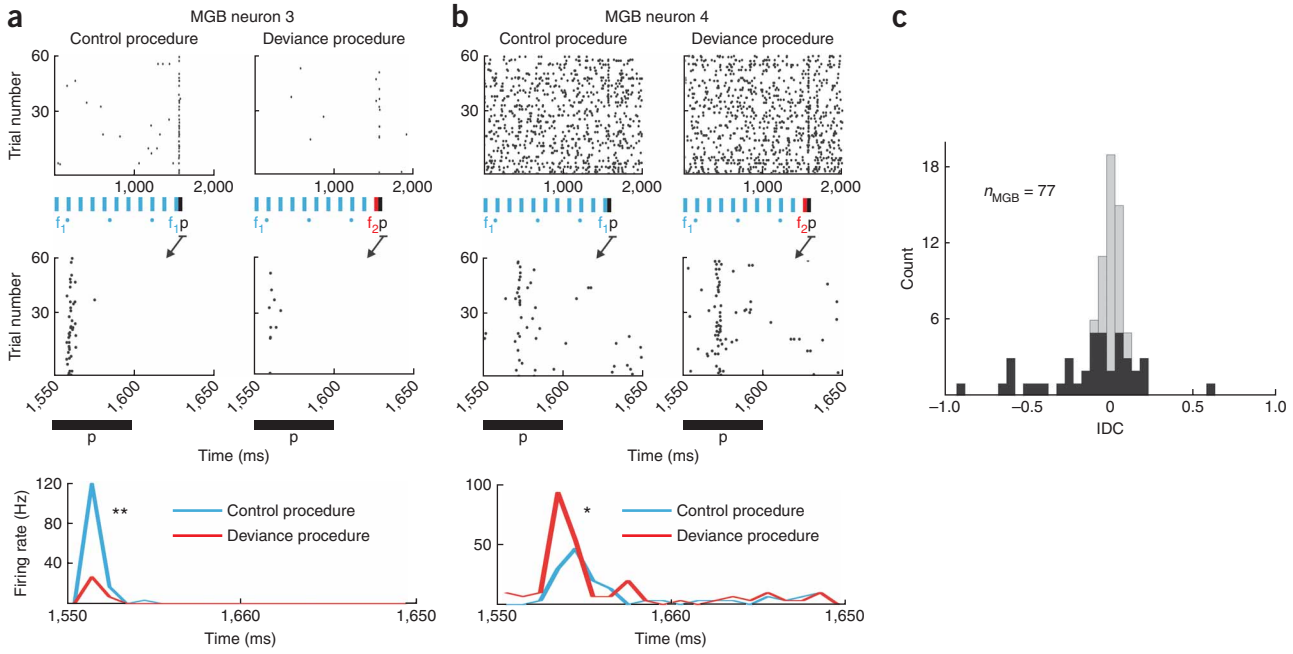

Figure 5 Effect of the deviant-stimulus procedure on MGB neuronal responses to a probe stimulus. (**a**,**b**) Raster displays showing responses of two MGB neurons to sequential auditory stimulus procedures. In the control stimulus procedure (left columns), pure tones of f_1 (blue bars) were presented 11 times before a probe stimulus (black bar). In the deviance procedure (right columns), pure tones of f_1 (blue bars) were presented ten times before a deviant stimulus, pure tone of f_2 (red bar) and a probe stimulus (black bar). The tones and probe stimuli had a 50-ms duration with 5-ms rise-fall time. In **a**, $f_1 = 30.44$ kHz, $f_2 = 33.64$ kHz and p = 8 kHz. In **b**, $f_1 = 30.44$ kHz, $f_2 = 33.64$ kHz and p = noise burst. Upper raster displays show neuronal responses during the whole time (2 s), whereas the lower ones show neuronal responses at the first 100 ms after the probe stimulus (magnified 1:20 from the upper displays). Peristimulus time histograms of MGB neuronal responses are shown at the bottom. * $P < 0.05$ and ** $P < 0.01$ (ANOVA). (**c**) Distribution of the modulatory effect (IDC) of TRN deviance detection on MGB neurons. Black bars showed modulation effects above the threshold and gray bars showed modulation effects below the threshold.

responses to the probe stimulus (noise burst) in the light-sound procedure than in the sound procedure without the light stimulus (sound procedure) (**Fig. 7a**,**c**). This neuron showed no responses to light stimuli (**Supplementary Fig. 3**). On TRN inactivation, the neuronal response to the probe stimulus increased significantly in both the sound procedure and the light-sound procedure ($P < 0.01$; **Fig. 7a–c**), again implying that the TRN strongly inhibits the dorsal thalamus. However, after TRN inactivation, the neuronal responses to the probe stimuli in the sound and light-sound procedures did not differ ($P = 0.26$; **Fig. 7b**,**c**). Notably, TRN inactivation abolished the effect of the preceding light stimulus on the auditory response of the MGB neuron.

We examined the effect of a light stimulus on the auditory responses of 118 MGB neurons. Of these neurons, 23 had enhanced auditory responses following the light stimulus and 20 had suppressed responses. The magnitude of the enhancement effect was greater than that of the suppressive effect (0.176 ± 0.026 versus −0.073 ± 0.010, $P < 0.01$).

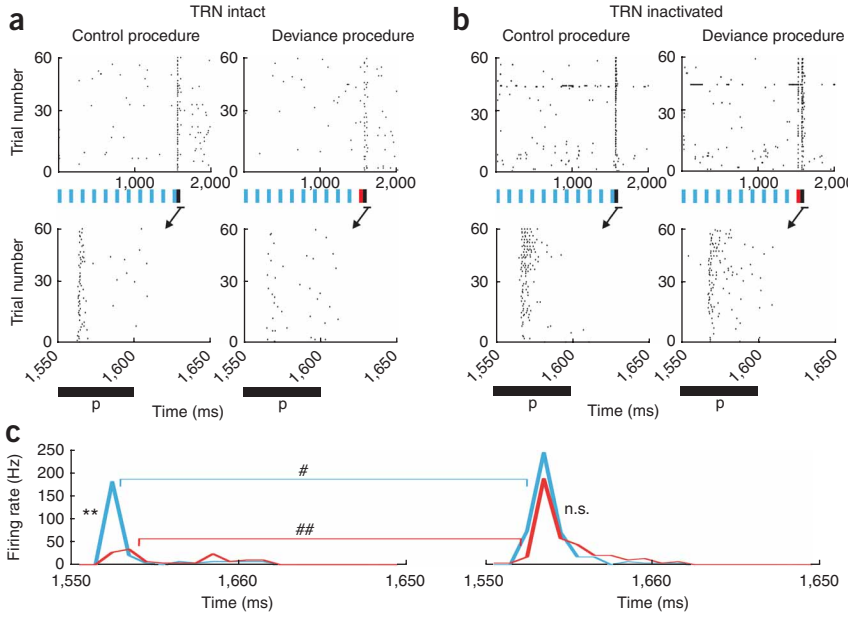

Figure 6 Effect of TRN inactivation on modulation of MGB neuronal responses by deviant procedures. (**a**,**b**) MGB neuronal responses to sequential stimulus procedures in the presence of an intact (**a**) or inactivated TRN (**b**). In the control stimulus procedure, pure tones of f_1 were presented 11 times before a probe stimulus (left columns). In the deviance procedure, pure tones of f_1 were presented ten times before a deviant stimulus, pure tone of f_2 and the probe stimulus (right columns). Neuronal responses for the whole 2 s (upper row) and the first 100 ms after the probe stimulus (lower row, magnification 1:20) are shown. $f_1 = 30.44$ kHz (blue bars), $f_2 = 33.64$ kHz (red bars) and p = noise burst (black bars). (**c**) Peristimulus time histograms of MGB neuronal responses are shown at the bottom. ** $P < 0.01$; n.s., not significant, $P = 0.27$ (ANOVA), control versus deviance procedures under the same conditions. # $P < 0.05$ and ## $P < 0.01$, intact versus inactive TRN.

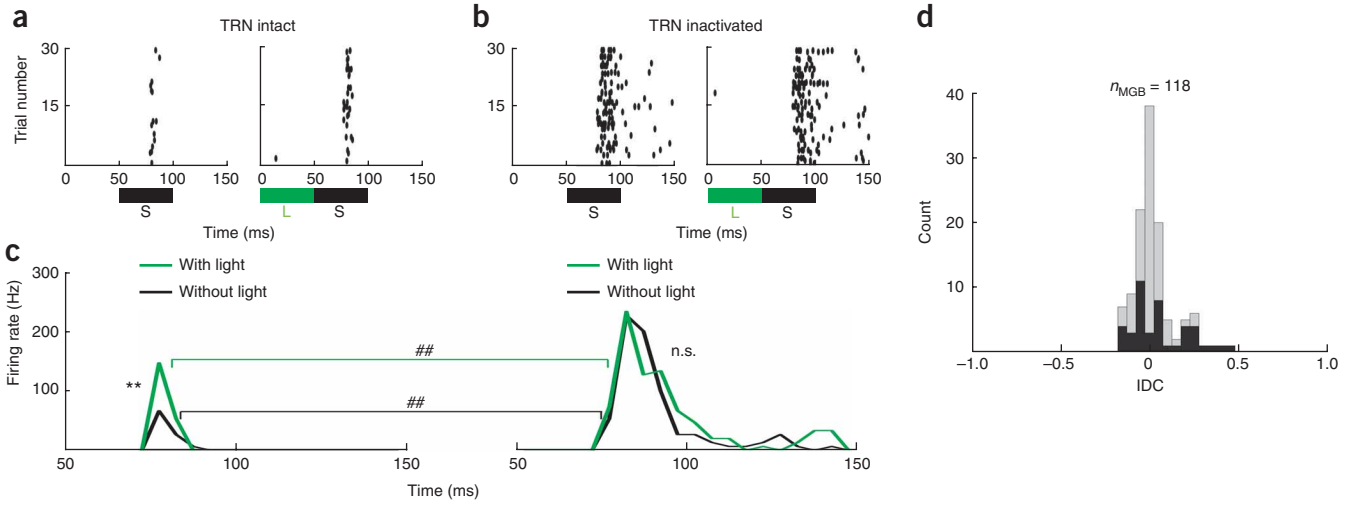

Figure 7 Effect of a preceding light stimulus on MGB neuronal responses to sound stimuli. (**a**,**b**) Responses to light and sound stimulus procedures in the presence of an intact (**a**) or inactive TRN (**b**). MGB neurons were tested in a control procedure (left panels) in which only a probe stimulus (S) was presented or a cross-modality procedure (right panels) in which a light stimulus (L, green bar) was presented before the probe stimulus (S, black bar). The probe stimulus was a 50-ms noise burst with a 5-ms rise-fall time. (**c**) Peristimulus time histograms of responses to the probe stimulus in the presence of an intact (left) or inactive TRN (right). ** $P < 0.01$ (ANOVA) for sound versus light-sound procedures under the same conditions and $^{\#\#}$ $P < 0.01$ (ANOVA) for intact versus inactive TRN. (**d**) Distribution of the cross-modality modulatory effect on MGB neurons. The modulatory effect (IDC) was defined as $\frac{R_{LS}-R_S}{R_{LS}+R_S}$, where R_{LS} and R_S are the responses to the probe in light-sound and sound procedures, respectively. Negative values indicate an inhibitory effect of the light stimulus and positive values indicate an enhanced effect. Black bars show modulation effects above the threshold and gray bars show modulation effects below the threshold.

DISCUSSION

Using the oddball procedure, we found that TRN neurons have substantially stronger responses to a pure-tone stimulus when it appears as the deviant stimulus than when it appears as the standard stimulus. Although some MGB neurons also had a deviance preference, the deviance-detection index was substantially greater in TRN neurons than in MGB neurons.

The aim of the second part of our study was to investigate the functional implication of DSP by TRN neurons. Of the 77 MGB neurons that we examined with the deviance procedure, 41 were modulated by the deviance procedure, with 27 being deviance-suppressed and 14 being deviance-enhanced neurons. The amplitude of the suppression was greater than that of the enhancement. The effect of deviance detection on MGB neuronal responses to the probe stimulus varied with the frequency used in the testing procedure (**Supplementary Fig. 4**).

After the TRN was inactivated, the MGB neurons showed substantial increases in their responses to the probe stimuli under both control and deviance procedures. However, responses to the probe stimuli did not differ between the control and deviance procedures, indicating that the modulatory effect of deviance detection on the MGB neurons were mostly attributable to TRN neurons. Of the 118 MGB neurons that we examined for the cross-modal modulatory effect, 23 had enhanced auditory responses following introduction of the light stimulus and 20 neurons had weakened responses.

The TRN neurons send strong inhibitory projections to the dorsal thalamus[1–4]. Our finding that MGB neurons showed substantially increased responses to the same auditory stimuli after the auditory TRN was inactivated (**Fig. 6**) confirms previous findings that TRN inhibition of the dorsal thalamus is strong and may last for a few seconds[17]. Injection of lidocaine in the TRN not only inactivates TRN neurons, but would also be expected to block the communication of the axons passing through the TRN (that is, the corticothalamic and thalamocortical axons). Although the axons of the thalamocortical neurons were affected, the effect of the lidocaine was localized and did not alter the generation of action potentials in the MGB (**Figs. 6** and **7**). With the use of control conditions before and after the drug application, the modulation effect of the direct corticothalamic projection to the MGB was shown to be minimal as this pathway is primarily excitatory[17,18] and MGB neurons showed increased responses (**Figs. 6** and **7**).

Using an oddball procedure[16], we have shown for the first time, to the best of our knowledge, that fast-adaptive TRN neurons in the auditory sector have a DSP. In the auditory system, DSP has previously been reported in inferior colliculus neurons[13,14] and cortical neurons[16]. Using the same procedure and parameters, we found that MGB neurons had a smaller DSP than TRN neurons. Although MGB neurons were also sensitive to deviant stimuli, TRN neurons were more sensitive with ISIs on the order of hundreds of milliseconds, a phenomenon that is linked to novelty detection[14,16].

Using a procedure that could examine the resulting effect of deviance detection by the TRN neurons, we found that some MGB neurons showed response enhancement, whereas others showed response suppression. The suppressive effect of DSP by TRN neurons on MGB neurons is understood to be caused directly by the inhibitory input to the MGB neurons. However, the enhancement of MGB neuronal responses is probably caused by disinhibition of the TRN neurons or thalamic interneurons. The DSP of one TRN neuron would inhibit other TRN neurons through their collaterals either synaptically or electrically[3,19–21]. They may also inhibit thalamic interneurons. In either case, this would result in the disinhibition in the dorsal thalamus (**Supplementary Fig. 5**).

Shifts in the attentional searchlight during novelty detection may involve projections from the prefrontal cortex and from the limbic system to the TRN, which are referred to as the nonspecific pathways[1,10,22]. The distributed limbic-cortical network is an essential component for memory retrieval and novelty detection[23–25]. Decreased activity in the nucleus accumbens, which provides other limbic inputs

to the TRN, was found in a large group of individuals with tinnitus[26]. Decreased limbic innervation of the TRN neurons would be expected to result in disinhibition of the MGB. This might account for increased activity in the auditory pathway of people suffering from tinnitus[26].

The nonspecific pathways may supplement specific pathways to the TRN[10,22,27]. Indeed, the integration of specific and nonspecific pathways through the TRN is involved in attention and cognition[10]. Some neurons in the TRN are multi-modal and have projections that cross nuclei, suggesting that the TRN has an intermediary role[11,12,28]. The fact that MGB neuronal responses to sound stimuli were modulated by a preceding light stimulus indicates that the intermodal interaction could occur at the TRN (**Supplementary Fig. 5**). Deviance detection by TRN neurons would enable these cells to recognize a new stimulus, while inhibiting other TRN neurons through their collaterals. Our finding that the MGB neuron was influenced by preceding pure tones of a frequency to which it normally did not respond (**Fig. 5** and **Supplementary Fig. 1**) indicates that the modulatory effect spreads beyond its response frequency range. The deviance detection effect would induce a shift in the 'searchlight' to direct attention to the stimulus[9] and the shift of attention through the TRN could be cross-modal. The strong adaptation or habituation that TRN neurons undergo in response to repetitive stimuli might reduce the redundancy of the environment and sharpen contrasts between differing stimuli.

Finally, in the deviance procedure that we used, some MGB neurons shifted from tonic mode to burst mode (**Supplementary Fig. 1**). The step function of the input-output relationship in burst mode (that is, the mode in which thalamic neurons are hyperpolarized by TRN input) would enable thalamic neurons to respond more strongly than if they were in the tonic mode[29–32]. This is another potential mechanism underlying deviance detection-induced enhancement of the MGB neuronal response and may supplement those that we propose here (**Supplementary Fig. 5**).

METHODS

Methods and any associated references are available in the online version of the paper at http://www.nature.com/natureneuroscience/.

Note: Supplementary information is available on the Nature Neuroscience website.

ACKNOWLEDGMENTS

The authors thank A. Palmer and M. Wallace for their critical readings and comments. This work was supported by the Natural Science Foundation of China (Overseas Cooperation Fund) and the Hong Kong Grants Council (PolyU 5412/06M).

AUTHOR CONTRIBUTIONS

X.-J.Y., S.H. and J.H. designed the experiments. X.-J.Y. and X.-X.X. performed the experiments. X.-J.Y. and J.H. analyzed the results and wrote the manuscript.

Published online at http://www.nature.com/natureneuroscience/.
Reprints and permissions information is available online at http://npg.nature.com/reprintsandpermissions/.

1. Jones, E.G. Some aspects of the organization of the thalamic reticular complex. *J. Comp. Neurol.* **162**, 285–308 (1975).
2. Steriade, M., Jones, E.G. & McCormick, D.A. *Thalamus: Organization and Function* (Elsevier Science, Oxford, 1997).
3. Yen, C.T., Conley, M., Hendry, S.H. & Jones, E.G. The morphology of physiologically identified GABAergic neurons in the somatic sensory part of the thalamic reticular nucleus in the cat. *J. Neurosci.* **5**, 2254–2268 (1985).
4. Houser, C.R., Vaughn, J.E., Barber, R.P. & Roberts, E. GABA neurons are the major cell type of the nucleus reticularis thalami. *Brain Res.* **200**, 341–354 (1980).
5. Deschênes, M., Madariaga-Domich, A. & Steriade, M. Dendrodendritic synapses in the cat reticularis thalami nucleus: a structural basis for thalamic spindle synchronization. *Brain Res.* **334**, 165–168 (1985).
6. Steriade, M. & Deschênes, M. The thalamus as a neuronal oscillator. *Brain Res.* **320**, 1–63 (1984).
7. Bal, T. & McCormick, D.A. Mechanisms of oscillatory activity in guinea-pig nucleus reticularis thalami *in vitro*: a mammalian pacemaker. *J. Physiol. (Lond.)* **468**, 669–691 (1993).
8. McCormick, D.A. & Prince, D.A. Acetylcholine induces burst firing in thalamic reticular neurones by activating a potassium conductance. *Nature* **319**, 402–405 (1986).
9. Crick, F. Function of the thalamic reticular complex: the searchlight hypothesis. *Proc. Natl. Acad. Sci. USA* **81**, 4586–4590 (1984).
10. Llinás, R. & Paré, D. in *Thalamus* (eds. Steriade M., Jones E.G. & McCormick D.A.) 501–516 (Plenum, New York, 1997).
11. Shosaku, A. & Sumitomo, I. Auditory neurons in the rat thalamic reticular nucleus. *Exp. Brain Res.* **49**, 432–442 (1983).
12. Simm, G.M., de Ribaupierre, F., de Ribaupierre, Y. & Rouiller, E.M. Discharge properties of single units in auditory part of reticular nucleus of thalamus in cat. *J. Neurophysiol.* **63**, 1010–1021 (1990).
13. Malone, B.J. & Semple, M.N. Effects of auditory stimulus context on the representation of frequency in the gerbil inferior colliculus. *J. Neurophysiol.* **86**, 1113–1130 (2001).
14. Pérez-González, D., Malmierca, M.S. & Covey, E. Novelty detector neurons in the mammalian auditory midbrain. *Eur. J. Neurosci.* **22**, 2879–2885 (2005).
15. Yu, X.-J., Xu, X.-X., Chen, X., He, S.-G. & He, J. Slow recovery from excitation of thalamic reticular nucleus neurons. *J. Neurophysiol.* **101**, 980–987 (2009).
16. Ulanovsky, N., Las, L. & Nelken, I. Processing of low-probability sounds by cortical neurons. *Nat. Neurosci.* **6**, 391–398 (2003).
17. Zhang, Z. *et al.* Corticofugal projection inhibits the auditory thalamus through the thalamic reticular nucleus. *J. Neurophysiol.* **99**, 2938–2945 (2008).
18. He, J., Yu, Y.Q., Xiong, Y., Hashikawa, T. & Chan, Y.S. Modulatory effect of cortical activation on the lemniscal auditory thalamus of the Guinea pig. *J. Neurophysiol.* **88**, 1040–1050 (2002).
19. Landisman, C.E. *et al.* Electrical synapses in the thalamic reticular nucleus. *J. Neurosci.* **22**, 1002–1009 (2002).
20. Long, M.A., Landisman, C.E. & Connors, B.W. Small clusters of electrically coupled neurons generate synchronous rhythms in the thalamic reticular nucleus. *J. Neurosci.* **24**, 341–349 (2004).
21. Warren, R.A., Agmon, A. & Jones, E.G. Oscillatory synaptic interactions between ventroposterior and reticular neurons in mouse thalamus *in vitro*. *J. Neurophysiol.* **72**, 1993–2003 (1994).
22. Zikopoulos, B. & Barbas, H. Prefrontal projections to the thalamic reticular nucleus form a unique circuit for attentional mechanisms. *J. Neurosci.* **26**, 7348–7361 (2006).
23. Knight, R. Contribution of human hippocampal region to novelty detection. *Nature* **383**, 256–259 (1996).
24. Tiitinen, H., May, P., Reinikainen, K. & Näätänen, R. Attentive novelty detection in humans is governed by pre-attentive sensory memory. *Nature* **372**, 90–92 (1994).
25. Carpenter, G.A. & Grossberg, S. Normal and amnesic learning, recognition and memory by a neural model of cortico-hippocampal interactions. *Trends Neurosci.* **16**, 131–137 (1993).
26. Mühlau, M. *et al.* Structural brain changes in tinnitus. *Cereb. Cortex* **16**, 1283–1288 (2006).
27. Llinás, R.R. & Paré, D. Of dreaming and wakefulness. *Neuroscience* **44**, 521–535 (1991).
28. Crabtree, J.W. & Isaac, J.T. New intrathalamic pathways allowing modality-related and cross-modality switching in the dorsal thalamus. *J. Neurosci.* **22**, 8754–8761 (2002).
29. Jahnsen, H. & Llinás, R. Electrophysiological properties of guinea-pig thalamic neurones: an *in vitro* study. *J. Physiol. (Lond.)* **349**, 205–226 (1984).
30. Jahnsen, H. & Llinás, R. Ionic basis for the electro-responsiveness and oscillatory properties of guinea-pig thalamic neurones *in vitro*. *J. Physiol. (Lond.)* **349**, 227–247 (1984).
31. Sherman, S.M. A wake-up call from the thalamus. *Nat. Neurosci.* **4**, 344–346 (2001).
32. Guillery, R.W. & Sherman, S.M. Thalamic relay functions and their role in corticocortical communication: generalizations from the visual system. *Neuron* **33**, 163–175 (2002).

ONLINE METHODS

Animals. We used male and female Wistar rats (280–360 g) with clean external ears. Anesthesia was induced with 1.5 g per kg of body weight urethane (20% (wt/wt) solution, intraperitoneal, Sinopharm Chemical Reagent) and maintained throughout surgery and recording with 0.5 g per kg per h urethane. Atropine sulfate (0.05 mg per kg, subcutaneous) was administered 15 min before induction of anesthesia to inhibit tracheal secretion. A local anesthetic (2% (wt/vol) xylocaine) was liberally applied to the wound. Rats were surgically prepared as described previously[33–35]. Briefly, rats were mounted in a stereotaxic device and a midline incision was made in the scalp. A craniotomy was performed to vertically access the MGB and the auditory sector of the TRN and the dura mater was then removed. Throughout the experiment, the rat was kept on a heating blanket and body temperature was maintained at 37–38 °C. All animal procedures were approved by the Animal Subjects Ethics Subcommittees of the Institute of Biophysics, Chinese Academy of Sciences and The Hong Kong Polytechnic University.

Recording. Tungsten microelectrodes with impedances of 2–7 MΩ (Frederick Haer) were stereotaxically implanted into the TRN and MGB from the top of the brain, according to a rat brain atlas[36]. The vertical coordinate of the electrode array was measured from a point slightly above the cortical surface. For recording, electrodes were positioned with a stepping-motor microdrive, which was controlled from outside the soundproof room. The signal recorded by the microelectrode, together with the acoustic stimulus signal, was amplified and stored using OpenEX (Tucker-Davis Technologies) and Axoscope software (Axon Instruments). The time of spike occurrence relative to stimulus delivery was calculated with Matlab software (Mathworks).

Anatomical confirmation. After the recording session, the rats were deeply anesthetized with sodium pentobarbital. They were killed by transcardial perfusion of with 0.9% (wt/vol) saline followed by 4% (wt/vol) paraformaldehyde in 0.1 M phosphate buffer (pH 7.3). The brains were removed and stored overnight in 0.1 M phosphate buffer containing 30% (wt/vol) sucrose. Transverse thalamic sections of 50-μm thickness were stained using the Nissl method. Images of Nissl-stained sections were overlaid onto a physiological map using the electrode penetration tracks and lesions for guidance. We used eight rats to confirm the correct positioning of the electrodes.

Acoustic stimuli. Acoustic stimuli were digitally generated using a computer-controlled Auditory Workstation (Tucker-Davis Technologies) and delivered to the ear via a coupled electrostatic speaker (EC1, Tucker-Davis Technologies) mounted in a probe. The SPL of the output of the probe was calibrated with a condenser microphone (Center Technology).

Oddball procedure. Stimulus frequencies eliciting optimal responses in TRN and MGB neurons were determined. During the majority of the experiments, we selected two frequencies, f_1 and f_2, that bordered a central frequency $(f_1 \times f_2)^{1/2}$ equaling its best frequency and that had a ratio of 0.141 octaves. Stimulus intensity was set to 70 dB. In most cases, the standard and deviant stimuli occurred at a ratio of 9 to 1. Otherwise, this ratio was 6 to 1, as specified. The stimuli were presented in a repetitive sequence of nine standard tones followed by a single deviant tone. The ISI was either 200 ms or 1,000 ms, with statistical comparisons being performed on data obtained with an ISI of 1,000 ms. PSTHs were calculated from over 180 trials for the standard tone and 20 trials for the deviant tone.

Analysis of MGB neuronal responses using the deviance procedure. The deviance procedure was designed to uncover possible modulatory effects of the TRN deviance-preference on the responses of MGB neurons to auditory stimuli. A few parameters of the deviance procedure were modified to elicit maximal effect. The deviance procedure consisted of the following sequence of stimuli: f_1, f_1, f_1, f_1, f_1, f_1, f_1, f_1, f_1, f_1, f_2 and p. In the control procedure, f_2 was replaced with f_1 to generate the following sequence: f_1, f_1, f_1, f_1, f_1, f_1, f_1, f_1, f_1, f_1, f_1 and p. The rationale for this was that the TRN neurons would be activated by f_2 in the deviance procedure, but not by the final f_1 in the control procedure. MGB neuronal responses to the probe stimulus were compared under the deviance and control procedures. Differences would show the modulatory effect of the TRN deviance preference. To exclude the last adaptation effect of the responses to the preceding sequence of tones (f_1, …, f_1 or f_1,…, f_2) on the responses to the probe stimulus, we chose frequencies of f_1 and f_2 that evoked no response from the MGB neuron being recorded. The ISI was typically set at 150 ms between consecutive f_1 stimuli and between f_1 and f_2. The f_2 stimulus was separated from the probe stimulus by 50 ms, or as otherwise specified. The inter-block stimulus was set at 3 s. When the ISI between f_2 and p was set at 50 ms, the probe stimulus followed f_2 without any delay, as the duration of all stimuli (f_1, f_2 and p) was set to 50 ms. Blocks of the deviance and control procedures were randomly presented by the computer.

An index that measured the modulatory effect on the auditory response of the MGB neurons by the preceding deviance procedure, IDC, was defined as $\frac{R_D - R_C}{R_D + R_C}$, where R_D and R_C are the responses to the probe stimulus in the deviance and control procedures, respectively. A negative value indicates a suppressive effect and a positive value indicates an enhanced effect. The threshold for determining a modulatory effect, IDC_{th}, was set on a neuron-by-neuron basis. The IDC_{th} for each individual neuron was calculated using the above equation with responses from the odd (30 trials) and even number (30 trials) of trials in the control procedure. The definitions for IDC and IDC_{th} also apply to the cross-modal procedure. When the absolute value of IDC exceeded the absolute value of IDC_{th}, the neuron was considered to have undergone modulation and was included in the statistics.

Combination of light and sound stimuli. A light stimulus (50 ms) was presented and was followed by a noise burst with a 50-ms interval (light-sound procedure). Only the sound stimulus was presented in the control procedure (sound procedure). White light was delivered through an array of light diodes, which were placed inside the soundproof chamber and controlled electronically outside the chamber. No sound was detected while switching the light diodes. MGB neuronal responses to the sound stimulus were compared under the light-sound and sound procedures. An initial examination of the neuronal response to the visual stimulus alone was performed to exclude the adaptation effect. The light-sound and sound procedures were randomly presented every 3 s. Neuronal response data were sorted for each procedure using a homemade program.

Drug application. Lidocaine was purchased from Sigma. Lidocaine injections (0.3 μl, 20 mg ml^{-1}) were administered in the TRN of seven rats using a microinjection system (Hamilton). A tungsten microelectrode was glued to the injection glass pipette to monitor the activity of the TRN. The distance between the two tips was approximately 200 μm.

Data analysis. Spike detection was carried out with OpenEX software (Tucker-Davis Technologies). Differences between varying conditions were analyzed with ANOVA. In all analyses, $P < 0.05$ was considered to be significant.

33. He, J. On and off pathways segregated at the auditory thalamus of the guinea pig. *J. Neurosci.* **21**, 8672–8679 (2001).
34. Guo, Y.P. *et al.* Corticothalamic synchronization leads to c-fos expression in the auditory thalamus. *Proc. Natl. Acad. Sci. USA* **104**, 11802–11807 (2007).
35. Xiong, Y., Yu, Y.Q., Chan, Y.S. & He, J. Effects of cortical stimulation on auditory-responsive thalamic neurones in anaesthetized guinea pigs. *J. Physiol. (Lond.)* **560**, 207–217 (2004).
36. Paxinos, G. & Watson, C. *The Rat Brain in Stereotaxic Coordinates* (Elsevier Academic Press, Amsterdam, 2005).