Double dissociation of 'what' and 'where' processing in auditory cortex

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Studies of cortical connections or neuronal function in different cerebral areas support the hypothesis that parallel cortical processing streams, similar to those identified in visual cortex, may exist in the auditory system. However, this model has not yet been behaviorally tested. We used reversible cooling deactivation to investigate whether the individual regions in cat nonprimary auditory cortex that are responsible for processing the pattern of an acoustic stimulus or localizing a sound in space could be doubly dissociated in the same animal. We found that bilateral deactivation of the posterior auditory field resulted in deficits in a sound-localization task, whereas bilateral deactivation of the anterior auditory field resulted in deficits in a pattern-discrimination task, but not vice versa. These findings support a model of cortical organization that proposes that identifying an acoustic stimulus ('what') and its spatial location ('where') are processed in separate streams in auditory cortex.

Nearly 25 years ago, a classic double-dissociation experiment fundamentally changed the view of how the immense volume of sensory information delivered to the cerebral cortex is routed and processed. On the basis of these behavioral findings, it was proposed that visual processing is divided into two essential functions: assigning meaning to an object (determining what it is), which was shown to occur in inferotemporal cortex, and accurately locating the object in space (determining where it is), which was found to occur in posterior parietal cortex[1,2]. In cortex, visual information being transferred to these two regions arises in primary visual cortex and constitutes a ventral or 'what' processing stream and a dorsal or 'where' processing stream. Subsequent studies using behavioral, electrophysiological or anatomical approaches have confirmed the existence of parallel processing streams in extrastriate visual cortex of humans[3,4], monkeys[1,5,6] and cats[7]. Another perspective on dorsal and ventral visual processing streams considers them to be involved in the control of object-directed actions and object recognition, respectively[8].

A current model of auditory cortical organization, which is based on the concept of parallel processing streams in the visual system, proposes that the auditory system may also contain discernable cortical specializations and separate cortical processing streams that are specialized for either object or pattern discrimination, or spatial processing[9–12]. Specifically, on the basis of monkey electrophysiological studies, it was proposed that fields rostral to primary auditory cortex may be specialized for auditory-pattern processing and fields caudal to primary auditory cortex may be specialized for accurately determining the spatial location of a sound source. Electrophysiological[13] and connectional[14] studies provide evidence bolstering the proposed processing streams in the monkey. In humans, lesion[15] and neuroimaging[16] studies have also suggested the existence of dual-processing streams in auditory cortex. However, the critical missing link in the chain of evidence in support of 'what' and 'where' functional specializations in auditory cortex is a behavioral double dissociation that is similar to that demonstrated in extrastriate visual cortex.

The cat auditory cortex is a simplified and tractable version of the networks present in monkeys and humans and is particularly appealing because, unlike the monkey, the majority of the auditory areas are easily approachable, as they are exposed on the surfaces of gyri (Fig. 1), rather than being buried in the depths of a sulcus. Earlier behavioral studies in the cat demonstrated that both acoustic spatial functions and the recognition of acoustic patterns are severely impaired following large ablations that removed primary, and much of nonprimary, auditory cortex[17,18]. Therefore, as both spatial and pattern processing were impaired following large cortical lesions, there was reason to hypothesize that regions of nonprimary auditory cortex may be specialized for the spatial localization of acoustic stimuli or the recognition of auditory patterns[11,12]. The anterior auditory field (AAF) lies just rostral to primary auditory cortex, whereas the posterior auditory field (PAF) lies caudal and ventral to primary auditory cortex (Fig. 1). Anatomically, both PAF and AAF have unique patterns of inputs. PAF receives dense projections from the posterior portion of the ventral division of the medial geniculate body (MGB) and smaller projections from the dorsal MGB[19,20]. In contrast, AAF receives strong projections from the rostral pole and lesser projections from the ventral MGB[19,20]. Neurophysiological investigations found that neurons in PAF have increased spatial sensitivity relative to other auditory cortical fields and enhanced

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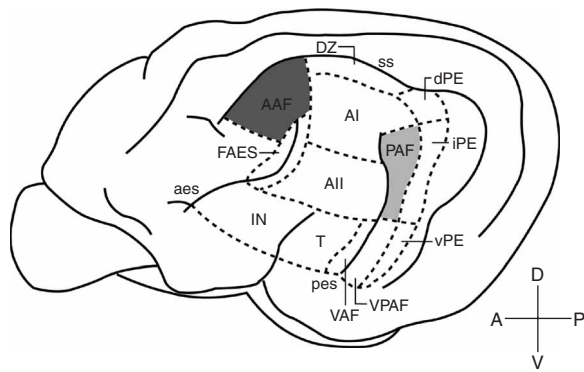
Figure 1 Lateral view of the left hemisphere of the cat cerebrum showing the auditory areas. Areas: AAF, anterior auditory field (dark gray); AI, primary auditory cortex; AII, second auditory cortex; dPE, dorsal posterior ectosylvian area; DZ, dorsal zone of auditory cortex; FAES, auditory field of the anterior ectosylvian sulcus; IN, insular region; iPE, intermediate posterior ectosylvian area; PAF, posterior auditory field (light gray); T, temporal region; VAF, ventral auditory field; VPAF, ventral posterior auditory field; vPE, ventral posterior ectosylvian area. Sulci (lowercase): aes, anterior ectosylvian; pes, posterior ectosylvian; ss, suprasylvian. Other abbreviations: A, anterior; D, dorsal; P, posterior; V, ventral. The areal borders shown in this figure are based on a compilation of electrophysiological mapping and cytoarchitectonic studies.

latency coding for sound-source location[21]. On the basis of the anatomical and physiological differences between AAF and PAF cortices, we hypothesized that it should be possible to doubly dissociate spatial and pattern processing between PAF and AAF cortices, respectively.

To test this hypothesis, we trained cats to carry out a series of experimental and control behavioral tasks, bilaterally placed cooling loops[22] over both AAF and PAF cortices (**Fig. 2**) and then tested the animals while deactivating AAF and PAF individually to determine their contributions to the acoustic behaviors. This experimental design permitted double dissociations to be performed in the same animal. The first task (spatial localization) required the cats to accurately localize the spatial position of a broadband noise burst. The second task (pattern discrimination) required the cats to discriminate between different temporal patterns of acoustic stimuli of the same temporal duration. As controls, the animals had to detect the presence or absence of an acoustic stimulus and accurately localize a visual target. Our results show a clear double dissociation between pattern- and spatial-processing regions in nonprimary auditory cortex and provide critical evidence that bolsters the concept of 'what' and 'where' processing streams in auditory cortex.

RESULTS
Spatial localization
To determine the contribution of AAF and PAF cortices to the accurate spatial localization of a sound source, we first trained the cats in a semicircular arena to identify the location of a 100-ms broadband noise burst (20 dB SPL, sound pressure level, above a background level of 58 dB SPL). After attending to a central visual stimulus (red light-emitting diode, LED), the cats had to orient to and approach the acoustic stimulus that was emitted randomly from 1 of 13 speakers placed at 15° intervals across 180° of azimuth (**Supplementary Fig. 1** online). Prior to, and following the conclusion of, each cortical deactivation, acoustic spatial-localization accuracy and precision was excellent, with performance across all 13 positions for each of the three cats at 90.0 ± 2.5%, 81.3 ± 3.3% and 88.1 ± 1.9% correct (**Fig. 3a**). This indicates that the animals were very proficient at carrying out the task and that daily cooling deactivations did not alter their performance over time. For all three cats, accuracy and precision was consistently better for more centrally located positions than for more peripheral locations.

Bilateral deactivation of PAF profoundly impaired the ability of all of the cats to accurately and precisely[23] localize the acoustic stimulus (**Fig. 3b**). Regardless of spatial location, performance dropped at all 13 tested positions to levels that were just above chance (7.7%). On average, sound localization performance fell to 15.1 ± 2.1%. At each position, this drop was significant ($P = 0.0032$). Although bilateral

deactivation of PAF massively impaired sound localization precision and accuracy, performance remained above chance (7.7%). Unilateral deactivation of PAF cortex resulted in deficits that were restricted to targets presented in the contralateral hemifield. This finding is consistent with an earlier study that examined the individual contributions of 19 cortical loci across visual, auditory, somatosensory and motor cortices to acoustic orienting during unilateral deactivation[24].

During bilateral deactivation of AAF cortex in the same animals, sound localization performance was unimpaired and not different from control levels (**Fig. 3c**). Unilateral deactivation of AAF cortex did not result in any sound-localization deficits. Simultaneous bilateral deactivation of both PAF and AAF cortices also impaired performance (16.7 ± 1.7%), but did not result in performance that was any worse than that identified during bilateral deactivation of PAF cortex alone (15.1 ± 2.1%). Finally, the PAF deactivation–induced impairments were stable, with no evidence of deficit attenuation over the 7 months of testing (**Supplementary Fig. 2** online).

The errors made by the animals during PAF deactivation provide additional information concerning the nature of the deficit. When we examined scatter plots of the target location tested versus the animals' responses, it was evident that the cats' performance was excellent both before and after cooling deactivation (**Fig. 4a**). In contrast, during bilateral deactivation of PAF cortex, the majority of the responses were to incorrect target locations, with nearly equal numbers of undershoots and overshoots (**Fig. 4b**). These errors were generally within 60° of the target. We can draw two conclusions from these results. First, deactivation of PAF cortex did not deafen the animals, as the acoustic stimulus triggered the animals to respond, although they failed to accurately or precisely localize the sound. Second, the bilateral deactivation of PAF did not globally impair the ability of the animals to localize the sound source. Although the animals were able to localize the stimulus in a small number of trials, the accuracy and precision in a hemifield was profoundly impaired. However, the animals continued to maintain the ability to localize the stimulus to either the left or right hemifield (**Fig. 4b**), as the animals were able to localize the stimulus during
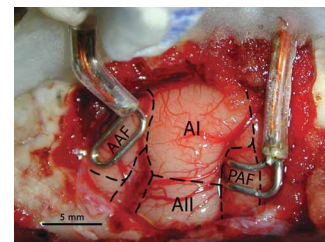

Figure 2 Cooling loops in contact with areas AAF and PAF of the left hemisphere at the time of implantation. Left is anterior. Loops were cooled daily for a period of 7 months. For abbreviations, see **Figure 1**. The areal borders presented in this figure are based on the postmortem analysis of SMI-32–processed tissue from the brain shown in this photo.
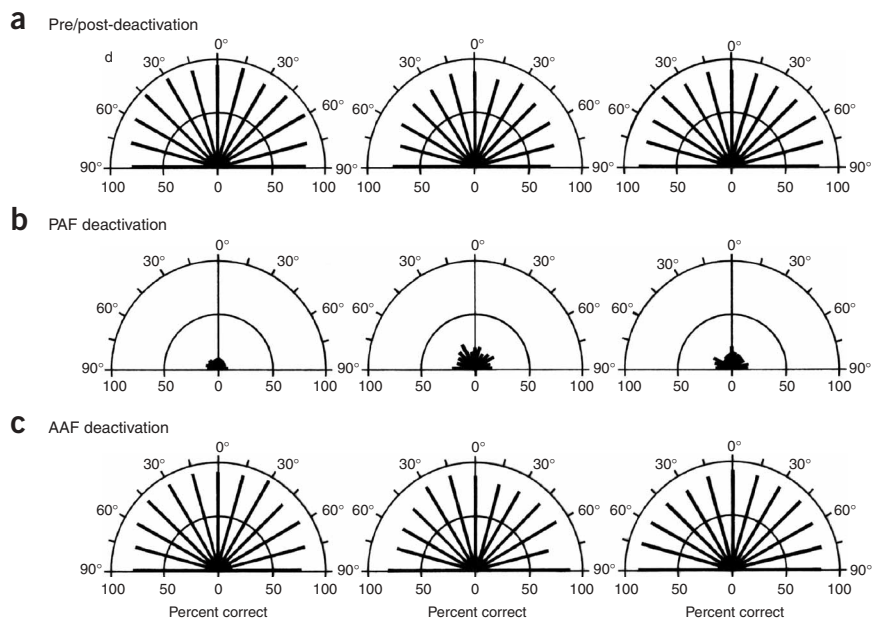
Figure 3 Polar plots of sound-localization performance. (**a**–**c**) Sound-localization performance from three cats (three vertical columns) before and following cooling deactivation (warm, **a**), during bilateral cooling deactivation of PAF cortex (**b**) and during bilateral cooling deactivation of AAF cortex (**c**) are shown. The two concentric semicircles represent 50% and 100% response levels, and the length of each bold line corresponds to the percentage of correct responses at each location tested. In each testing session, two blocks of 35 trials were conducted for each of the three conditions (warm (pre-cooling), bilateral cooling and rewarm (post-cooling)). Each testing session consisted of 210 trials. We conducted 25 testing sessions. Therefore, for the AAF and PAF deactivation conditions for each animal, data presented are from 100 trials at each of the 12 peripheral target positions.

bilateral PAF deactivation to the correct hemifield at a rate of 93.4 ± 1.3% (**Fig. 4b**). The pattern of errors that we identified during bilateral deactivation of AAF cortex was very similar to that seen during control testing conditions (**Fig. 4c**). Finally, an analysis of the catch trials revealed that the percent correct for these trials (no secondary stimulus presented) did not change, compared with control levels, during bilateral deactivation of either PAF or AAF (**Supplementary Fig. 3** online). Therefore, we concluded from these results that PAF, but not AAF, cortex is critical for the accurate and precise spatial localization of a sound source.

Pattern discrimination

To examine pattern processing in auditory cortex, we trained the same cats to carry out a temporal pattern discrimination in a two-choice apparatus (**Supplementary Fig. 4** online) using procedures that were similar to those of a classical delayed match-to-sample task. The stimuli consisted of broadband noise bursts (825–1,525 ms in duration, 78 dB SPL) with an imbedded irregular gap sequence that made the stimuli similar to Morse code sequences (**Supplementary Fig. 4**). The animals learned a temporal pattern, were presented with the same or a different sequence and had to report whether
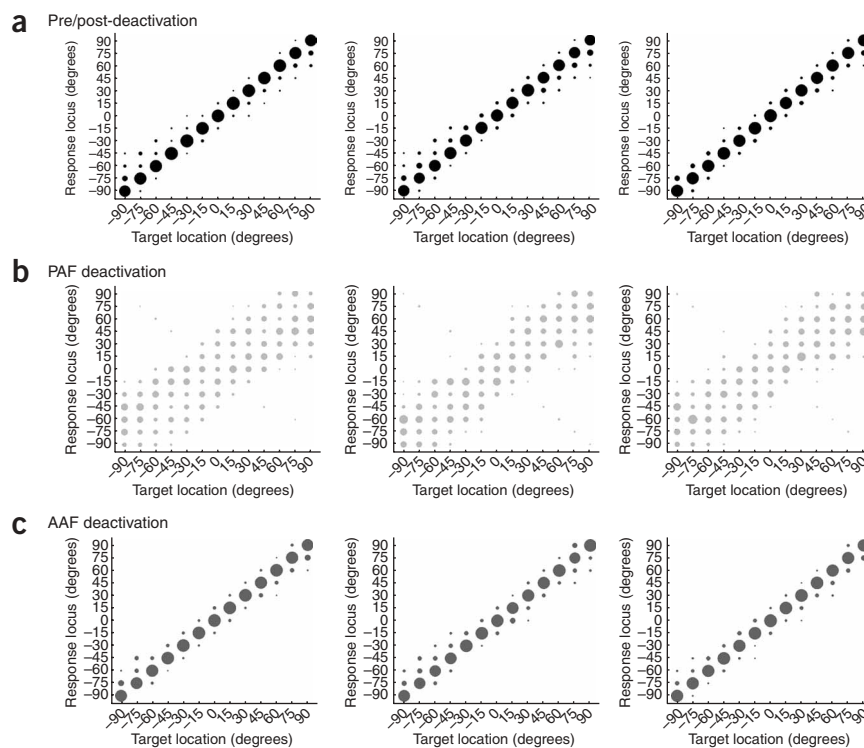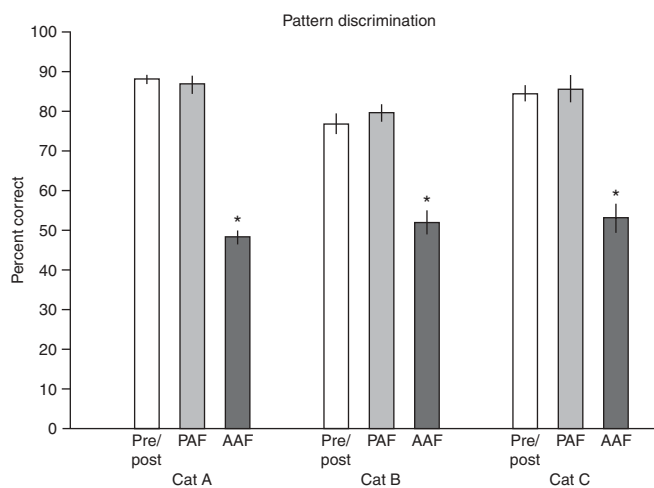
the pattern was a match or a nonmatch. Over the course of testing, we quickly discovered that if a nonmatch stimulus was presented, then its temporal duration could be no more than 10% longer or shorter than the original sample stimulus or the animal would simply discriminate the difference in temporal duration and not rely on discriminating the differences in the temporal patterns. Therefore, if a nonmatch stimulus was presented, it had the same temporal duration as the sample stimulus and differed only in its gap sequence (**Supplementary Fig. 4**).

Overall, the cats became very good at discriminating between temporal patterns. Normal average performance levels for each animal were 88.0 ± 1.1%, 76.8 ± 2.5% and 84.5 ± 1.9% correct (**Fig. 5**). During bilateral deactivation of PAF cortex, performance was no different from normal control levels (**Fig. 5**). Furthermore, unilateral deactivation of

Figure 4 Scatter plots showing accuracy and errors on the sound-localization task. (**a**–**c**) Acoustic spatial-localization accuracy and precision for each cat (three vertical columns) before and following cooling deactivation (**a**), during bilateral cooling of PAF cortex (**b**) and during bilateral cooling of AAF cortex (**c**). Target position is indicated on the *x* axis (negative values indicate left hemifield). Orienting response is indicated by the *y* axis. Area of the circle at each position indicates the percentage of responses made to that location.

Pattern discrimination

Figure 5 Mean temporal pattern-discrimination performance (mean ± s.e.m.) for each cat (A, B and C) before and following cooling deactivation (pre/post, white), during bilateral cooling of PAF cortex (light gray) and during bilateral cooling of AAF cortex (dark gray). Chance = 50%. Asterisk indicates significant difference ($P < 0.01$) from control (pre/post). Mean performance for each condition is from 20 testing sessions of 50 trials each. s.e.m. is the standard error across the 20 testing sessions. For the pattern-discrimination task, the cats completed 150 discrimination trials per day (50 warm, 50 cool and 50 rewarm). Therefore, for the AAF and PAF deactivation conditions for each animal, data presented are from 1,000 trials.

deactivations over several months altered the structure or long-term function of either AAF or PAF cortices.

Just before they were killed, we systemically injected radiolabeled 2-deoxyglucose (2DG) into each cat while an AAF loop was cooled in one hemisphere and a PAF loop was cooled in the contralateral hemisphere. The extent of the deactivation was determined from 2DG radiograms, and we identified regions that showed greatly reduced 2DG uptake ($>25\%$) compared with surrounding structures (**Fig. 7**). Adjacent sections were processed for Sternberger monoclonal antibody 32 (SMI-32, Covance) to delineate the borders of AAF and PAF. All regions of deactivation were highly circumscribed and extended beyond the perimeter of the loops by 1–1.5 mm. Cooling of the AAF cryoloops deactivated much of the anterior ectosylvian gyrus between the stereotaxic coordinates A12 and A19 (**Fig. 7a**). The deactivation included the dorsal half of the lateral bank of the anterior suprasylvian sulcus and the dorsal half of the medial bank of the anterior ectosylvian sulcus. Therefore, this region deactivated all of area AAF or area A[26,27]. Cooling of the PAF cryoloops deactivated a region of the anterior-dorsal posterior ectosylvian gyrus just posterior to the posterior ectosylvian sulcus (**Fig. 7b**). The deactivation extended down the posterior bank of the posterior ectosylvian sulcus to the fundus (**Fig. 7b**). The deactivation did not include the anterior bank of the sulcus, as a heat shielding compound was applied to the anterior side of

PAF did not alter performance. However, during bilateral deactivation of AAF cortex in the same cats, performance significantly ($P < 0.01$) dropped to levels that were not different from chance (50%). For each cat, performance fell to levels of 48.3 ± 1.7%, 52.0 ± 2.9% and 53.3 ± 3.6% correct, respectively (**Fig. 5**). This deficit was not localized to one hemisphere, as unilateral deactivation of either left or right AAF cortex did not alter performance. Finally, simultaneous bilateral deactivation of both PAF and AAF cortices impaired performance to levels that were no different than those identified during bilateral deactivation of AAF cortex alone. Therefore, we concluded from these results that AAF, but not PAF, cortex is critical for discriminating temporal-pattern sequences.

Control tasks

To confirm the specificity of our results, we conducted two control tasks. The first task used procedures that were virtually identical to those of the pattern-discrimination task. In this task, however, the cats detected whether a 100-ms broadband noise burst (78 dB SPL) was emitted. The purpose of this detection task was to dissociate whether the bilateral AAF deactivation deficit on the pattern discrimination task was a perceptual deficit or a procedural deficit. Indeed, we found that the animals did not have a procedural impairment and performance on the detection task was excellent, regardless of which one of the cortical sites was bilaterally deactivated (**Fig. 6**).

The second control task was virtually identical to the sound-localization task. In this version, however, the secondary stimulus (broadband noise burst) was replaced with a visual stimulus (illumination of an LED) so that the task became a visual-localization task (**Supplementary Fig. 1**). It was necessary to carry out this control task to demonstrate that the sound-localization deficit identified during bilateral PAF deactivation was a unimodal deficit and not a generalized orienting deficit. This expectation was confirmed when we identified that neither bilateral PAF (**Supplementary Fig. 5** online) nor bilateral AAF (**Supplementary Fig. 5**) deactivation resulted in any deficits in accurate localization of a visual stimulus.

Extent of deactivations

The cytoarchitecture of Nissl-stained sections of both AAF and PAF cortices, even after months of daily cooling deactivations, was characteristic of healthy cortex. Consistent with earlier studies[22,25], we were unable to identify any physical damage, gliosis or necrosis of cortex lying beneath the cooling loops. Furthermore, there was no alteration in cytochrome oxidase histochemistry. Therefore, neither the presence of the cryoloops nor repeated cortical
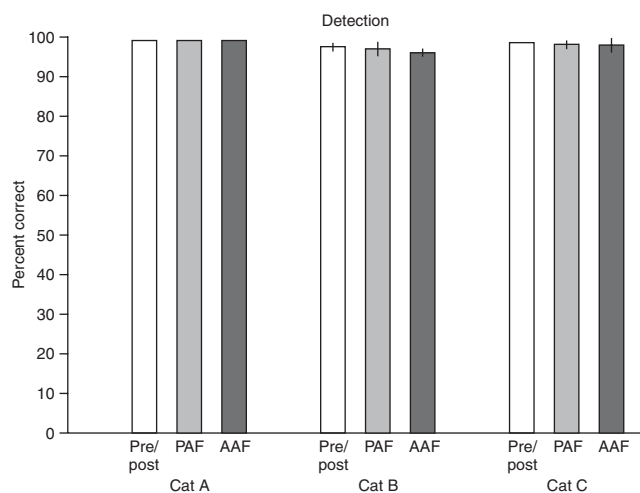

Detection

Figure 6 Mean acoustic stimulus–detection performance (mean ± s.e.m.) for each cat (A, B and C) before and following cooling deactivation (pre/post, white), during bilateral cooling of PAF cortex (light gray) and during bilateral cooling of AAF cortex (dark gray). Chance = 50%. No significant differences were identified. s.e.m. is not shown when <1.0. Mean performance for each condition is from ten testing sessions of 100 trials each. For the detection task, five blocks of 20 trials each were conducted for each of the three testing conditions. For each testing session, 300 trials were performed (100 per condition). Therefore, for the AAF and PAF deactivation conditions of each animal, data presented are from 1,000 trials.
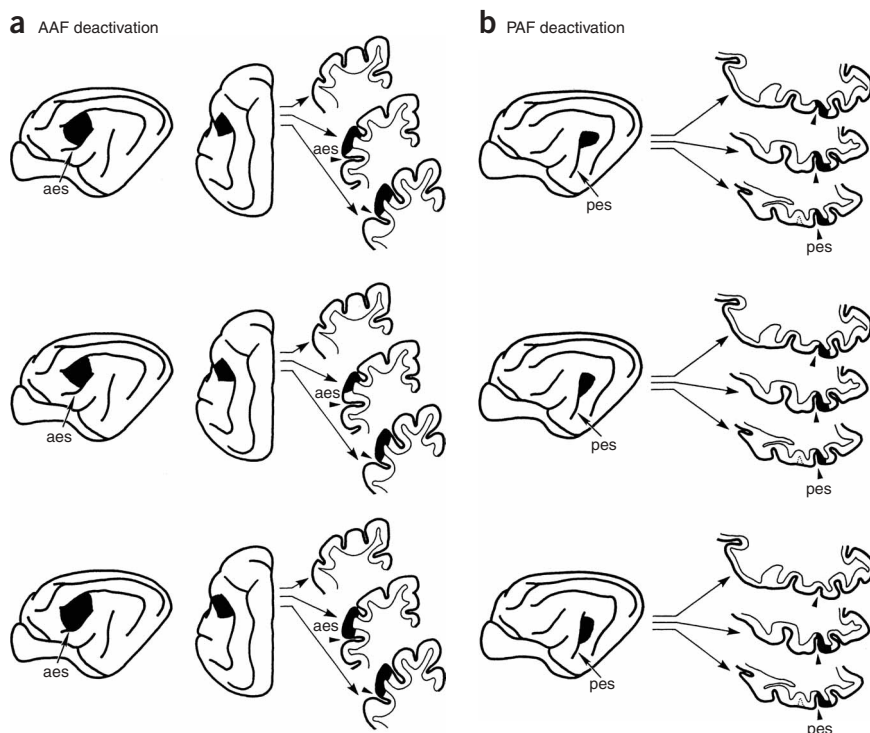
Figure 7 Deactivation reconstructions for the AAF cooling loop in the left hemisphere and the PAF cooling loop in the right hemisphere. (**a**) AAF cooling loop. The locus of deactivation (blackened region) is shown on standardized lateral (left is anterior) and dorsal (top is anterior) views of the left hemisphere (adapted from the drawings of others[50]) and the depth of deactivation is shown on coronal sections in the vicinity of the deactivation locus. (**b**) PAF cooling loop. The locus of deactivation (blackened region) is shown on standardized lateral views of the left hemisphere and the depth of deactivation is shown on horizontal sections (left is anterior) in the vicinity of the deactivation locus.

the PAF loops to keep the cooling deactivations localized to the posterior bank of the sulcus. Therefore, this region deactivated all of area PAF or area P[27]. Finally, a comparison of the SMI-32–processed tissue with the 2DG autoradiograms confirmed that neither the cooling of AAF nor PAF spread into primary auditory cortex.

DISCUSSION

The aim of the present study was to determine whether it is possible to doubly dissociate two fundamentally different cerebral operations in nonprimary auditory cortex. The notion of a double dissociation was proposed previously[28], popularized by other studies[29] and is considered to be the gold standard of behavioral neuroscience, as the results show that two cortical regions mediate independent functions and behaviors. Indeed, our results show that cerebral operations involving the localization of sound and the discrimination of acoustic patterns can be doubly dissociated from each other in posterior and anterior regions of auditory cortex, respectively. Classically, double dissociations are sought by testing two independent groups of subjects, each with a different locus of brain damage (for example, see refs. 30,31). However, our study did not examine two different populations, but instead used reversible deactivation to demonstrate the dissociations in the same experimental animals. Probably the most compelling human study to consider dual-processing in auditory cortex combined functional magnetic resonance imaging and magnetoencephalography to confirm a dissociation of 'what' and 'where' processing in the same population of subjects[32]. However, although functional imaging has being used to reveal double dissociations in the same subject (for example, see

refs. 32,33), activation of a site during task performance does not imply that deactivation of the same site will necessarily produce impairments in that task.

The concept of parallel processing streams in auditory cortex is based on monkey electrophysiological studies, where it was proposed that fields rostral to primary auditory cortex may be specialized for auditory pattern processing and fields caudal to primary auditory cortex may be specialized for accurately determining the spatial location of a sound source[11,12]. In the cat, however, the relationship between primary auditory cortex and the surrounding nonprimary auditory cortex was unclear. On the basis of evolutionary perspectives[34] and cochleotopic arrangement of primary auditory cortex[27], early reports have suggested that acoustic pattern processing in the cat may occur in areas posterior to primary auditory cortex and spatial processing may occur in areas anterior to primary auditory cortex[9,10]. However, more recent electrophysiological investigations have suggested that response properties of neurons in PAF seem to be uniquely suited for carrying out spatial-localization functions, as neurons in PAF have increased spatial sensitivity[21], a more uniform distribution of preferred locations[21], greater tolerance to changes in stimulus intensity[35,36] and their latencies vary strongly with stimulus location[21]. Furthermore, the selectivity of neurons in AAF for the rate and direction of frequency-modulated sounds makes them particularly suited for the analysis of acoustic patterns such as animal vocalizations[37]. Indeed, our study demonstrates that PAF is involved in the accurate and precise localization of a sound source and AAF is concerned with the ability to discriminate differences in simple acoustic patterns. Therefore, our findings behaviorally confirm observations concerning the response properties of neurons in PAF and AAF.

Our results demonstrate a clear division of labor in auditory cortex. Although a one-to-one relationship might not be expected between functional streams in visual cortex and functional streams in auditory cortex, our results significantly strengthen the notion that functional segregations and processing streams are a common attribute of mammalian cortical sensory systems[7]. Specifically, the proposal that 'what' and 'where' streams may exist in auditory cortex is substantially supported[9–12]. However, the spatial and pattern processing dichotomy is not the only proposed cortical processing configuration. Visual cortical processing pathways subserving perception (ventral stream) and action (dorsal stream)[8] have been hypothesized. This theory emphasizes the output requirements of the dorsal and ventral pathways, rather than the input or sensory distinctions. Evidence in support of this model has been obtained from double-dissociation studies of neurological patients[8,38,39], as well as functional imaging studies of healthy subjects[40]. When applied to our findings, this proposal would suggest that AAF is involved in perception and PAF is involved with action. Deactivation of AAF disrupted the perception of the gap sequences and the deactivation of PAF disrupted the action of accurately directing the head and body, and subsequent approach, to the acoustic stimulus. Therefore, although we did not specifically design

our tasks to test the perception-action dichotomy, our results do support this cortical segregation. Finally, it is also important to consider that there may be more than two processing streams. These 'streamlets'[14] or 'streams within streams' may very well be present in nonprimary auditory cortex. Given the large number of ways an acoustic pattern or object can be defined[41], there may well be multiple auditory object areas in the 'what' processing pathway. Furthermore, although our results substantially support the proposal that 'what' and 'where' streams may exist in auditory cortex, further verification of this will require a demonstration that other perceptual attributes that help to identify a sound, such as its pitch or timbre, can also be disrupted independently of sound localization.

Although the initial proposition that the existence of parallel processing streams in the auditory cortex was derived from nonhuman primate electrophysiological studies that showed neurons in posterior auditory cortex being selective for sound-localization perception[11–13], recent anatomical studies have also supported the concept of parallel auditory-processing streams in monkeys[42], with the streams converging on frontal cortex[14]. Sound-localization studies in humans have identified posterior auditory cortex activation during functional imaging[32,43,44], and spatial deficits have been identified in patients with damage to posterior auditory cortex[45]. Other studies using functional imaging in human subjects have considered the question of parallel auditory pathways in temporal and frontal cortices[46,47]. Although the experimental procedures differed between the two studies, both groups identified cortical regions that were selectively activated by sound recognition ('what') and different cortical regions that were selectively activated by sound localization ('where'). More recently, a meta-analysis of 38 studies reviewed functional magnetic resonance imaging and positron emission tomography evidence to determine the reliability of the dual-pathway model in humans[48]. The analysis identified that the majority of the studies found posterior activation when subjects carried out spatial tasks and anterior activation when subjects carried out nonspatial tasks[48]. Therefore, evidence supporting the existence of at least two processing streams in nonprimary auditory cortex has been identified in cats, monkeys and humans.

METHODS

Subjects. We acquired three mature (>6 months) female domestic cats from a commercial laboratory animal breeding facility (Liberty Labs), housed them in an enriched colony environment and provided them with water *ad libitum*. Food intake was restricted to 1 h at the end of each day (Purina cat chow). All procedures were conducted in accord with the US National Research Council's *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research* (2003), the Canadian Council on Animal Care's *Guide to the Care and Use of Experimental Animals* and were approved by the University of Western Ontario Animal Use Subcommittee of the University Council on Animal Care.

Apparatus. All tasks were conducted in a sound-attenuated room (Acoustic Systems) lined in Sonex foam (Illbruck). All acoustic stimuli were generated using a stimulus generation and presentation workstation and SigGenRP stimulus design software from Tucker-Davis Technologies.

Localization tasks. Training and testing were conducted in an orienting arena that allowed for the presentation of either acoustic or visual stimuli (**Supplementary Fig. 1**). The apparatus was a semicircular arena (diameter of 90 cm) that consisted of 13 pairs of miniature speakers and red, 2 V (direct current) LEDs. The speakers (Kobitone part #25RF006, Mouser Electronics) were 2.5 cm in diameter with a frequency response of 800–5,000 Hz. The speaker and LED combinations were mounted 15° apart along 180° of the azimuthal plane. A food-reward tray was located beneath each speaker and LED pair and was manually loaded following each behavioral response. The speakers emitted broadband noise bursts (100 ms in duration). Prior to any training or testing,

the loudspeakers were matched in intensity within ±1 dB for one-third of the octave frequency bands between 800–5,000 Hz using a one-third octave equalizer. For the experimental stimulus, we used broadband noise bursts rather than pure tones because orienting responses to short broadband noise bursts have been shown to be much more accurate than responses to tones[49]. The broadband noise burst stimuli were presented at 20 dB above background levels. Training was conducted in a dimly lit chamber and ambient light levels (23 cd m^{-2}) were monitored using an Extech datalogging light meter (model #401036).

Discrimination and detection tasks. Both tasks were conducted in a two-alternative forced-choice (2AFC) apparatus (**Supplementary Fig. 4**) that consisted of a 25 × 45-cm gray start box that opened into a gray decision area that was 25 cm deep. The start box was separated from the decision area by two doors: one gray and opaque and the other transparent. The decision area led to two white 30 × 40-cm goal compartments that were separated by a white opaque wall. Embedded in the lid of the start box was one 10-cm speaker (Powerline Piezo #KSN1165A, Martin Sound) and one red (2 V) LED. During the later stages of training and during testing, the cats wore a loose fitting harness and a lightweight tether that supported the cooling tubes and microthermocouple wires. The tether, tubes and wires were connected to an eye loop directly above the animal. The lid of the start box was hinged, enabling the cat to be easily returned to the box for the next trial without interfering with its tether.

Auditory and visual localization tasks. Two individuals conducted the localization experiments: the experimenter and the animal handler. The experimenter controlled the stimulus presentation, recorded the behavioral responses and viewed a video monitor that displayed images from a video camera that looked down on the apparatus and was used to determine the accuracy of the orienting response. The orienting response on each trial was determined by the experimenter's inspection of the trial on the video monitor. Cooling deactivation sessions were videotaped. The recorded responses were reviewed when the experimenter was unable to accurately determine the orienting response during testing. At the conclusion of all behavioral testing, a blind observer evaluated all of the recorded responses. This evaluation did not yield results that were different from those determined by the experimenter at the time of the actual testing sessions.

The animal handler was responsible for positioning the animal in the center of the apparatus and was blind to the stimulus presentation sequence. During the early stages of behavioral training, the animal handler securely held the cat in position in the center of the apparatus during stimulus presentation. By the conclusion of training, the cat merely positioned itself in the center of the apparatus and awaited the presentation of the stimulus. Therefore, the animal handler could not inadvertently provide cues to the cat by contact.

Following acclimation to the testing apparatus, each cat was trained to stand in the center of the arena and approach the 0° position when the red LED at this position was illuminated. A piece of low-incentive, dry cat chow was then presented from the reward tray below the stimulus. During training, the animal's attention was first attracted to the central LED (**Supplementary Fig. 1**). Then, the LED was extinguished and the sound was presented at one of the 12 peripheral speakers or at the central speaker (**Supplementary Fig. 1**). After the animal approached the stimulus, it received the moist food reward from the food tray below the speakers. The rapid and accurate turning of the head, or head and body, and accurate approach toward the locus of the acoustic stimulus constituted a correct orienting response. Any response other than a prompt direct approach to the appropriate stimulus was scored as incorrect. The cat was conditioned to approach the 0° position when an acoustic stimulus could not be localized and receive the low-incentive food. Premature responses, or a lack of response, were not scored and went unrewarded. Blocks were composed of 35 trials: two trials to each of the 12 peripheral positions, four trials to central position and seven catch trials (no secondary stimulus). Five blocks of data were collected. Catch trials, where no target stimulus was presented, were randomly conducted. In a catch trial, the cats were trained to approach the 0° position and receive the low-incentive food.

At the time of cooling loop implantation, while the animal was still in the stereotaxic apparatus, a plastic '+' symbol was cemented into the dental acrylic between the cooling loops. This symbol was stereotaxically placed over the center of the animal's head—on the midline and at stereotaxic level AP0. During

behavioral testing, the experimenter viewed the monitor looking down on the cat. When the symbol on the cat's head was exactly in the center of the apparatus and the cat was attending to the central LED, the secondary stimulus was presented. If the animal's head was not in alignment, then a trial was not conducted. Therefore, there was no variability in the position of the animal's head.

During the final stages of training and during testing, the behavioral procedures remained the same, although the cats wore a loose fitting harness and a lightweight tether that supported the cooling tubes and microthermocouple wires. The tether, tubes and wires were connected to a loop directly above the animal. Training took ∼3 months and was complete when a criterion performance level of ≥80% correct across the entire field was reached on 2 consecutive d. For the sound localization task, two blocks of 35 trials were conducted for each of the three conditions. Each testing session consisted of 210 trials. We conducted 25 testing sessions. Therefore, for the AAF and PAF deactivation conditions for each animal, the data presented are from 100 trials at each of the 12 peripheral target positions.

As a control, the animals were also trained to orient to a visual stimulus. For the visual task, training took ∼1 month and the testing procedures were identical to the acoustic-localization task, with the only difference being that the target stimulus consisted of a flashed red 2 V (direct current) LED.

Auditory discrimination task. The pattern-discrimination task was conducted in a 2AFC apparatus (**Supplementary Fig. 4**). The cats discriminated between different Morse code–type sequences of identical temporal duration (**Supplementary Fig. 4**). The sequences were emitted from a speaker in the lid of the start box and consisted of gap sequences (25-ms gaps) of long (75 ms) and short (25 ms) broadband noise bursts (78 dB SPL). A cat began in the start compartment, the LED was illuminated and the sample stimulus was played 500 ms later. After a 500-ms delay, the opaque door, followed by the transparent door, was raised and the animal approached a centrally placed gray, square block and received a food reward from behind the block (**Supplementary Fig. 4**). This sample stimulus presentation was repeated five times. Following the five sample presentations, the sixth (choice) trial was identical to the first five except for two changes: the red LED in the start box flashed to indicate the start of the choice trial and the gray square was removed and a black circular block and black square block were placed in the left and right goal compartments (**Supplementary Fig. 4**). The animals were trained to receive a food reward from behind the black circle when the sixth presentation was a match and to receive a food reward from behind the black square when it heard a nonmatching stimulus. Training took ∼8 months and was complete when a criterion performance level of ≥75% correct was achieved on 2 consecutive d. The match and nonmatch stimuli were presented in a balanced, irregular sequence and the circle and square alternated between the two sides of the apparatus in a pseudorandom order. A block of 20 trials consisted of ten match and ten nonmatch stimuli.

For the pattern-discrimination task, the cats completed 150 discrimination trials per day (50 warm, 50 cool and 50 rewarm). These were particularly long testing sessions because the sample stimulus was presented five times before the actual discrimination on each trial. We conducted 20 testing sessions. Therefore, for the AAF and PAF deactivation conditions of each animal, the data presented are from 1,000 trials.

Auditory detection task. The detection task was conducted in the 2AFC apparatus (**Supplementary Fig. 4**) in a manner similar to that of the auditory-discrimination task. The cat began in the start compartment, the LED was flashed and a 100-ms broadband noise burst (78 dB SPL) was, or was not, emitted 500 ms later. After a 500-ms delay, the opaque door, followed by the transparent door, was raised and the animal chose between either a solid black circle or a solid black square (**Supplementary Fig. 4**). To receive a food reward, we trained the cats to approach the circle when the auditory stimulus was present and to approach the square when the stimulus was absent. Training took ∼1 month and was complete when a criterion performance level of ≥75% correct was achieved on 2 consecutive d. Both the left-right positions of the square and circle and the trials with or without the auditory stimulus were presented in independent, balanced irregular sequences. A block of 20 trials contained ten stimulus trials and ten nonstimulus trials. Multiple blocks were conducted in an individual testing session.

For the detection task, five blocks of 20 trials each were conducted for each of the three testing conditions. For each testing session, 300 trials were performed (100 per condition). Ten testing sessions were conducted. Therefore, for the AAF and PAF deactivation conditions of each animal, the data presented are from 1,000 trials.

Cooling loop implantation. For all surgical procedures, general anesthesia was induced with sodium pentobarbital (∼25 mg per kg of body weight to affect, intravenous). Bilateral craniotomies were made over the anterior and posterior ectosylvian gyri. Cooling loops[22] were then placed bilaterally over the AAF and PAF cortices (**Fig. 2**). The loops were secured to the skull with bone screws and dental acrylic. The dura was replaced and bone defects around the implanted cooling loops were repaired with original bone, Gelfoam (Pfizer) and dental acrylic (for detailed cryoloop implantation procedures, see ref. 22).

Reversible cooling deactivation. Each cryoloop was fashioned out of 23G hypodermic tubing and had a copper/constantin microthermistor attached at the union of the inlet and outlet tubes. The loops were designed to fit snugly, after final adjustment, in contact with AAF or PAF cortex (**Fig. 2**). Cortex was cooled by pumping chilled methanol through the loop tubing. Loop temperature was monitored and accurately governed within 1 °C of the desired value by controlling the rate of methanol flow. Synaptic transmission in the mammalian brain is blocked by temperatures below 20 °C (ref. 7). For a loop cooled to 3 °C, thermocline measures show that the 20 °C isotherm lies at the base of layer VI. A stable cortical temperature was reached in ∼5 min of initiating cooling, and normal brain temperature was regained in ∼2 min after the cessation of cooling as a result of the infusion of warm blood[7] (for detailed cryoloop procedures, see ref. 22).

Testing. During testing sessions, the cat wore a harness to support a tether carrying the cooling tubes and temperature-monitoring wires. All cats were tested during warm, cool and rewarm phases of the cooling cycle, and we attempted to divide the trials equally between the three phases. Daily deactivation protocols were randomized so the animals could not predict which cortical sites would be deactivated during any given testing session.

Data analysis. For both orienting tasks, we calculated percent correct responses. Performance was assessed with a mixed ANOVA with one within hemisphere variable (warm versus cold, locus of cooling loop). Orienting responses were assessed with multifactor mixed ANOVA variables (warm versus cold, azimuth, locus of cooling loop). The order of sessions was counter-balanced between areas (loops), functional states (active versus deactivated) and hemispheres. When a difference was detected with the ANOVAs, we conducted follow-up within-subject t-tests (Tukey test). The P value from the t-test is provided when the difference between variables was significant. If a cooling-induced deficit was significant, additional t-tests were carried out to determine whether performance was different from chance (7.7% correct). For the discrimination and detection tasks, mean performance while cortex was either warm or cold was compared for each subject examined using within-subject t-tests. No exclusionary criteria were applied to any of the data in any of the tasks.

2DG administration and tissue processing. To obtain a complete measure of cooling deactivation, we used reduced uptake of 2DG as a marker of deactivated cortex. A single bolus of 100 μCi kg^{-1} 2DG (specific activity 55 mCi mmol^{-1}) was injected (intravenous) into the awake cat 5 min after cortical temperatures stabilized. The cats were fully conscious to maximize 2DG uptake and their bodies were comfortably restrained in a veterinary cat sack. We killed each cat 30 min later; the brain was fixed, removed and frozen. Frozen brains were sectioned in a cryostat (–20 °C) at 35 μm, placed on subbed coverslips and dried on a ∼50 °C hot plate. 2DG-containing sections were apposed with ^{14}C standards to Agfa-Gevaert Structurix films. Sections were stored in X-ray cassettes at –40 °C. Following a 5–12-week exposure, the films were developed and fixed. Sections were then fixed to the slides and stained for Nissl substance. Adjacent sections were stained for myelin, SMI-32 or cytochrome oxidase activity.

Cryoloop placement assessment. We confirmed the alignment of the deactivation loci with areas AAF and PAF by comparing the 2DG results with the

histology from the Nissl- and SMI-32–processed tissue. We used SMI-32 histochemistry to localize areas AAF and PAF and confirm that the deactivation loci included as much of each area as possible without spreading into primary auditory cortex. Ideally, the locations of AAF and PAF would have been determined before cryoloop placement by carrying out detailed tonotopic mapping to ascertain the borders of the two areas. However, as this mapping would have severely compromised the integrity of the cortex, it would have been impossible to dissociate in postmortem analysis whether any damage was caused by the recording or by the cooling loops. Therefore, as techniques to confirm the location of AAF and PAF could not be used to localize the two areas before implantation, we confirmed the location of the two areas during postmortem analysis. The placement of the loops was guided by comparing the results of a number of mapping studies and determining characteristic locations for AAF and PAF on the basis of gyral and sulcal patterns (**Fig. 1**). However, this approach was not successful every time and postmortem analysis revealed that three animals that we had prepared for this study had to be excluded from the behavioral analysis because the AAF loops were sited too far anterior (involving SII). In all three of these animals, AAF deactivation was incomplete ($\sim$50% deactivated) and no impairment was identified on the pattern-discrimination task.

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

AUTHOR CONTRIBUTIONS
S.G.L. conceived and designed the experiments and carried out all of the surgical procedures. S.G.L. and S.M. conducted the behavioral training and testing. S.G.L. analyzed the data and supervised the histological processing of the tissue. S.G.L. and S.M. drafted and edited the manuscript.

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# Supplementary Online Materials

To complement:

"Double Dissociation of "What" and "Where" Processing in Auditory Cortex"
Stephen G. Lomber and Shveta Malhotra
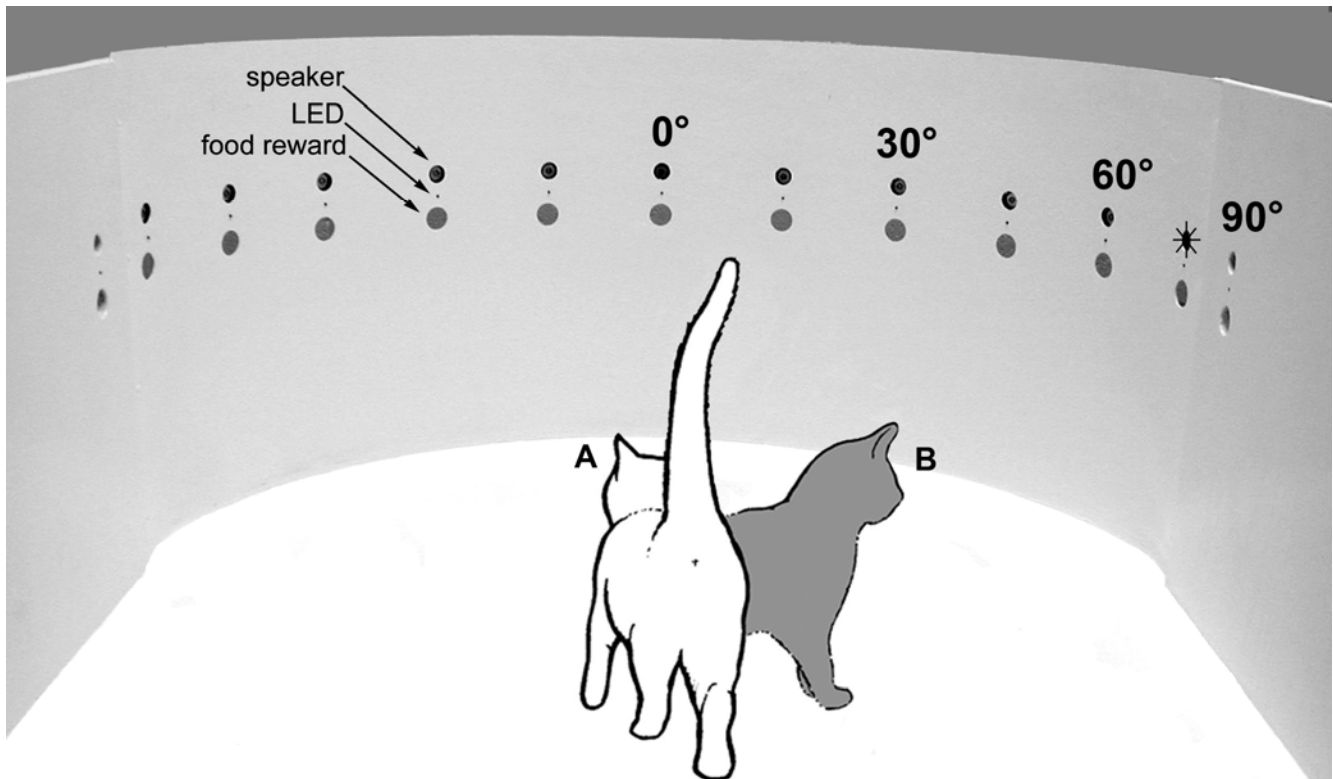
Supplementary Figure #1:
Orienting arena for the localization of acoustic and visual targets. A loudspeaker (top circle) and a light-emitting diode (LED, black dot) were located above a food reward locus (lower circle) at each of thirteen regularly spaced (15⁰) intervals (for sake of clarity, only 30⁰ intervals are labeled). **A)** The animal was first required to fixate on the central (0⁰) LED. **B)** It then had to orient to, and approach, a secondary acoustic (100ms broad-band noise) or visual (illumination of an LED) stimulus to receive a food reward.
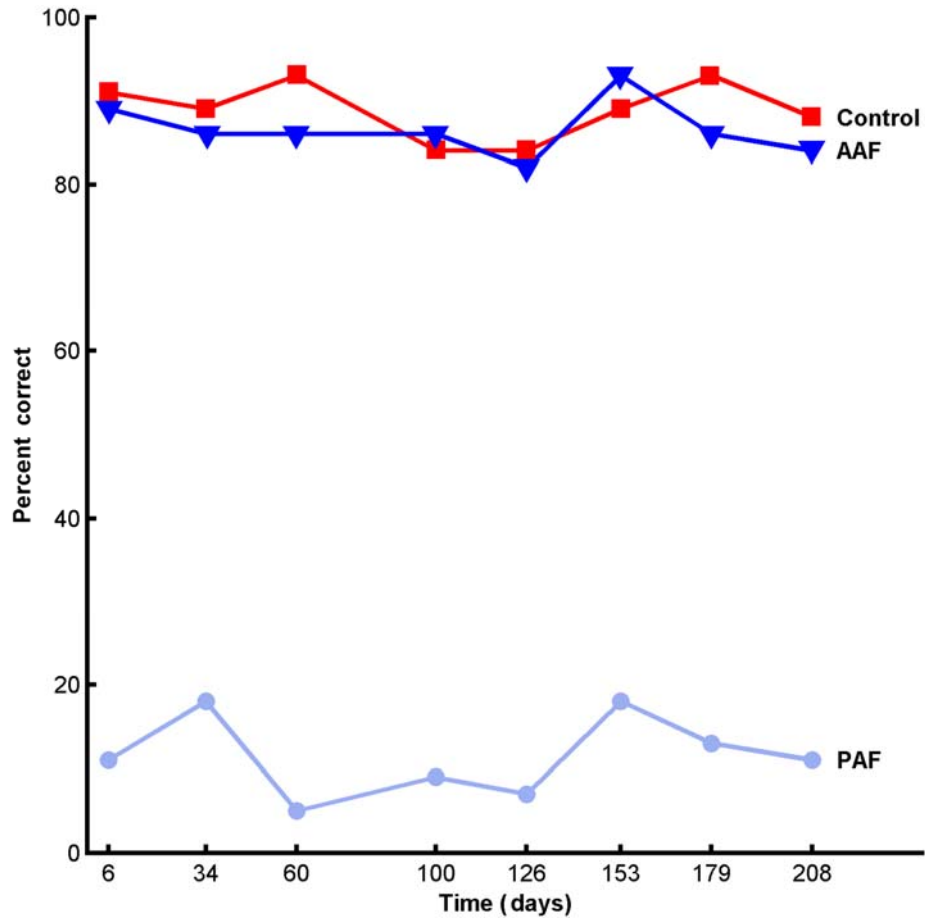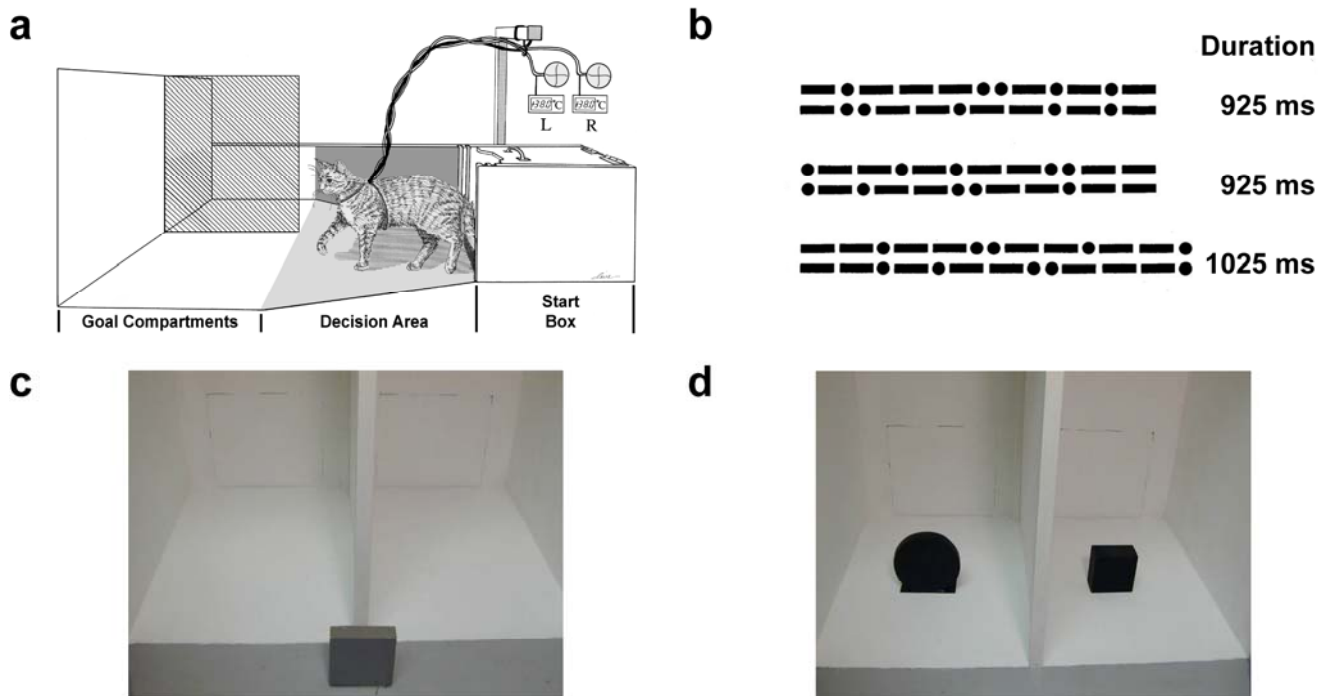
Supplementary Figure #2:
Performance on the acoustic localization task over the seven months of testing. Percent correct indicates performance over all thirteen tested positions. Note the excellent performance during warm and rewarm sessions (control; red) and during bilateral deactivation of AAF (dark blue). Throughout the testing period performance during bilateral deactivation of PAF (light blue) remained low and there was no evidence of deficit attenuation. Data is from Cat A.
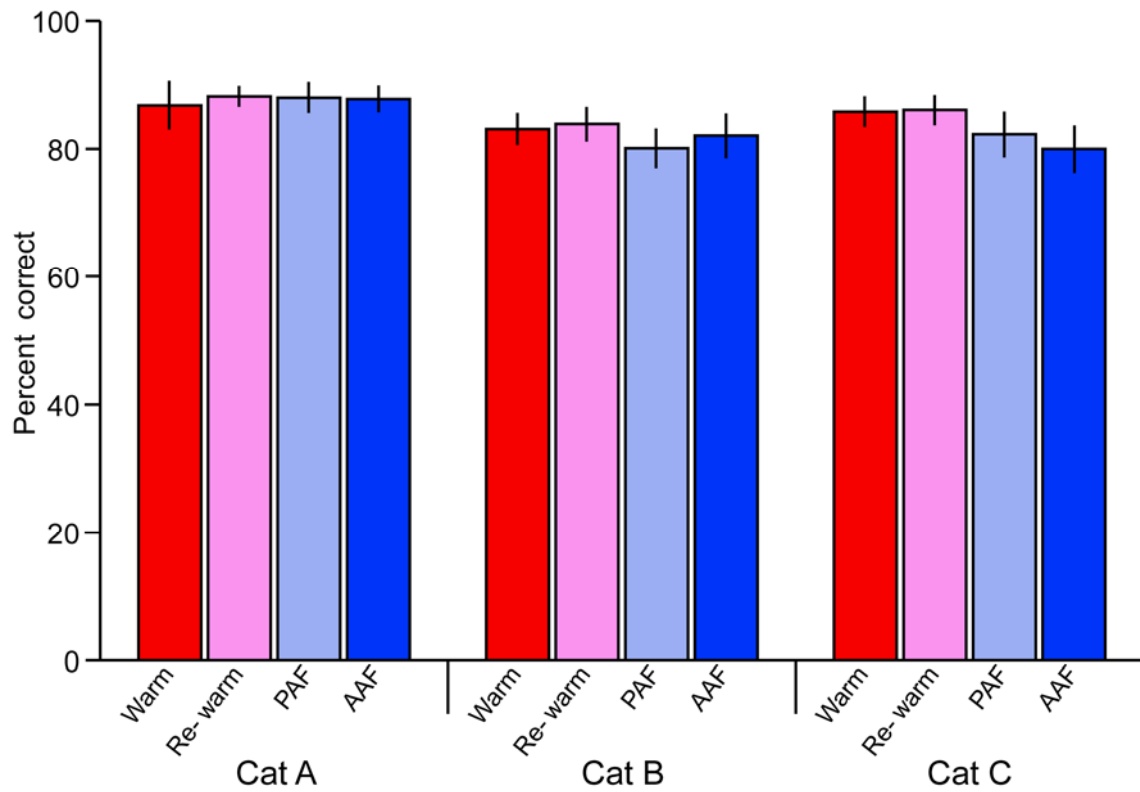
Supplementary Figure #3:
Performance on catch trials (no secondary stimulus presented) during the acoustic localization task. For each cat, there was no difference in performance on the catch trials between the four experimental conditions (warm, re-warm, PAF deactivation, AAF deactivation).

a

Goal Compartments | Decision Area | Start Box

b

Duration

925 ms

925 ms

1025 ms

c

d

Supplementary Figure #4:
Apparatus and procedures for the discrimination of acoustic temporal patterns. **a)** A two-alternative forced-choice apparatus was used which consisted of a 25 x 45cm gray start box which opened into a gray decision area that was 25cm deep. The start box was separated from the decision area by two doors; one gray and opaque and one transparent. The decision area led to two white 30 x 40cm goal compartments which were separated by a white opaque wall. Embedded in the lid of the start box was one 10 cm speaker and one red (2V) light-emitting diode (LED). During later stages of training and during testing, the cats wore a loose fitting harness and a lightweight tether that supported the cooling tubes and microthermocouple wires. The tether, tubes and wires were connected to an eye loop directly above the animal. The pumps for cooling the cryoloops, and thermometers for measuring cryoloop temperature are shown in the upper, right corner of the illustration. The lid of the start box was hinged, enabling the cat to be easily returned to the box for the next trial without interfering with its tether. **b)** Examples of stimuli. The cats discriminated different Morse Code-type sequences of identical temporal duration. The three examples show three pairs of stimuli (a sample and a non-matching stimulus, both of identical duration). The sequences were emitted from a speaker in the lid of the start box and consisted of gap sequences (25 msec gaps) embedded in long (75 msec) and short (25 msec) broad-band noise bursts (78 dB SPL). **c)** A cat began in the start compartment, the LED was illuminated, and 500 msec later the sample stimulus was emitted. After a 500 ms delay, the opaque door followed by the transparent door was raised and the animal approached a centrally-placed grey square block and received a food reward from behind the block. This sample stimulus presentation was repeated 5 times. **d)** Following the five sample presentations, the sixth (choice) trial was identical to the first five except for two changes: 1) the red LED in the start box flashed to indicate the start of the choice trial, and 2) the grey square was removed and a black circular block and black square block were placed in the left and right goal compartments. The animals were trained to receive a food reward from behind the black circle when the sixth presentation was a match, and to receive a food reward from behind the black square when it heard a non-matching stimulus.
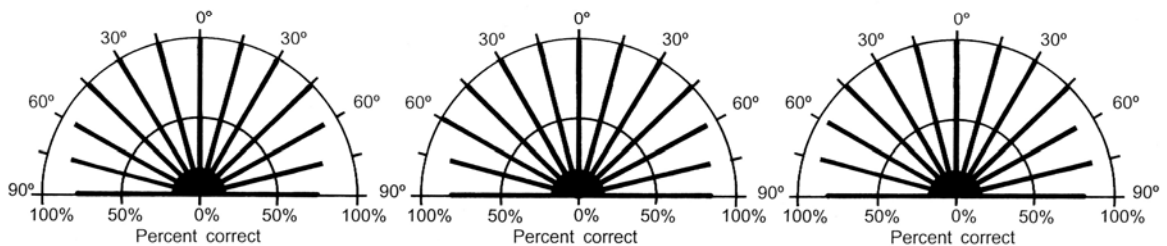
4

Visual Localization
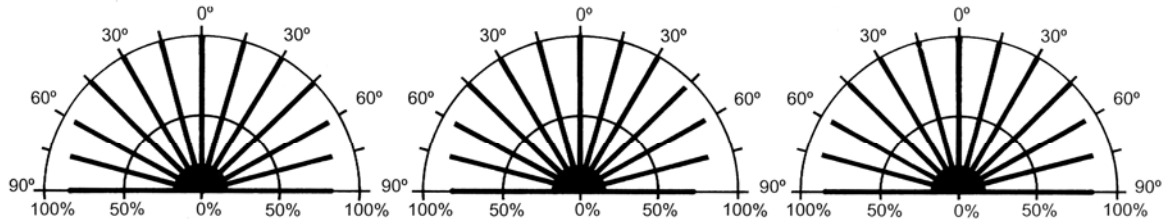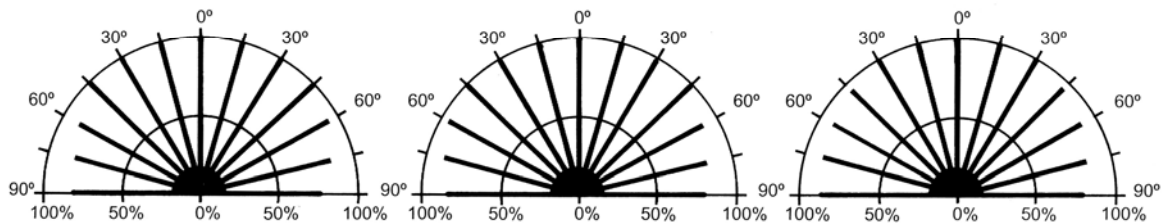
Supplementary Figure #5:
Orienting responses to a visual stimulus during bilateral deactivation of PAF or AAF in each of the three cats examined. **a)** Control data collected after cryoloop implantation, prior to cooling (Pre), and shortly after termination of cooling (post). **b)** Data collected during bilateral cooling deactivation of PAF. **c)** Data collected during bilateral cooling deactivation of AAF. The two concentric semicircles represent 50% and 100% response levels and the length of each bold line corresponds to the percentage of correct responses at each location tested. Each graph represents 120 trials presented at the central position and 60 trials presented at each peripheral locus.