

Adult deafness induces somatosensory conversion of ferret auditory cortex

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In response to early or developmental lesions, responsiveness of sensory cortex can be converted from the deprived modality to that of the remaining sensory systems. However, little is known about capacity of the adult cortex for cross-modal reorganization. The present study examined the auditory cortices of animals deafened as adults, and observed an extensive somatosensory conversion within as little as 16 days after deafening. These results demonstrate that cortical cross-modal reorganization can occur after the period of sensory system maturation.

aging | cross-modal reorganization | hearing loss | plasticity | reorganization

The study of neural plasticity has revealed the considerable vulnerability of the developing brain to altered sensory experience (1). This vulnerability is particularly evident when the loss of peripheral sensory input results in the cross-modal reorganization of cortex. In their classic study, Rauschecker and Korte (2) showed that the ectosylvian visual area responded vigorously to auditory and/or somatosensory stimuli in cats visually deprived from birth. Similar developmental studies have been performed in a variety of species and their common finding was that cortical areas normally devoted to processing one sensory modality were converted to the other sensory systems following early visual deprivation (3–8) or early deafening (9–13, but see 14).

In contrast to these established developmental effects, little is known about the potential for cross-modal reorganization from lesions occurring after the sensory systems have matured. The few animal studies of adult cross-modal reorganization have described far less robust effects and collectively appear inconclusive. Blinding of adult rabbits resulted in somatosensory innervation of primary visual cortex near its border with somatosensory cortex (15). However, in deafened auditory cortex (16), visual responses were observed in the primary auditory area of cats deafened at 1 week of age, but not when cats were deafened at a later stage. In humans, regions of multi-sensory cortex become more visually active after late-onset deafness (17), which is not surprising given the presence of visual inputs before the hearing loss.

Despite these limited and equivocal results regarding late-onset cross-modal reorganization, there is considerable evidence that the adult cortex is capable of reacting to loss of peripheral input (18, 19). Investigations of adult subjects that received peripheral insults such as digit amputation (20), focal retinal lesions (21, 22), and frequency-specific cochlear lesions (23) revealed that the initially silenced cortical locus eventually developed responses similar to those of unaffected neighboring neurons (18, 24). Although these effects occurred within the same modality, the fact that intra-modal reorganization had occurred is consistent with the likelihood that the sensory cortices of adults are indeed mutable.

Hearing impairment is one of the most prevalent neurological disorders in humans, affecting 16% of adults in the United States (25). Despite the prevalence of this form of sensory loss, the possible cross-modal effects have largely been inferred from clinical observations. For example, the longer the duration of

deafness before receiving a cochlear implant, the lower the probability that the implant will be effective (26–28), and this phenomenon, although dependent on cochlear nerve viability, appears to be affected by the level of cortical cross-modal reorganization that occurred in the interim (27). Furthermore, because vision influences hearing in numerous perceptual effects, it is reasonable to expect that adult hearing loss would uncover visual effects (e.g., 17). However, the nature and magnitude of cross-modal reorganization in subjects with adult hearing loss has not been experimentally examined to our knowledge. One well studied animal model of auditory system is that of the ferret (e.g., 29). In this species, the period of auditory development has been established, such that auditory spatial selectivity, tonotopic organization, and binaural properties reach maturity in auditory cortical areas by approximately 60 d of age (30, 31). Therefore, to evaluate the potential for cross-modal reorganization in animals with mature sensory systems, the present investigation examined neuronal responses in auditory cortex in ferrets deafened as adults.

Results

Ferrets ($n = 6$) were deafened at approximately 152 d of age for a duration of approximately 76 d. A total of 69 recording penetrations were made in “auditory” cortex, with neurons sampled at 225 recording sites. In each case, recordings made in the auditory cortices of deafened animals were devoid of acoustically driven responses but consistently revealed neurons responsive to somatosensory stimulation ($84\% \pm 4\%$; average \pm SEM). As illustrated in Fig. 1, recording sites corresponding to A1 (primary auditory cortex) and anterior auditory field were activated by somatosensory stimulation primarily on the face, head, and neck. This somatosensory responsiveness also extended into adjoining auditory cortical fields. The few non-somatosensory sites that were encountered were unresponsive to all sensory stimulation and were usually found at the outer borders of the auditory cortices.

Fig. 2 shows that somatosensory responses in auditory cortex of deafened ferrets occurred across the full thickness of the cortical mantle. As depicted in the response histograms, somatosensory responses were robust and repeatable and showed reliable response latency. Receptive fields within a given penetration often had similar distributions on the body surface and different penetrations revealed neurons with different receptive fields, but evidence for a global somatotopy was not observed. As shown in Fig. 1, penetrations 1 and 2 exhibited the same receptive field distribution as that identified at penetration 19, despite being at widely different medial-lateral locations. Similarly, the receptive field at site 3 was virtually the same as those at sites 8, 9, 11, 13, 16, and 20. Instead of somatotopy, the trend was for the representation of rostral parts of the body, with most

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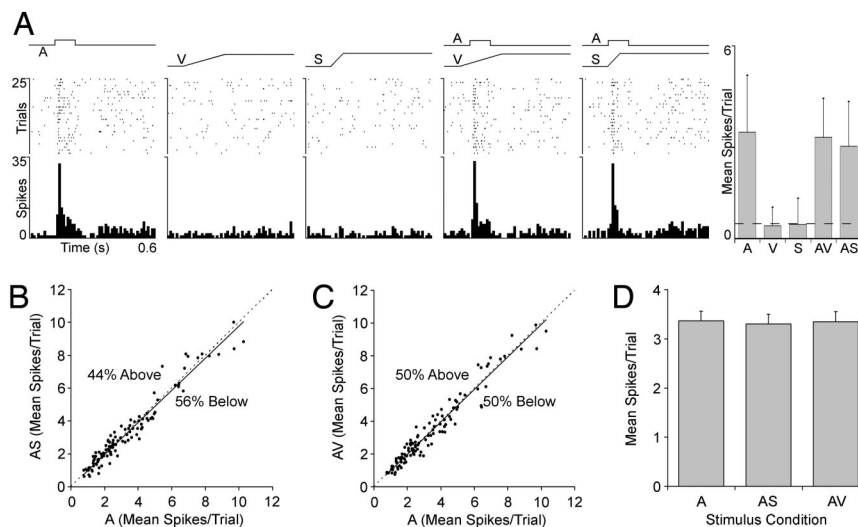


Fig. 3. Responses of auditory neurons from hearing adult ferret to auditory, visual, somatosensory, and multi-sensory stimulation. (A) Responses of a typical neuron in A1 of a hearing adult to auditory (square-wave labeled A, contralateral white noise, 75 dB SPL, 100 ms), visual (ramp labeled V, light bar moved across the visual field), somatosensory (ramp labeled S, tactile probe indented skin on contralateral cheek), and combined stimulation (AV and AS) are shown in the rasters (1 dot represents 1 spike; each row represents 1 trial) and histograms (10-ms time bins). As summarized in the bar graph (mean spikes/trial \pm SD; spontaneous activity indicated by dashed line), the neuron responded vigorously to the auditory stimulus, with no response to the visual or somatosensory stimulus. Because the response to the auditory stimulus alone was not statistically different from that of the combined stimuli conditions (AV or AS), this auditory neuron did not show subthreshold cross-modal effects. For the population of auditory neurons examined ($n = 111$), B and C plot the responses to the auditory stimulus alone (A; x axis) to those evoked by the combined stimuli (AS or AV; y axis). In both graphs, most responses fell on or near the line of unity (dashed), with similar numbers either slightly above or below. (D) Bar graph shows the population response average (mean spikes/trial \pm SEM) to the auditory stimulus alone (A), auditory-somatosensory combined stimuli (AS), and auditory-visual combined stimuli (AV), which were not significantly different ($P > 0.05$).

Given the large volume of auditory cortical tissue converted to somatosensory responsiveness in the deafened animals, it was expected that a large projection from the head representation of S1 (and/or SII) would be revealed. However, labeled neurons that project to A1 in adult-deafened ferrets originated largely in the same areas of auditory cortex as they did in the hearing animals. Similarly, labeled thalamic neurons that project to A1 in adult-deafened ferrets originated almost exclusively in the medial geniculate nucleus of the thalamus; none were observed in the somatosensory ventrobasal complex.

Discussion

In adult ferrets deafened after the established age for auditory cortical maturity (30, 31), we observed extensive cross-modal reorganization of the areas corresponding to auditory cortices. This cross-modal reorganization was characterized by a consistent somatosensory conversion in neuron responsiveness such that, after approximately 76 d of deafness, 84% of neurons sampled in auditory cortex now responded to somatosensory stimulation. These somatosensory responses demonstrated features specialized for that modality. Responses were activated best by the displacement of hairs or by light touch on delimited areas of the body surface (i.e., exhibited a receptive field). Somatosensory responses occurred across all cortical laminae and predominantly exhibited bilateral receptive fields on the head without an obvious somatotopy. This cross-modal reorganization was observed consistently in each animal and across all of the auditory cortical regions examined.

Despite reports of visual inputs to auditory cortex in hearing ferrets (32) or early-deafened humans (10, 12), studies of early-onset deafness (11, 13) have also observed somatosensory (and visual) reorganization in auditory cortex. Moreover, somatosensory responses were found in visual cortical areas of adult rabbits following late-onset blindness (15). These findings, coupled with the present observations, indicate that the somato-

sensory modality may be as relevant to cross-modal reorganization as the visual modality.

It has been suggested that the mechanisms underlying cross-modal reorganization may be similar to those responsible for intra-modal reorganization of adult sensory maps following peripheral sensory loss (36). These mechanisms include changes in synaptic effectiveness (e.g., unmasking) of preexisting connections and/or the development of new connections via axonal sprouting (for review, see ref. 19). Accordingly, the cross-modal conversion of responses in adult-deafened auditory cortex might be the result of unmasking sub-threshold somatosensory inputs that were already present in hearing cortex, or as an amplification of the subtle signals that produce somatosensory evoked oscillations in neurons in hearing auditory cortex (37). However, by using techniques that have proven successful in identifying sub-threshold cross-modal processing in other cortical structures (33–35), the present experiment failed to identify sub-threshold somatosensory inputs to hearing auditory cortex in all but a small fraction of the sample (<4%). Furthermore, tracer studies failed to reveal cross-modal connections that could underlie sub-threshold effects, although these same techniques have been adequate in doing so in other structures (34, 38). These observations, however, do not rule out the possibility that somatosensory inputs to normal auditory cortex might arrive from non-specific areas.

Alternatively, the establishment of new intracortical connections via axonal sprouting has been observed in relation to cortical reorganization induced in adulthood (15, 21, 39). The remodeling of a deactivated cortical area via axonal sprouting occurs progressively over a period of weeks to months, such that the neurons nearest to the source are the first to become responsive to the replacement modality (15). However, several clues suggest that it is unlikely that the cross-modal conversion observed in the present study resulted from newly formed cortico-cortical connections. First, within 16 d of deafness, cross-modal reorganization was observed in A1 at distances >4 mm from the nearest somato-

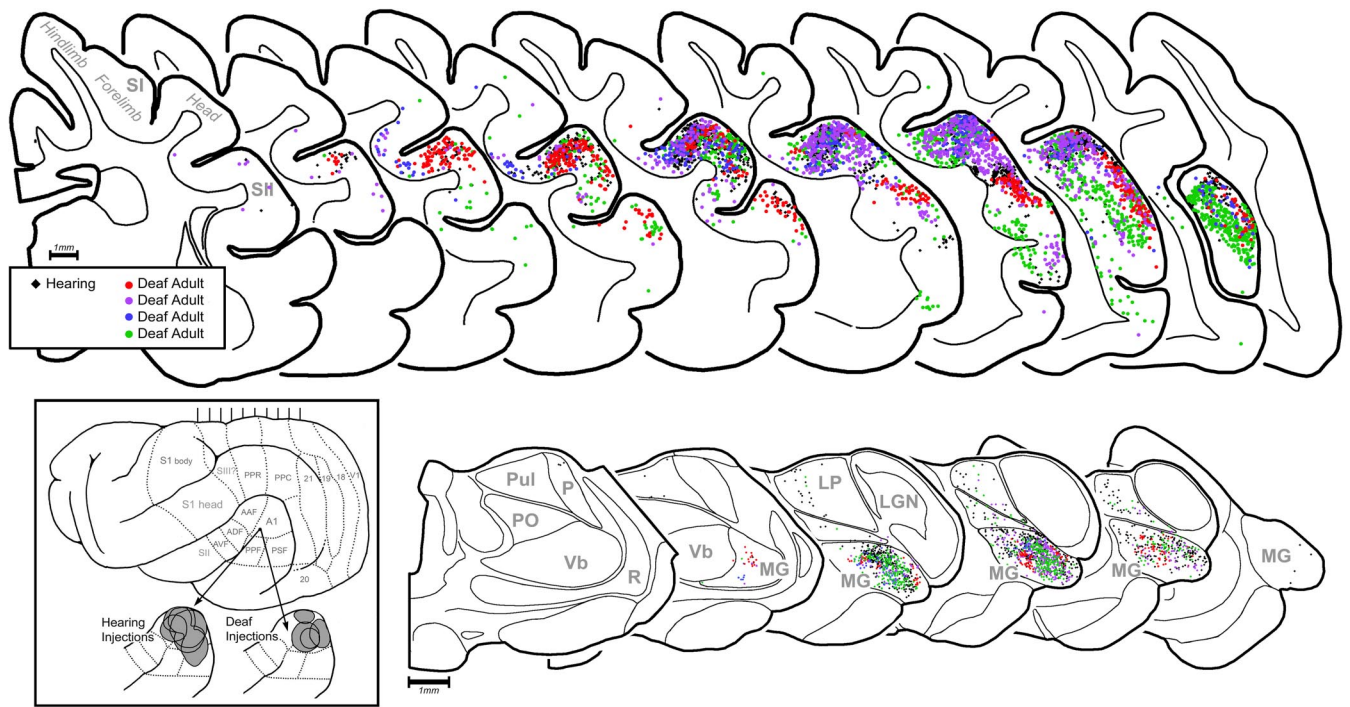


Fig. 4. Anatomical tracer injected into A1 revealed the same pattern of connections in both adult-deafened (~ 76 d duration) and hearing ferrets. (*Inset*) Lateral view of ferret cortex with expanded views of the auditory cortices depicting the tracer deposits (gray) for hearing and deafened animals. (*Top*) Serially arranged coronal sections containing somatosensory and auditory cortices. Each dot represents 1 labeled neuron (black dots represent 1 hearing adult ferret; colored dots represent 4 deafened adult ferrets). The distribution of black and colored dots is essentially co-extensive; areas of somatosensory cortex (S1; SII) are largely devoid of label. No labeled neurons were identified in sections anterior or posterior to those depicted. (*Bottom*) Serially arranged sections through thalamus with the auditory (MG, medial geniculate), somatosensory (Vb, ventrobasal), visual (LGN, lateral geniculate; Pul, pulvinar), and non-specific (PO, posterior; LP, lateral posterior) nuclei depicted. Each dot represents 1 labeled neuron (black dots, hearing; colored dots, deafened). The distribution of black and colored dots is essentially co-extensive within the MG; somatosensory thalamus (Vb) is devoid of label in both conditions.

sensory representation. Second, anatomical connections between auditory cortex and S1/SII somatosensory regions were not observed in the deafened animals. Furthermore, no connections between deaf auditory cortex and somatosensory thalamus were identified. Thus, these results do not support the notion that somatosensory reorganization of the auditory cortex following late-onset deafness was caused by axonal sprouting of new intracortical or thalamocortical connections.

Although neither unmasking of previously sub-threshold inputs nor sprouting of new connections appear to be strong candidates for the mechanism of cross-modal reorganization following late-onset deafness, the possibility remains that the cross-modal effects observed in cortex were manifest from changes that occurred at a distant, sub-cortical locus. It is well established in hearing animals that somatosensory afferents converge on auditory neurons at various sub-cortical levels within the auditory system, including the cochlear nucleus and inferior colliculus (40, 41). In hearing animals, dorsal cochlear nucleus neurons respond to somatosensory stimulation of the pinna, vibrissa, neck, and forelimb (42), and neurons in the external nucleus of the inferior colliculus respond to displacement of hairs and light touch on the bilateral or contralateral body surface, with no apparent somatotopic organization (43–45). These somatosensory response properties observed in sub-cortical auditory areas of hearing animals are remarkably similar to those of the somatosensory neurons found in the deafened auditory cortex. Furthermore, a significant increase in cross-modal somatosensory responsiveness in the dorsal cochlear nucleus has been observed after just 2 weeks of hearing loss in adults (46). In addition to unmasking of existing inputs to sub-cortical auditory structures, axonal sprouting and ingrowth

of new connections may also occur at these locations. In fact, such a scenario has been demonstrated for intra-modal somatosensory reorganization following limb de-afferentation in adults, in which axonal sprouting in the medulla, where afferents from the trigeminal nucleus grow into the deprived cuneate nucleus, result in massive somatosensory cortical remodeling (47). Therefore, it is possible that deafness-induced changes in somatosensory processing at the sub-cortical level could account for the massive redistribution of that information manifested as cortical cross-modal reorganization. Furthermore, given that the auditory pathways are highly crossed in their projections from brainstem to cortex, deafness-induced somatic inputs to the first station of this relay (40, 46) could generate a large proportion of bilateral receptive fields at higher levels, as was observed.

Regardless of the mechanism, the finding that the adult auditory system extensively remodels its cortical representations to process signals from the body surface indicates that deafened auditory cortex recovers the function of receiving and processing patterned input signals. Whether a reorganized brain of this type can actually make functional or perceptual use of the re-routed somatosensory information is not known, but it certainly increases the complexity of the problems facing efforts to re-activate a de-afferented auditory system with neuroprosthetic implants.

Materials and Methods

All procedures were performed in compliance with the Guide for Care and Use of Laboratory Animals (National Institutes of Health publication 86–23), the National Research Council's Guidelines for Care and Use of Mammals in Neuroscience and Behavioral Research (2003), and the Institutional Animal Care and Use Committee at Virginia Commonwealth University.

Deafening. Ferrets aged 112 to 198 days postnatal (DPN; mean = 152 ± 32; $n = 7$) were deafened, under isoflurane anesthesia, using a single co-administration of kanamycin (300 mg/kg, s.c.) and ethacrynic acid (25 mg/kg, i.v.); following protocol of refs. 48–50). At approximately 2 weeks ($n = 7$) and 9 weeks ($n = 6$) following deafening, auditory brainstem responses were assessed for each ear separately. The auditory stimulus was a calibrated click (2,000–3,000 trials each, 0.1-ms square-wave click, rarefaction), delivered through a speaker positioned directly in front of one ear. Sub-dermal recording leads were positioned over the right and left mastoid processes, at mid-cranium and on mid-back. Evoked electrical activity was signal averaged and threshold response levels were determined for each ear of each animal. Only those animals with a bilateral hearing threshold of >90 dB hearing level were included in the subsequent experiments. Bilateral auditory brainstem responses were also tested on hearing animals (threshold ≈15 dB hearing level).

Electrophysiology. Ten weeks after the deafening procedure, 6 deaf ferrets were surgically prepared for electrophysiological recording (mean 76 ± 9 d deafness duration; range, 64–92 d at an average 226 ± 35 DPN; range, 183–275 DPN). A single deaf adult ferret (age, 186 DPN) was prepared after 2 weeks of deafness. Four age-matched hearing controls were also used (mean, 199 ± 4 DPN; range, 197–205 DPN). Under pentobarbital anesthesia (40 mg/kg i.p.) and aseptic conditions, a craniotomy was made over the left auditory cortices and a head-support device implanted. Following recovery, the recording experiment occurred 2 to 4 d after implantation.

Electrophysiological recordings were initiated by anesthetizing the animal (35 mg/kg ketamine and 2 mg/kg acepromazine i.m.) and securing the implanted well to a supporting bar. The animal was intubated through the mouth and ventilated with expired CO₂ monitored and maintained at ≈4.5%. Fluids, supplemental anesthetic agents (8 mg/kg/h ketamine; 0.5 mg/kg/h acepromazine) and a muscle relaxant (to prevent spontaneous movements; pancuronium bromide 0.2 mg/kg/h i.p.) were continuously infused. The implanted well was opened and the recording electrode, either a glass-insulated tungsten electrode or a silicon multi-channel electrode, was inserted into auditory cortex.

Neuronal activity was amplified and routed to a PC. To reduce sampling bias during single-unit recording penetrations, neurons were studied at 250- μ m intervals. Neurons were identified by their spontaneous activity and their responses to an extensive battery of manually presented auditory (clicks, claps, whistles, and hisses), visual (flashed or moving light or dark stimuli), somatosensory (air puffs, strokes and taps using brushes and von Frey hairs), and manual (pressure and joint rotation) stimuli. Thus, at each location, the sensory response modality of the neuron (auditory, visual, somatosensory, multi-sensory, unresponsive) was identified and tabulated and the sensory receptive field(s) were mapped and graphically recorded.

In 4 hearing adults, additional sensory tests were performed on auditory cortical neurons to quantify sub-threshold somatosensory or visual effects. Given the uniform responses of neurons in the deafened animals, only selected neurons from the deafened animals were tested quantitatively. Quantitative sensory tests consisted of computer-triggered auditory, visual, and somatosensory stimuli presented alone and in combination. Free-field auditory cues were electronically generated white-noise bursts (100 ms, 75 dB SPL) from a hoop-mounted speaker 44 cm from the head (45° azimuth/0° elevation). Projected onto a translucent hemisphere (92 cm diameter), visual cues were bars of light whose size, direction, velocity, and amplitude were independently controlled. An electronically driven, modified shaker with independently programmable amplitude and velocity settings was used to indent the skin or deflect hairs within the tactile receptive field. When no receptive

field could be identified, standard visual and somatosensory stimuli were presented: a large light bar (5 × 15°) was moved across the contralateral visual field from nasal to temporal at 200%/s, and the tactile probe was positioned on the contralateral cheek. During the combined-modality presentations, the visual stimulus preceded the auditory and somatosensory cues by 50 ms (51). Each stimulus presentation was separated by 3 to 7 s, and each condition was presented 25 times. Neuronal responses were digitized (rate >25 kHz), and individual waveforms were templated and routed to a computer for analysis. For each waveform (i.e., single neuron), a peristimulus-time histogram was constructed for each of the test conditions from which the response (mean spikes per trial) was measured. To determine if sub-threshold multi-sensory effects were present, the response to auditory stimulus alone was compared statistically (paired *t* test, $P < 0.05$) with the responses during the combined stimuli conditions (auditory-somatosensory and auditory-visual conditions) (33–35).

Using a 32-site silicon multichannel electrode (≈1 M Ω impedance; 4 shanks × 8 sites; 200 μ m separation between sites; NeuroNexus Technologies), single-unit extracellular recordings were performed on an adult ferret deafened for only 16 d (170 DPN at time of deafening). For each recording site, neuronal activity was amplified (Medusa 16-channel pre-amps; Tucker-Davis Technologies), displayed on an oscilloscope, and played on an audio monitor. Using similar techniques as those described earlier, manual and computer-triggered stimuli were presented to determine neuron responsiveness. After mapping the somatosensory receptive field for each responsive neuron, the computer-triggered somatosensory stimulus was delivered repeatedly (50 trials, separated by 3–7 s). Neuronal responses from each of the recording sites were digitized at 25 kHz using a Tucker-Davis neurophysiology workstation (System III) and routed to a computer for analysis, as described earlier.

The depth of each neuron within a penetration was noted and, in a data table, correlated with its various measures of sensory responsiveness. Several recording penetrations were made in each animal and their location was plotted on a digital photograph of the cortical surface. Each recording penetration using a glass-insulated tungsten electrode was marked at its terminus with a small electrolytic lesion (0.3 mA for 0.5 s) to facilitate its histological reconstruction. At the conclusion of the recording experiment, the animal was euthanized and the brain was fixed, blocked, and serially sectioned (50 μ m). The sections were processed using standard histological procedures, and a projecting microscope was used to make scaled reconstructions of the recording penetrations. Auditory cortical fields were approximated using sulcal landmarks according to the criteria of Bizley et al. (29).

Neuroanatomy. The cortical connectivity of 4 adult ferrets deaf for approximately 76 d (opposite hemisphere from recording in same animals) and 4 hearing adult ferrets was examined. Under pentobarbital anesthesia (40 mg/kg i.p.) and aseptic surgical conditions, a craniotomy was made over auditory cortex. Biotinylated dextran amine (3 k molecular weight, 10% in citrate buffer) was pressure-injected (0.8–1.5 μ L volume) into the A1 region. After a period of 3 to 9 d, the animal was euthanized and the brain processed to visualize the transported tracer. Serial, coronal sections (50 μ m thick) were digitized using NeuroLucida software (MBF Biosciences). Digitized plots included the tissue outline, gray-white border, and the location of retrogradely labeled neuronal cell bodies. Sections were graphically arranged and neural regions were identified using accepted landmarks (29, 52).

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