Restoration of Acoustic Orienting into a Cortically Deaf Hemifield by Reversible Deactivation of the Contralesional Superior Colliculus: The Acoustic “Sprague Effect”

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ABSTRACT

Removal of all contiguous visual cortical areas of one hemisphere results in a contralateral hemianopia. Subsequent deactivation of the contralesional superior colliculus (SC) nullifies the effects of the visual cortex ablation and restores visual orienting responses into the cortically blind hemifield. This deficit nullification has become known as the “Sprague Effect”. Similarly, in the auditory system, unilateral ablation of auditory cortex results in severe sound localization deficits, as assessed by acoustic orienting, to stimuli in the contralateral hemifield. The purpose of this study was to examine if auditory orienting responses can be restored into the impaired hemifield during deactivation of the contralesional SC. Three mature cats were trained to orient towards and approach an acoustic stimulus (broad-band, white noise burst) that was presented centrally, or at one of twelve peripheral loci, spaced at 15 deg intervals. Following training, a cryoloop was chronically implanted over the dorsal surface of the right SC. During cooling of the cooling loop to temperatures sufficient to deactivate the superficial and intermediate layers (SZ, SGS, SO, SGI), auditory orienting responses were eliminated into the left (contracooled) hemifield while leaving acoustic orienting into the right (ipsicooled) hemifield unimpaired. This deficit was graded from periphery-to-center in a temperature-dependent way. After the effectiveness of the SC cooling loop was verified, auditory cortex of the middle and posterior ectosylvian and anterior and posterior sylvian gyri was removed from the left hemisphere. As expected, the auditory cortex ablation resulted in a profound deficit in orienting to acoustic stimuli presented at any position in the right (contralesional) hemifield, while leaving acoustic orienting into the left (ipsilesional) hemifield unimpaired. The ablations of auditory cortex did not have any impact on a visual detection and orienting task. The additional deactivation of the contralesional SC to temperatures sufficient to cool the superficial and
intermediate layers nullified the deficit caused by the auditory cortex ablation and acoustic orienting responses were restored into the right hemifield. This restoration was graded from center-to-periphery in a temperature-dependent fashion. The deactivations were localized and confirmed with reduced uptake of radiolabelled 2-deoxyglucose (2DG). Therefore, deactivation of the right superior colliculus following the ablation of the left auditory cortex yields a fundamentally different result to that identified during deactivation of the right superior colliculus prior to the removal of left auditory cortex in the same animal. Hence, the “Sprague Effect” is not unique to a particular sensory system and deactivation of the contralesional SC can restore either visual or acoustic orienting responses into an impaired hemifield following cortical damage.
INTRODUCTION

In 1965, Sprague and Meikle described a series of studies that demonstrated that ablations of what was then considered visually-responsive cortex in the cat, induced a dense blindness in the contralateral visual field, which they assayed with a visual orienting task. In a subsequent study, Sprague (1966) showed that removal of a minimum of the superficial and intermediate layers of the contralesional superior colliculus could reverse the impact of the visual cortex ablation on visual orienting, and went one step further to show that it was not necessary to ablate the contralesional superior colliculus, but merely sever the intertectal commissure (Sprague 1966). The restoration of visual orienting following large visual cortical ablations is a phenomenon that has become known as ‘the Sprague Effect.’ This restoration has been repeatedly demonstrated in numerous studies of the cat (Sherman 1977; Wallace et al. 1989, 1990; Rosenquist et al. 1996; Ciaramitaro et al. 1997; Lomber et al. 2002) and a recent human case also suggests that the effect can be identified in human subjects (Weddell 2004).

In the auditory system, although large unilateral lesions involving primary auditory and much of the remaining acoustically-responsive cortex (Fig. 1) do not result in deafness in the contralesional hemifield, as each hemisphere receives input from both ears, they do result in profound sound localization deficits confined to the contralesional hemifield (Neff et al. 1956; Thompson and Welker 1963; Neff 1968; Strominger 1969; Cranford et al. 1971; Whitfield et al. 1972; Casseday and Diamond 1977; Jenkins and Masterton 1982). While large ablations of acoustically-responsive cortex produce a deficit in the contralesional hemifield, much smaller deactivations in auditory cortex also produce contralateral impairments. Specific removal or deactivation of primary auditory cortex (AI), the posterior auditory field (PAF), or the auditory field of the anterior ectosylvian sulcus (AES) produces sound localization deficits in the
contralateral hemifield (Strominger 1969; Whitfield et al. 1972; Casseday and Diamond 1977; Jenkins and Masterton 1982; Jenkins and Merzenich 1984; Malhotra et al. 2004; 2006). However, the effects of the large lesions appear to be more profound than the smaller individual deactivations.

In the midbrain, the superior colliculus (SC) plays a key role in the accurate spatial targeting of the head and eyes to both visual and acoustic stimuli (Apter 1946; Hess et al. 1946; Sprague and Meikle 1965; Tunkl 1980; Lomber et al. 2001). The SC is a laminated structure and can be divided into superficial and deeper layers (Kanaseki and Sprague 1974), with the superficial layers receiving input almost exclusively from visual structures (Graybiel 1975; Harting and Guillery 1976; Harting et al. 1992), whereas deeper layers receive afferents from visual, auditory, and somatosensory cortices (Tortelly et al. 1980; Clemo and Stein 1984; Meredith and Clemo 1989; Harting et al. 1992). Accordingly, superficial layer neurons are exclusively visual, while deeper neurons respond to visual, acoustic, and somatosensory stimuli, and many respond to more than one modality (Stein et al. 1976; Meredith and Stein 1986; Peck 1990; Wallace et al. 1993). Visual and auditory space and the body surface are mapped across the populations of neurons and the maps are in register across modalities and layers (reviewed by Stein 1984). Visual space can be mapped in both the superficial (Feldon et al. 1970) and deep (Meredith and Stein 1990) layers of the SC, while auditory space is only mapped in the deeper layers (Middlebrooks and Knudsen 1984; Palmer and King 1982). Therefore, it was not surprising that deactivation of the SC must include both the superficial and deeper layers (SGI) in order to produce a deficit in accurate orienting to targets presented in the contralateral field (Lomber et al. 2001). In contrast, deactivation of only the superficial layers (SGS) is required to produce a deficit in orienting to visual targets presented in the contracooled field (Lomber et al. 2001).
This view for a bipartite separation of function among the superficial and deep collicular layers has been bolstered by numerous anatomical, physiological and behavioral studies (eg Casagrande et al. 1972, Casagrande and Diamond 1974; Edwards 1980; Stein and Meredith 1991, 1993; Harting et al. 1992).

Overall, as ablation of all visually- or acoustically-responsive cortex results in modality-specific deficits in the contralesional hemifield, and deactivation of the contralesional SC can reverse the visual impairment, we asked the question: Is the restoration of orienting responses into an impaired hemifield following deactivation of the superior colliculus unique to the visual system? We hypothesized that deactivation of the superior colliculus contralesional to a large ablation of auditory cortex would restore acoustic orienting responses into the impaired hemifield. To test this hypothesis we trained cats to orient to an acoustic stimulus and examined their behavior during both individual and simultaneous deactivation of: 1) acoustically-responsive cortex in one hemisphere; and 2) the contralesional superior colliculus. The auditory cortex ablations resulted in profound deficits in orienting to acoustic stimuli presented at any position in the contralesional hemifield. The additional deactivation of the superficial and intermediate layers of the contralesional SC restored acoustic orienting responses into the right hemifield. These results confirmed our hypothesis that the “Sprague Effect” is not unique to the visual system and deactivation of the contralesional SC can restore either visual or acoustic orienting responses into an impaired hemifield following cortical damage.

Place Figure 1 about here
METHODS

Overview

Three mature (>6 month old) domestic cats were obtained from a commercial laboratory animal breeding facility (Liberty Labs, Waverly, NY) and housed as a colony with unlimited access to water. Food intake was controlled and limited to the behavioral training/testing sessions and to one hour at the conclusion of each day, when the animals had unlimited access to dry cat food. All procedures were conducted in accord with the Canadian Council on Animal Care Guide to the Care and Use of Experimental Animals (1993) and National Research Council’s Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (2003) and with the approval of the Animal Care and Use Committee of the University of Western Ontario.

The three cats were trained on two detection and orienting tasks, one that employed an acoustic stimulus and one that employed a visual stimulus. Following training, each cat had a single cooling loop chronically implanted over the dorsal surface of the right SC. The animals were then tested to confirm the effectiveness of the SC loop. Then, auditory cortex of the middle and posterior ectosylvian and anterior and posterior sylvian gyri was removed from the left hemisphere (Fig. 1). Finally, performance on the acoustic localization task was then tested with or without the collicular cryoloop operational.

Apparatus

Training was conducted in an orienting arena that allowed for the presentation of either acoustic or visual stimuli. The apparatus (Fig. 2) was a semicircular arena (diameter 90cm) that consisted of thirteen pairs of miniature speakers and red, 2V (DC) light-emitting diodes (LEDs).
The speakers (part #25RF006, Mouser Electronics®, Mansfield, TX) were 2.5cm in diameter with a frequency response of 800Hz – 5kHz. The speaker/LED combinations were placed 15º apart along 180º of the azimuthal plane. The pairs were located 45cm from the animal’s start position and positioned at cat’s eye level. A food reward tray was located beneath each speaker/LED pair. The speakers emitted broad-band noise bursts (100 msec in duration) and were calibrated at 78 dB SPL. Stimuli were generated using a Tucker-Davis (Alachua, FL) stimulus presentation workstation and SigGenRP stimulus design software. The calibration was conducted with a Larson Davis (Pleasant Grove, UT) model 800B sound level meter (SLM) with a 0.5 inch microphone placed equidistant between the L90 and R90 speakers. An A-weighting was used to determine the background noise level. For the experimental stimulus, we used broad-band, white noise bursts rather than pure tones because orienting responses to short broad-band noise bursts have been identified to be much more accurate than responses to tones (Populin and Yin 1998). Testing was conducted in a sound-attenuated room lined with Sonex foam (Illbruck, Minneapolis, MN). Therefore, the normal background noise of room ventilation was present, 58 dB(A), and the broad-band, white noise burst stimulus was presented 20dB above background (78 dB). Training was conducted in a dimly lit room and ambient light levels (23 cd/m²) were monitored using an Extech® (Tampa, FL) datalogging light meter (model #401036).

Two individuals conducted the experiments: an 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 upon 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 videotaped responses were reviewed when the experimenter was unable to accurately determine the orienting response during testing. The animal handler was responsible for monitoring the animal and positioning it in the center of the apparatus and was blind to the stimulus presentation sequence. In the early stages of behavioral training it was necessary for the animal handler to securely hold the cat in position in the center of the apparatus. By the conclusion of training, the cats were merely positioned 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.

Tasks and training

Each cat was pre-trained to stand in the center of the arena and approach the illumination of the red LED at the 0º position. 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. Then, the LED was extinguished and the sound was presented at one of the 12 peripheral speakers or the central speaker. After the animal approached the stimulus it received the moist food reward from the food tray below the speakers. Any response other than a prompt direct approach to the appropriate stimulus was scored as incorrect. The cat was conditioned to approach the 0º position when an acoustic stimulus could not be identified and receive the low incentive food. Premature responses were not scored and went unrewarded. Twenty-eight trials formed a block, with each of the 12 peripheral positions tested twice and the central position tested four times. Ten blocks of trials were collected in each session for a total of 280 trials. Catch trials, where no target stimulus was presented, were randomly conducted. As a control, the
animals were also trained to orient to a visual stimulus. For the visual task, testing procedures were identical with the only difference being that the target stimulus consisted of a flashed (100msec) red 2V (DC) LED. During the final stages of training and during testing, 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 was complete when a criterion performance level of at least 80% correct across the entire field was reached on two consecutive days.

*Cryoloop implantation*

On the day of surgery, all animals received an anti-inflammatory medication (dexamethasone, 1.0 mg/kg, i.m.) and atropine (0.03 mg/kg, s.c.) to reduce respiratory and alimentary secretions. The cannulated cephalic vein permitted the administration of anesthetic and the infusion of fluids (2.5% dextrose and 1/2 strength lactated Ringer’s solution). Sodium pentobarbital (~25 mg/kg to effect) was infused (iv) to induce general anesthesia. The cat was then installed in a stereotaxic apparatus and prepared for surgery using procedures described elsewhere.

Cooling loops fashioned from 23-gauge stainless steel hypodermic tubing (Lomber et al. 1999) were shaped to conform to the dorsal surface of the superior colliculus. The collicular cryoloops were circular with an inside loop diameter of 2.5 mm. Attached to the union of each loop was a microthermocouple. Collicular cryoloops were implanted using standard procedures (Keating and Gooley 1988; Lomber and Payne 1996; Lomber et al. 1999, 2001). During the implantation it was necessary to sever the splenium of the corpus callosum to permit retraction of the cerebral hemispheres and visualization of the collicular surface lying anterior to the
tentorium. This procedure disrupted transmission of some acoustic or visual transcallosal fibers (Lomber et al. 1994). Intracranially, the insulated shafts of the cryoloops were in contact with the bony tentorium and exited the cranial vault posteriorly. The cryoloops were fixed to the skull with bone screws and dental acrylic.

Following cryoloop implantation, the dura mater was replaced and bone defects around the implanted cooling loops were repaired with bone and Gelfoam®. Dermal incisions were repaired with silk sutures that were removed approximately ten days later. During the initial period after awaking, the cats were also given buprenorphine analgesic (0.01 mg/kg, s.c.). Ambi-pen™ (G.C. Hanford Mfg. Co., Syracuse, NY) systemic antibiotic (300,000 units, i.m.) was administered every two or three days for one week to guard against possible infection. In all cases, post-surgical recovery was uneventful.

**Behavioral testing of the effects of SC deactivation**

Baseline performance levels were reestablished following cooling loop implantation and prior to any deactivations, to verify that neither the surgical procedures nor the presence of the cryoloops interfered with performance, and to ensure stationarity of motivational and performance states. During testing, the cats wore a harness and a tether that supported the cooling tubes and thermocouple wire. The cat enjoyed full freedom of movement in the arena. Cooling deactivation of the superior colliculus was effected by pumping cold methanol through the lumen of the cryoloop tubing. Cryoloop temperature was monitored continuously via a microthermocouple attached to the union of the loop. Cooling of collicular cryoloops to 2°C was sufficient to deactivate the superficial and intermediate layers of the superior colliculus (Lomber
et al. 2001). Orienting data were also collected at higher cryoloop temperatures to assess the effects of partial SC deactivation.

Testing sessions were typically carried out once a day with 10 testing blocks collected in each session. Performance was tested in the presence and absence of cooling the superior colliculus cryoloop, and a three-step testing paradigm was used: 1) Baseline data were collected prior to any cooling. 2) Testing began with cooling deactivation of the collicular cryoloop. 3) Baseline levels were reestablished after cessation of cooling and reactivation of the superior colliculus. Each of the testing steps consisted of at least two blocks of trials. Performance on blocks of trials, or groups of blocks, was compared both within and between testing sessions.

Auditory cortex ablation

Three months after implantation of the SC cooling loops and subsequent testing, auditory cortex of the left hemisphere was ablated. Each cat was prepared for surgery as described for the SC cryoloop implants. A midline incision was made in the scalp and the left temporalis muscle was detached and reflected laterally. A craniotomy was made over auditory cortex and the bone piece was stored in sterile saline. The dura mater was then incised and reflected to expose the cerebrum. The ablations of auditory cortex were made by subpial aspiration and encompassed all of the contiguous regions of acoustically-responsive cortex with the intention to remove the anterior ectosylvian gyrus, the middle ectosylvian gyrus, the anterior half of the posterior ectosylvian gyrus, and the dorsal halves of the anterior and posterior sylvian gyri (Fig. 1). The following landmarks were used as borders for the ablations: the middle suprasylvian sulcus, the crown of the posterior ectosylvian gyrus, the middle of the ectosylvian sulcus, and the ventral end of the posterior ectosylvian sulcus (Fig. 1). Saline-soaked sterile gelatin sponges were placed in
the cortical defect, and when hemostasis was achieved, the dura and stored bone piece were restored to their normal position. The temporalis muscles were sutured together, and the skin incision was repaired. The cats were then recovered using procedures described for the SC cryoloop implantations.

**Behavioral testing of the effects of auditory cortex ablation and in combination with SC deactivation**

Following the ablation of auditory cortex in the left hemisphere, the cats were tested daily for three months. After three months of post-ablation testing, daily cooling deactivation of the right SC resumed. Cooling deactivation of the right SC was conducted using the three-step testing paradigm described earlier. The majority of the orienting data was collected during cooling of the SC cryoloops to 2°C (to deactivate the superficial and intermediate layers of the superior colliculus (Lomber et al. 2001)), although orienting data were also collected at higher cryoloop temperatures to assess the effects of partial SC deactivation.

**Terminal procedures**

At completion of testing, two cats (SEA1 & SEA2) were anesthetized (sodium pentobarbital, 25-30mg/kg, i.v.) and temperatures in the superior colliculus were measured with microthermocouples during cooling of the cryoloops to 10°C and 2°C. From these measurements it was possible to map the depth from the collicular surface that contained deactivated neurons. The purpose was to identify the position of the 20°C thermocline. Twenty degrees Celsius is the critical temperature below which synaptic activity is silenced (Jasper et al. 1970; Bénita and Condé 1972; Lomber et al. 1999). Positions between the 20°C thermocline and
the cooling loop were at temperatures below 20°C and were silenced, whereas positions distal to the 20°C thermocline, relative to the cooling loop, were warmer than 20°C and partially or fully active.

Cortical temperatures during cooling were measured simultaneously at 4 different coronal levels in the brain using multiple microthermocouples (150µm in diameter) manufactured for us by Omega Engineering (Stamford, CT). The microthermocouples were first positioned, and then the loop was cooled to several temperatures. 100-120 sites were sampled at each of the coronal levels. This procedure ensured that temperature measurements for a given cryoloop temperature setting were taken at exactly the same sites in cortex. For each measurement, cortex was cooled for approximately 5 minutes prior to a recording being made, as occurred in the behavioral component of the study. This protocol was then repeated at multiple, sequentially sampled sets of sites. After completion of the mappings, the craniotomies were closed and each animal was recovered from the anesthesia.

After completion of both mappings, the cats were then anesthetized with an overdose of sodium pentobarbital (50 mg/kg, i.v.) and perfused with fixatives in accordance with the recommendations of the American Veterinary Medical Association Panel on Euthanasia (Beaver et al. 2001). The brains were fixed with 10% formalin, blocked, removed from the cranium, cryoprotected with 30% sucrose and 50µm-thick coronal sections were cut and stained for Nissl substance, myelin and cytochrome oxidase.

The third cat (SEA3) received a systemic intravenous injection of $^{14}$C-2 deoxyglucose (2DG; 100 µCi/ kg, i.v.), as described previously (Payne and Lomber 1999). One day prior to 2DG administration a venous catheter was inserted into a cephalic vein. During 2DG administration, the cat was fully conscious to maximize uptake. The cat was comfortably restrained in a
veterinary cat sack and the inlet and outlet tubes of the SC cryoloop were connected to the cooling circuit. After temperature stabilization at 2°C (~5 min), the first of four boluses of 25 µCi kg⁻¹ of 2-deoxy-D-[U-¹⁴C] glucose was administered. The remaining boluses were injected at 5 min intervals. Ten minutes following the final injection, heparin (2,000 units/kg, i.v.) and sodium nitrite (1cc of 0.1% solution, i.v.) were administered and the cat was deeply anesthetized with sodium pentobarbital (45 mg/kg, i.v.) and perfused with fixatives in accordance with the recommendations of the American Veterinary Medical Association Panel on Euthanasia (Beaver et al. 2001). The brain was quickly exposed, (~4min), removed from the skull, blocked and photographed. The brain was coated with egg albumin and placed in methylbutane (-35°C). After thirty minutes, the brain was transferred to a -80°C freezer for subsequent tissue processing.

The brain was sectioned in the coronal plane on a cryostat (-20°C) at 35µm and every fifth section was collected on coverslips. Dried sections were applied to X-ray film and processed using routine procedures (Payne and Lomber 1999). The extent of the deactivated area was then determined by delineating the region of decreased 2DG uptake. Cooling-induced decreases in 2DG uptake are obvious (Payne and Lomber 1999) and only require imaging equipment to assay the gradients on the fringes of the deactivation. For these purposes we used an MCID Elite™ imaging analysis system (Imaging Research, Inc.®, St. Catherines, Ontario, Canada). The borders of the region of decreased 2DG uptake (greater than 25% reduction) were determined by standardizing the brains with ¹⁴C standards (Amersham Corp.®, Arlington Heights, IL) and calibration curves (Gonzalez-Lima 1992) and comparing the region with the similar site from a population of normal, non-deactivated brains that were not part of this study. Every fifth section was processed histochemically for the presence of cytochrome as we have done in the past.
(Payne and Lomber 1996) and adjacent sections were stained using conventional methods for the presence of Nissl bodies or myelin.

Lesion Assessment

The location and size of the auditory cortex ablations was assessed directly by examining the defect in the gross brain both immediately following the perfusion and in photographs. In addition, microscopic assessments were made following histological processing and staining for Nissl substance or cytochrome oxidase. The auditory cortex was examined and the remaining regions of cortex were identified using architectonic criteria (Rose 1949; Sanides and Hoffman 1969; Sousa-Pinto 1973; Kelly and Wong 1981; Winer 1992; Clascá et al. 1997), and plotted onto standardized sections illustrated by Reinoso-Suárez (1961). Examples of the cortical lesions reconstructions for the three cats examined in this study are given in Figure 3. Retrograde degeneration in the thalamus was assessed microscopically and mapped using the designations of Jasper and Ajmone-Marsan (1954) and Berman and Jones (1982).

RESULTS

In the first part of the Results, we describe the auditory cortex ablations and extent of the cooling deactivations. In the second part of the Results, we describe the behavioral consequences of SC cooling deactivation and combined SC deactivation with ablations of auditory cortex in the opposite hemisphere.
Ablation reconstruction

In all three cats, the auditory cortex ablations (Fig. 3) removed virtually all the cortex that is generally recognized to be acoustically-responsive (Fig. 1). Reconstructions of the auditory cortex ablation show that the cortical tissue removed included all of the anterior ectosylvian gyrus as far rostral as coronal level A15 -16, the full extent of the middle ectosylvian gyrus, the anterior half of the posterior ectosylvian gyrus, and the dorsal halves of the anterior and posterior sylvian gyri. (Fig. 3, A-C, gray). The dorsal margin of the ablation was the middle suprasylvian sulcus, the posterior border was the crown of the posterior ectosylvian gyrus, the anterior end of the ablation was anterior to the posterior half of the anterior ectosylvian sulcus, and the ventral border of the ablation tended to be the ventral end of the posterior ectosylvian sulcus. Therefore, the ablated region included the classically-defined area AI (Reale and Imig 1980), the dorsal zone (Middlebrooks and Zook 1983), the region previously described as the suprasylvian fringe (Woolsey 1960; Paula-Barbosa et al. 1975; Niimi and Matsuoka 1979; Beneyto et al. 1998), the posterior auditory field or area P (Imig et al. 1982; Phillips and Orman 1984), the anterior auditory field or area A (Knight 1977; Reale and Imig 1980), the ventral posterior auditory field or area VP (Imig et al. 1982), the acoustically-responsive field of the anterior ectosylvian sulcus (Clarey and Irvine 1986; Meredith and Clemo 1989; Mucke et al. 1982), area AII (Woolsey 1960), the insular area, the majority of the anterior sylvian area as defined by Clascá et al. (1997, 2000), the temporal area (area Te of Clascá et al. (2000)), the ventral auditory field (VAF or V; Reale and Imig 1980), the dorsal (dPE), intermediate (iPE) and ventral (vPE) divisions of the posterior ectosylvian gyrus (EPD, EPI & EPV of Winer (1992)), and portions of area PS of Updyke (1986). With the exception of the visual field of the anterior ectosylvian sulcus (AEV), there was little or no involvement of visual or sensorimotor cortices. However, the involvement
of this field in the lesion was unlikely to have any bearing on this study because deactivation of AEV does not interfere with orienting to either visual or acoustic targets (Lomber and Payne 2004).

In the thalamus, the ablations resulted in extensive degeneration in both the ventral and dorsal divisions of the medial geniculate nucleus ipsilateral to the cortical ablation. Some degeneration was also evident in all subdivisions of the lateral posterior - pulvinar (LP-Pul) complex as defined by Raczkowski and Rosenquist (1983). These observations are consistent with similar qualitative observations made in earlier studies that performed equivalent ablations of auditory cortex (Strominger 1969; Whitfield et al. 1972; Casseday and Diamond 1977). There was little evidence of any degeneration in the A-laminae, C-complex, medial interlaminar nucleus (MIN) or geniculate wing divisions of the dLGN. Therefore, there appeared to be little or no undercutting of visual fibers passing from the dLGN to visual cortex beneath auditory cortex. This observation was behaviorally confirmed by the lack of any deficits in visual orienting behavior following the auditory cortex ablations.

Cortical structure beneath the cooling loops

Dissection and exposure of the brain revealed that the cryoloops were in contact with the dorsal surface of the right superior colliculus. We verified that neither the surgical procedures nor the presence and repeated cooling of the cryoloops disturbed the superior colliculus. In all instances, cytoarchitecture appeared normal (Kanaseki and Sprague 1974) with no signs of
damage, necrosis or gliosis. The only evidence of the presence of cooling loops was small cryoloop contact impressions on the collicular surfaces.

*Locus and extent of cooling deactivation*

Thermal readings taken from two cats (SEA1 & SEA2) revealed that cooling of the superior colliculus cryoloops to 10°C created a 20°C thermocline at a depth of about 1.2mm (Fig. 4A), which marks the boundary between the fully inactive and active zones (Lomber et al. 1999). Both the stratum griseum superficiale (SGS) and a major portion of the stratum opticum (SO) are contained between this boundary and the surface, and we infer that neurons in this region were deactivated (grey region in Fig. 4A). This inference was substantiated in the third cat (SEA3) because cooling of the SC cryoloop to 10°C reduced 2-deoxyglucose uptake throughout SGS with little impact on SGI (compare Fig. 5A to Fig. 5B). Reduction of the cryoloop temperature to 2°C ‘pushed’ the 20°C thermocline to a depth of 2.2mm, and towards the lower border of stratum griseum intermediale (SGI; Fig. 4B). Accordingly, we infer that the vast majority of neurons in SGS, SO, and SGI were silenced when the loop temperature was reduced to 2°C (grey region in Fig. 4B).

Thermal and 2DG measures show that the functional impact of the cooling was confined to the superior colliculus. There was no evidence that deactivating temperatures spread to the inferior colliculus, or its brachium.

*Place Figures 4 and 5 about here*
Acoustic orienting behavior

SUPERIOR COLLICULUS COOLING DEACTIVATION. Both before (Fig. 6A) and after (Fig. 6B) implantation of the superior colliculus cryoloop over the dorsal surface of the right SC, all three cats (Fig. 6, i-iii) were highly proficient at detecting and orienting towards the broad-band, white noise burst emitted from any of the 13 speakers positioned throughout the 180º field. The only positions showing any weakness in orienting were the left and right 90º stimulus locations where performance was slightly imperfect (Fig. 6, A and B). The similarities between the pre- and post-implant performance indicate that neither the surgical implantation of the cooling loops nor the continual presence of the loops interfered with accurate sound localization.

Unilateral cooling of the right superior collicular loop to 2±1°C virtually eliminated acoustic orienting responses into the left (contracooled) hemifield (Fig. 6C). The animals approached the default (0 deg) position when the stimulus was presented in the impaired field. This reduction in correct orienting responses was from 99% (before cooling; Fig. 6B) to <1% (after cooling; Fig. 6C). In contrast, acoustic orienting responses into the right (ipsicooled) hemifield were prompt and strong, and indistinguishable from normal (Fig. 6C). The boundary between the impaired and unimpaired hemifields was centered on the midline and was extremely sharp. Moreover, performance during the cooled phases of a testing session was the same several months after cryoloop implantation as it was after implantation. Therefore, there was no evidence for deficit attenuation over time and that any dural growth around the cooling loops was negligible. Furthermore, accurate orienting performance to every position examined returned to normal levels following the daily termination of cooling. The similarities between the warm and rewarm
performance indicate that the repeated daily cooling of the cryoloops did not impair sound localization accuracy following rewarming of the cortex. These results were consistent with SC deactivation results described in earlier studies (Lomber et al. 2001, 2002) and confirmed the effectiveness of the SC cryoloop in each cat.

We cooled the right SC to \(2\pm 1^\circ C\) because earlier studies had determined that cooling an SC loop to \(2\pm 1^\circ C\) would fully deactivate both the superficial and intermediate levels of the SC (Lomber et al. 2001). In the present study, we sought to determine the minimum level of cooling necessary to cause a complete impairment of acoustic orienting into the contralateral hemifield. In each animal, we systematically decreased the temperature of the SC cryoloop in 3°C increments. Figure 7 shows the results from this experiment. At SC cryoloop temperatures \(\geq 11^\circ C\), there was no decrease in accurate acoustic orienting responses to any positions in the contralateral hemifield (Fig. 7, A and B). However, at temperatures below \(11^\circ C\), the size of the acoustic orienting deficit in the contralateral field increased as the temperature of the SC cryoloop decreased (Fig. 7). This contralateral (left) hemifield deficit was graded from periphery-to-center in a temperature dependent way (Fig. 7, C and D). Decreasing loop temperatures never effected accurate acoustic orienting into the ipsilateral (right) hemifield (Fig. 7). The deficit was complete when the loop temperature reached \(2^\circ C\) (Fig. 7E). This result was consistent for all three cats.

SUPERIOR COLLICULUS COOLING DEACTIVATION FOLLOWING AUDITORY CORTEX ABLATION. Both before (Fig. 6A) and after (Fig. 6B) the right SC loop implantation, all three cats (Fig. 6, i-iii) were highly proficient at the acoustic orienting task. However, following the
removal of auditory cortex of the left hemisphere all three cats (Fig. 8, i-iii) failed to orient to any positions in the contralesional (right) hemifield (Fig. 8B). These large ablations of auditory cortex were without impact on the ipsilesional (left) hemifield (Fig. 8B). The cats were tested daily for three months following the auditory cortex ablation. The deficit was stable and there was no evidence of deficit attenuation.

Three months following the ablation, daily cooling deactivation of the right SC resumed. Deactivation of the right SC cryoloop to 2±1°C restored acoustic orienting responses throughout all but the peripheral-most (75° and 90°) positions in the right hemifield, contralateral to the auditory cortex ablation (Fig. 8C). Minor deficits in orienting to the most peripheral positions (75° and 90°) in the left hemifield, ipsilateral to the ablation, also appeared during cooling of the right SC (Fig. 8C). The quality of the orienting responses into the restored hemifield were rapid and direct, and appeared to be indistinguishable from orienting responses evoked during control conditions. Cessation of right SC deactivation resulted in the loss of the restored responses into the right hemifield and the three animals returned to only orienting to acoustic targets presented in the left hemifield (Fig. 8B). Therefore, the restored responses were completely reversible.

Deactivation of the right superior colliculus following the ablation of the left auditory cortex (Fig. 8C) yielded a fundamentally different result to that identified during deactivation of the right superior colliculus prior to the removal of left auditory cortex (Fig. 6C) in the same animal. Prior to the removal of auditory cortex, deactivation of the right SC resulted in a profound orienting deficit specific to the contralateral (left) field (Fig. 6C). After the removal of left auditory cortex, deactivation of the right SC did not cause an orienting deficit in the contralateral field (Fig. 8C). Instead, this deactivation nullified the deficit caused by the left auditory cortex ablation and acoustic orienting responses were restored into the right hemifield. These findings
are similar to the original results described by Sprague (1966) in the visual system where it was described how deactivation of the contralaesional superior colliculus (SC) nullifies the effects of the visual cortex ablation and restores visual orienting responses into the cortically blind hemifield. Possible mechanisms mediating this acoustical version of the “Sprague Effect” are considered in the Discussion.

The restoration of acoustic orienting responses during cooling of the SC was graded from center-to-periphery in a temperature-dependent way (Fig. 9). At higher cryoloop temperatures the restoration in orienting was only partial (Fig. 9, C-E). At the lowest temperatures, when restoration was complete, a minor deficit in the far periphery of the left hemifield could be identified (Fig. 9F). Figure 10 shows graphically the gradual restitution of acoustic orienting over a 12°C range of increased cooling deactivation of the superior colliculus. Therefore, since an SC cryoloop temperature of 2°C is required for a complete restoration of acoustic orienting responses (Fig. 9), and cooling an SC cryoloop deactivates SGS, SO, and SGI, we can now deduce that restoration of acoustic orienting responses requires the deactivation of SGS, SO, and SGI. Merely cooling an SC loop to 10°C, which deactivates only SGS and SO, is not sufficient to fully restore acoustic orienting responses.

Visual orienting behavior

Although the ablations of auditory cortex had a profound effect on acoustic orienting into the contralateral hemifield (Fig. 6B), the ablation did not have any impact on visual orienting into the same hemifield (Fig. 11), and all responses were robust. These results confirm the specificity of
the ablation on acoustic processing. These results also confirm that the motor reporting system was operational following the ablation of auditory cortical areas.

DISCUSSION

Behavioral summary

We obtained four major results from our examination of acoustic and visual orienting responses following removal of auditory cortex during cooling deactivation of the contralesional superior colliculus:

1) Unilateral cooling deactivation of the superficial and intermediate layers of the superior colliculus (SZ, SGS, SO & SGI) results in a profound deficit in orienting to acoustic stimuli presented at any position in the contralateral, but not ipsilateral, hemifield.

2) Ablation of auditory cortex results in a profound deficit in orienting to acoustic, but not visual, stimuli presented at any position in the contralateral hemifield.

3) Following the unilateral ablation of auditory cortex, the additional deactivation of the superficial and intermediate layers of the contralesional superior colliculus nullifies the consequences of the auditory cortex lesion and restores auditory orienting responses into the previously impaired hemifield to nearly normal, both qualitative and quantitative, performance levels.

4) A graded restoration was apparent during decreased cooling of the superficial and intermediate layers of the superior colliculus, and was complete when the intermediate layers were fully deactivated.
In conclusion, similar to the visual system, following auditory cortex ablation, deactivation of the contralesional superior colliculus results in a restoration of acoustic orienting responses. Therefore, the “Sprague Effect” can be identified in both visual and acoustic modalities.

**Experimental considerations**

In this study we positioned the SC cooling loops and tested their function *before* performing the ablations of auditory cortex. This procedural order consideration was critical for an accurate interpretation of the results. While we hypothesized that deactivation of the contralesional superior colliculus would reverse the orienting deficits caused by unilateral destruction of auditory cortex, we expected that three results were possible: 1) that we would confirm the hypothesis; 2) that cooling of the SC would have no impact on behavior following the auditory cortex lesions (the “null” hypothesis); or 3) that cooling the SC would have an additive effect and there would be an orienting deficit in both hemifields. Regardless of the procedural order, in both the first and third possibilities, we would know that the SC cooling loops were functioning because a discernable change in behavior would be observed. For the first possibility, the deficit would be reversed and for the third possibility the deficit would become greater, including both hemifields. However, if the auditory cortex had been ablated *before* the SC loop implantation and if the second possible result (the “null” hypothesis) was identified, it would be impossible to determine if the result was legitimate or if the cooling loop was not adequately deactivating the SC. Therefore, in this experiment it was critical for the SC loop to be implanted first, and tested to verify that it was fully functional, *before* the ablation of auditory cortex.
Contributions of the superior colliculus to orienting behaviors

The superior colliculus (SC) plays an important role in orienting of the head and eyes to visual or acoustic stimuli (Apter 1946; Hess et al. 1946; Sprague and Meikle 1965; Lomber et al. 2001). Internally, the SC can be divided into superficial, intermediate and deeper layers (Kanaseki and Sprague 1974), with the superficial layers connected almost exclusively to visual structures (Graybiel 1975; Harting and Guillery 1976; Harting et al. 1992), whereas intermediate and deeper layers receive afferents from multiple sensory cortices (visual, auditory, and somatosensory; Clemo and Stein 1984; Harting et al. 1992; Meredith and Clemo 1989; Tortelly et al. 1980) as well as brainstem sources (King et al. 1998). Accordingly, superficial layer neurons are exclusively visual, while intermediate and deep neurons respond to visual, acoustic, and somatosensory stimuli, and many respond to more than one modality (Stein et al. 1976; Meredith and Stein 1986; Peck 1990; Wallace et al. 1993). Furthermore, visual space has been identified to be mapped in both the superficial (Feldon et al. 1970) and intermediate and deep (Meredith and Stein 1990) layers of the SC, while auditory space is only mapped in the intermediate and deep layers (Middlebrooks and Knudsen 1984; Palmer and King 1982). Therefore, it was not surprising when we identified that cooling deactivation of the SC had to extend into the intermediate layers (SGI; Fig. 4B) in order to produce a deficit in orienting to targets presented in the contracooled field. In contrast, earlier studies had reported that deactivation of only the superficial layers (SGS) is required to produce a deficit in orienting to visual targets presented in the contracooled field (Lomber et al. 2001). Therefore, the results of the present behavioral study agree with the earlier behavioral and electrophysiological reports that have shown that normal functioning of the superficial layers (SGS and SO) are necessary for
proficient visual orienting and that normal functioning in the intermediate and deep layers (SGI) are necessary for accurate acoustic orienting.

Previous studies utilizing physical ablations of the superior colliculus have described ipsiversive turning of the cats following unilateral lesions (Sprague and Meikle 1965). However, this condition has generally been reported to be short-lived. The animals quickly recover from the surgery and the ipsiversive turning is greatly reduced after one-week post-op and generally absent after one month (Sprague and Meikle 1965; Sprague 1996). Using unilateral reversible deactivation of the superior colliculus we have not observed any profound ipsiversive turning of the animals during repeated daily cooling deactivation (Lomber et al. 2001, present study). In agreement with these earlier studies (Sprague and Meikle 1965; Sprague 1996) we did qualitatively observe shorter orienting latencies to the ipsicooled side and an absence of orienting contralaterally.

While the consequences of unilateral SC ablations on acoustic orienting have been well documented, only two studies have examined the consequences of bilateral SC deactivations on acoustic localization (Tunkl 1980; Lomber et al. 2001). In agreement with the present investigation, both of these studies show that unilateral collicular deactivations result in acoustic orienting deficits confined to the contralesional field (Tunkl 1980; Lomber et al. 2001). However, a bilateral ablation (Tunkl 1980) or cooling (Lomber et al. 2001) of the SC both show that these deactivations do not result in bilateral deficits. In fact, following deactivation of one SC, the additional deactivation of the contralateral SC restores acoustic orienting to the previously impaired hemifield. Overall, the only impairments are in the peripheral-most positions (left and right fields beyond 60 deg; Lomber et al. 2001). This restoration only occurs when both the superficial and intermediate layers of the SC are deactivated on both sides.
(Lomber et al. 2001). Therefore, deactivation of the contralateral superior colliculus can not only restore acoustic orienting following a cortical ablation, but it can also restore acoustic orienting following an SC deactivation. This restoration does not occur at the cortical level, as large bilateral lesions of all acoustically-responsive cortex produce bilateral deficits in carnivores and primates (Girden 1939; Neff et al. 1956; Thompson and Welker 1963; Neff 1968; Strominger 1969; Ravizza and Diamond 1974; Heffner 1978; Kavanagh and Kelly 1987; Heffner and Heffner 1990; Heffner 1997).

Contributions of auditory cortex to acoustic orienting

For behavioral tasks involving sound localization and accurate orienting to an acoustic stimulus, the effects of cortical lesions are fairly well documented. Large unilateral lesions involving primary auditory and much of the remaining acoustically-responsive cortex result in sound localization deficits confined to the contralateral hemifield. This result has been documented in cats (Neff et al. 1956; Thompson and Welker 1963; Neff 1968; Strominger 1969; Cranford et al. 1971; Whitfield et al. 1972; Casseday and Diamond 1977; Jenkins and Masterton 1982; present study), ferrets (Kavanagh and Kelly 1987), dogs (Girden 1939), and old-world monkeys (Heffner 1997). These ablations result in a large area of acoustical space in which the subject is unable to localize sounds (Jenkins and Masterton 1982), encompassing nearly all the contralateral hemifield. From our observations, it appears that the border between the impaired and unimpaired hemifields is relatively sharp. Heffner (1997) suggested that a small region, not exceeding 18 degs, along the medial aspect of the impaired hemifield was a region of reduced localization ability that was not as impaired as the more lateral aspects of the impaired hemifield.
If this “transitional” region between the unimpaired and impaired hemifields exists, then, owing to the resolution of our testing paradigm, we suggest that it must be less than 15 degs.

Although the forebrain plays a significant role in orienting to an acoustic stimulus in primates and carnivores, the forebrain does not seem to play such a significant role in lower species such as rats or barn owls, two species in which sound localization has been extensively studied. Bilateral destruction of primary auditory cortex in the rat does not result in orienting errors to acoustic stimuli (Kelly and Glazier 1978; Kelly 1980; Kelly and Kavanagh 1986). Furthermore, when these ablations are expanded to include all regions of acoustically-responsive cortex, no significant sound localization deficits can be identified (Kelly and Glazier 1978; Kelly 1980; Kelly and Kavanagh 1986). In the barn owl, lesions of the forebrain do not significantly impair accurate orienting and approach to an acoustic stimulus as long as the midbrain (optic tectum) is intact (Knudsen et al. 1993). Subsequent studies have identified that the forebrain of the barn owl is critical for accurate orienting to the remembered location of a sound source (Knudsen and Knudsen 1996) while the optic tectum appears to be critical for stimulus-guided responses to a sound source (Knudsen and Knudsen 1996).

In the cat, while large ablations of acoustically-responsive cortex produce a deficit in the contralesional hemifield, much smaller deactivations also produce contralateral impairments. Removal or deactivation of primary auditory cortex (AI), the posterior auditory field (PAF), or the auditory field of the anterior ectosylvian sulcus (AES) produces sound localization deficits in the contralateral hemifield (Strominger 1969; Whitfield et al. 1972; Casseday and Diamond 1977; Jenkins and Masterton 1982; Jenkins and Merzenich 1984; Malhotra et al. 2004). However, the effects of the large lesions appear to be more profound than the smaller individual deactivations. For example, as noted in Malhotra et al. (2004), during unilateral deactivation of
AI, PAF, or AES the animals would continue to orient into the impaired hemifield and make an incorrect choice. This contrasts with the results of the present study in which the cats failed to orient into the impaired hemifield. The animals would choose the default (0 deg) position when the stimulus was presented in the impaired field. The larger lesions seemed to produce a form of acoustic neglect (Clarke and Thiran 2004). Therefore, the reversal of the acoustic orienting deficits by deactivating the contralesional superior colliculus is even more striking.

**Task-specific deficits**

SUPERIOR COLLICULUS. In the present study we examined the conditioned ability of cats to orient and approach an acoustic target. However, it is also possible to study unconditioned responses to a sound source because cats will reflexively orient their heads to a white-noise sound burst. Unfortunately, we have been unable to identify any studies that have directly compared sound localization using head orienting versus whole-body orienting during deactivations of the superior colliculus. The only information available on reflexive head orienting was from the study of Thompson and Masterton (1978) that examined unconditioned reflexive head orienting to a white-noise burst, in one cat, following unilateral damage of the superior colliculus. Thompson and Masterton (1978) reported that a unilateral lesion of the SC did effect head orienting to visual stimuli, but did not effect head orientation to sound, except for lengthening the latency of the response to the contralesional side. The results from this study are difficult to interpret because the lesion of the SC was not complete. We have previously described that deactivation of only the superficial layers of the SC will impair orienting to visual stimuli while deactivation of the entire SC, including the intermediate and deeper layers, is required to impair orienting to acoustic targets (Lomber et al., 2001). Thompson and Masterton
(1978) reported that “a lesion of the superior colliculus that results in all the signs of dysfunction for visual orientation need not interfere with the essential elements of head orientation to sound”. While the results of Lomber et al. (2001) agree with this statement, it also establishes the likelihood that while the SC lesions of Thompson and Masterton (1978) were sufficient to reveal visual deficits, they were likely incomplete and may have been insufficient to produce acoustic deficits.

AUDITORY CORTEX. In sound localization tasks, the most common reporting mechanism has been to use orienting of the head or whole body towards the stimulus, which is often accompanied with an approach to the sound source. Consistent in these studies are the findings that unilateral deactivations of all acoustically-responsive cortex impairs sound localization within the hemifield contralateral to the deactivated cortex, and that bilateral ablation of auditory cortex impairs sound localization throughout the entire field (Neff et al. 1956; Jenkins and Masterton 1982; Kavanagh and Kelly 1987; Heffner and Heffner 1990; present study). Unfortunately, we have been unable to identify any studies that have compared sound localization using head orienting versus whole-body orienting during deactivations of auditory cortex. Beitel and Kaas (1993) examined unconditioned head orienting responses to white-noise bursts following both unilateral and bilateral ablations of auditory cortex in its entirety. Beitel and Kaas (1993) found that bilateral removal of auditory cortex severely impaired the ability of cats to accurately orient to a sound source. However, in cats with unilateral ablations of auditory cortex, there were no deficits in orienting to sounds presented in either hemifield (Beitel and Kaas 1993). This result is contrary to the results using conditioned orienting tasks that found that unilateral destruction of all acoustically-responsive cortex resulted in sound localization impairments in the contralateral, but not ipsilateral, hemifield. Therefore, while the conditioned
and unconditioned orienting deficits are consistent for bilateral ablations of auditory cortex, profound conditioned orienting deficits follow unilateral ablations of auditory cortex while no unconditioned orienting deficits follow similar unilateral ablations.

Possible mechanisms mediating the acoustic Sprague Effect

Within the visual system, studies have sought to determine if the restoration of visual orienting responses is triggered by ablation of collicular neurons that project axons through the intercollicular commissure or whether the lesion of the intercollicular commissure disrupts projections from non-collicular sources that also course through the same commissure. Wallace et al. (1989) concluded that the restoration in visual orienting was mediated by the severance of axons from non-collicular sources that course through the posterior intercollicular commissure. Subsequent experiments (Wallace et al. 1990) showed that small ibotenic acid ablations of the rostro-lateral substantia nigra pars reticulata, and possibly the overlying ventral zona incerta, consistently produced a visual recovery whereas lesions of the other collicular afferents from mesencephalic sources did not. Wallace et al. (1990) postulated that damage to the crossed nigrocollicular projection disinhibits the superior colliculus ipsilateral to the cortical lesion and the resultant excitation leads to recovery. Overall, these results show the significance of contralateral mesencephalic structures in maintaining a deficit in orienting into a visual hemifield contralateral to a large visual cortical lesion. More recent studies have shown that the substantia nigra inputs to the SC involved in striatal-nigral-collicular circuits project to the contralateral colliculus through the collicular commissure and spread through the SO before descending into the intermediate layers (McHaffie et al. 2005, 2006). Therefore, it would seem possible that cooling the superficial layers (SGS and SO) could inactivate these nigro-tectal fibers while
disrupting visual but not auditory orienting functions. Therefore, it would seem likely that the mechanisms underlying the visual and acoustic versions of the Sprague Effect may be different.

Much of the anatomical information that is available to assist in the deciphering of the circuitry underlying the Sprague Effect in the visual system does not yet exist in the auditory system. While some information on auditory cortical projections to the SC is available (Tortelly et al. 1980; Meredith and Clemo 1989), we have been unable to locate information on auditory cortical projections to the substantia nigra, striatum, or basal ganglia. Presumably, projections from these structures to the tectum are involved in mediating the recovery of acoustic orienting responses.

Past studies concerning the causes of the “Sprague Effect” have concentrated on disinhibition as the prime mechanism mediating the restoration in orienting performance. Such a view is supported by experiments that show that lesion of one superior colliculus reduces the impact of suppressive surrounds of neurons in the contralateral superior colliculus (Waleszczyk et al. 1993), and it is tempting to invoke a similar rationale to explain the results of the present study. For example, from our deactivations we could speculate that neurons deeper in the superior colliculus that receive signals from the superficial layers (Behan and Appell 1992), including those that project to the opposite side (Behan and Kime 1996a), are less active than normal. Based on electron microscopic characterization of intercollicular axon terminals as being of both the excitatory asymmetric and inhibitory symmetric types (Behan 1985), the net effect of cooling is both to depress excitation and to disinhibit target neurons in the deep layers of the contralesional superior colliculus (Behan and Kime 1996a,b), and to effect a restoration in orienting.
Overall, these observations point to the complexity of interactions between brain structures and pathways, and suggest that the acoustic orienting deficits may not arise simply by the interference with circuitry on one side of the brain. Important data suggest that imbalances in the levels of activities of structures on the two sides of the brain may also be an important factor, because structures in the normally functioning side may gain preferential control over behaviors due to diminished competition from the opposite side (Sprague, 1966; Mesulam, 1981; Kinsbourne, 1987; Rizzolatti and Berti, 1990; Vallar, 1993). In addition, an important aspect of SC interactions that may additionally contribute to the imbalanced levels of activity and to deficits in orienting are the prominent and reciprocal inhibitory pathways between the two superior colliculi (Behan, 1985). Analyses of circuits and modeling of reciprocal influences suggests that as activity is depressed in one SC, activity increases on the uncooled side because of its release from contralateral inhibition (Lomber and Payne, 1996; Hilgetag et al., 2001).

Conclusions and future directions

In the present study, we concluded that the “Sprague Effect” is not unique to a particular sensory system and deactivation of the contralesional SC can restore either visual or acoustic orienting responses into an impaired hemifield following cortical damage. The next step in these investigations will be to examine if the deficits found following individual deactivations of specific cortical regions (such as AI, PAF, or AES) that cause inaccurate orienting to acoustic targets can be reversed following deactivations of the contralesional superior colliculus. If these deficits can also be reversed then it would be possible to devise experiments involving chronic recording from the superior colliculus during both individual and combined deactivations of ipsilateral cortical and contralateral collicular sites. These examinations would provide
information on changes in neural activity in different layers of the superior colliculus following these deactivations and help in the dissection of the mechanisms and microcircuits underlying the acoustic “Sprague Effect”.

Acknowledgments

Professor Sprague past away in December of 2002, prior to the completion of this study. He was inspirational, a true gentleman of neuroscience, and he is missed. This manuscript is dedicated to our memories of him. We thank Erin Woller and Amee Hall for help with various phases of this project. This work was supported by grants from the Canadian Institutes for Health Research and National Institute for Deafness and Other Communication Disorders.
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Figure Legends

PUBLISHER’S NOTE: Please print all figures at one-column width except Figures 6 & 8. Figures 6 and 8 should be printed at full-page width.

Fig. 1. Lateral view of the left hemisphere of the cat cerebrum showing the generally recognized auditory areas. Sulci are indicated in italics (aes - anterior ectosylvian sulcus, pes - posterior ectosylvian sulcus, ss - suprasylvian sulcus). Auditory cortical areas: AI - primary auditory cortex; AII - second auditory cortex; AAF - anterior auditory field; AES - auditory field of the anterior ectosylvian sulcus; dPE - dorsal posterior ectosylvian gyrus; DZ - dorsal zone of auditory cortex; IN - insular region; iPE - intermediate posterior ectosylvian gyrus; PAF - posterior auditory field; T - temporal region; VAF - ventral auditory field; VPAF - ventral posterior auditory field; and vPE - ventral posterior ectosylvian gyrus. A – anterior; D – dorsal; P – posterior; and V – ventral. Compiled from Reale and Imig (1980), Ribaupierre (1997) and Tian and Rauschecker (1998). Gray region shows the intended ablation of the contiguous auditory areas.

Fig. 2. Acoustic and visual orienting arena. 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 (15°) intervals (for sake of clarity, only 30° intervals are labeled). A) The animal was first required to fixate on the central (0°) LED. B) It then had to orient to, and approach, an acoustic (100ms broad-band noise) or visual (100 msec LED flash) target to receive a food reward.
**Fig. 3.** Outline drawings to show the position and extent of the auditory cortex ablations in the left hemisphere (gray region) in each cat (A, Cat SEA1; B, Cat SEA2; C, Cat SEA3). Each part (A, B & C) shows a lateral view of the cat cerebrum with three coronal sections (i-iii) for each of the three cats. Outlines adapted from the drawings of Reinoso-Suárez (1961). Although the extent of the ablation varied for each cat, with (A) being the largest ablation and (C) being the smallest, the recognized auditory areas (Fig. 1) were removed in each subject.

**Fig. 4.** Temperature measurements recorded from identical sites in the superior colliculus (using the nomenclature of Kanaseki and Sprague 1974) while the cooling loop (circles) was cooled to 10°C (A) and 2°C (B). (i) Dashed line indicates the position of the 20°C thermocline estimated from these measurements. (ii) Gray region demarcates region of the SC with temperatures <20°C during cooling of the loop to 10°C (A) and 2°C (B). With cooling to 10°C, the 20°C thermocline lay at the base of SGS, whereas cooling to 2°C pushed the position of the 20°C to the base of SGI. Left is medial and scale bar = 1mm. CA - cerebral aqueduct; PAG - periaqueductal gray; SAI - stratum album intermediale; SAP - stratum album profundum; SGI - stratum griseum intermediale; SGP - stratum griseum profundum; SGS - stratum griseum superficiale; SO - stratum opticum; and SZ - stratum zonale.
**Fig. 5** Coronal 2-deoxyglucose (2DG) autoradiograms of the midbrain to show diminished 2DG uptake in the superficial layers of the superior colliculus (SC) during cooling of a cryoloop to 10°C (B). (A) 2DG uptake in the SC when the cooling loop was not operational. Compare high levels of 2DG uptake (dark) in the superficial layers of the SC (A) to low uptake levels in the cooled SC (B). Circles indicate position of the cryoloop over the dorsal surface of the SC. Scale bar = 1mm. PAG - periaqueductal gray; SGI - stratum griseum intermediale; and SGS - stratum griseum superficiale.

**Fig. 6.** Orienting responses to an acoustic stimulus from each of the three cats (i-iii). A) Control data collected prior to cryoloop implantation (Pre-Implant) and auditory cortex ablation (Pre-Lesion). B) Data collected prior to auditory cortex ablation (Pre-Lesion), but after implantation of the superior colliculus cryoloop (Post-Implant). Note that the presence of the collicular cryoloop did not alter performance. C) Data collected during cooling of the collicular cryoloop to 2°C. Note that deactivation of the right superior colliculus resulted in a complete neglect of acoustic stimuli in the left (contracooled) hemifield. Dorsal view icons of the cat brain indicate the presence or absence of an auditory cortex ablation, cryoloop implantation (stippled oval) and cryoloop operational status (black = operational). In this and subsequent data graphs, the two concentric semicircles represent 50% and 100% response levels and the length of each bold line corresponds to the percentage of responses at each location tested. For each experimental condition (A-C) and each locus tested, data from at least 100 stimulus presentations are shown.
Fig. 7. Acoustic orienting responses during cooling of the right superior colliculus cryoloop to decreasing temperatures. Right cryoloop at A) 38°C, B) 11°C, C) 8°C, D) 5°C, E) 2°C. For conventions, see Fig. 6. Note progressive reduction of auditory responses as cryoloop temperature was lowered, until orienting to the acoustic stimuli presented in the left (contracooled) hemifield was abolished. Data from Cat SEA 2. For each experimental condition (A-E) and each locus tested, data from at least 24 stimulus presentations are shown.

Fig. 8. Orienting responses to an acoustic stimulus from each of the three cats (i-iii). A) Data collected prior to auditory cortex ablation (Pre-Lesion), but after implantation of the superior colliculus cryoloop (Post-Implant). B) Data collected following the auditory cortex ablation (Post-Lesion) in the left hemisphere and after implantation of the superior colliculus cryoloop (Warm). Note that the left auditory cortex ablation eliminated acoustic orienting responses in the right hemifield. C) Data collected following the auditory cortex ablation (Post-Lesion) and during cooling deactivation of the right collicular cryoloop to 2°C (Cool). Note that deactivation of the right superior colliculus resulted in a restoration of auditory orienting responses into the right hemifield. For conventions, see Fig. 6. i-iii) show the data collected from each of the three cats. For each experimental condition (A-C) and each locus tested, data from at least 100 stimulus presentations are shown.
Fig. 9. Acoustic orienting responses during cooling of the right superior colliculus (SC) cryoloop to different temperatures in a cat with an ablation of auditory cortex in the left hemisphere. SC cryoloop at A) 38°C, B) 14°C, C) 11°C, D) 8°C, E) 5°C and F) 2°C. Data from Cat SEA2. For conventions, see Fig. 6. Note progressive restoration of auditory orienting responses as cryoloop temperature was lowered below 14°C. Restoration progressed from the midline into the periphery as cryoloop temperature decreased to 2°C. For each experimental condition (A-F) and each locus tested, data from at least 24 stimulus presentations are shown.

Fig. 10. Graph illustrating the mean percent correct responses into either the right (filled symbols and solid line) or left (open symbols and dashed line) hemifield during progressive cooling of the cryoloop in contact with the right superior colliculus (circle). Note that responses into the right hemifield begin at zero as a consequence of the auditory cortex ablation in the left hemisphere. Each symbol represents data from ten or more testing blocks. Circles, squares, and triangles represent data from Cats SEA1, SEA2, and SEA3, respectively. The results were very similar for all three animals.

Fig. 11. Visual orienting data collected from each cat following the removal of auditory cortex in the left hemisphere. Note that for each cat (i-iii), the left auditory cortex ablation eliminated acoustic orienting responses into the right hemifield (Fig. 8B) while not changing visual orienting responses into the same hemifield. For conventions, see Fig. 6.
Fig. 1. Lateral view of the left hemisphere of the cat cerebrum showing the generally recognized auditory areas. Sulci are indicated in italics (aes - anterior ectosylvian sulcus, pes - posterior ectosylvian sulcus, ss - suprasylvian sulcus). Auditory cortical areas: AI - primary auditory cortex; AII - second auditory cortex; AAF - anterior auditory field; AES - auditory field of the anterior ectosylvian sulcus; dPE - dorsal posterior ectosylvian gyrus; DZ - dorsal zone of auditory cortex; IN - insular region; iPE - intermediate posterior ectosylvian gyrus; PAF - posterior auditory field; T - temporal region; VAF - ventral auditory field; VPAF - ventral posterior auditory field; and vPE - ventral posterior ectosylvian gyrus. A anterior; D dorsal; P posterior; and V ventral. Compiled from Reale and Imig (1980), Ribaupierre (1997) and Tian and Rauschecker (1998). Gray region shows the intended ablation of the contiguous auditory areas.
Fig. 2. Acoustic and visual orienting arena. 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 (15°) intervals (for sake of clarity, only 30° intervals are labeled). A) The animal was first required to fixate on the central (0°) LED. B) It then had to orient to, and approach, an acoustic (100ms broad-band noise) or visual (100 msec LED flash) target to receive a food reward.
Fig. 3. Outline drawings to show the position and extent of the auditory cortex ablations in the left hemisphere (gray region) in each cat (A, Cat SEA1; B, Cat SEA2; C, Cat SEA3). Each part (A, B & C) shows a lateral view of the cat cerebrum with three coronal sections (i-iii) for each of the three cats. Outlines adapted from the drawings of Reinoso-Suárez (1961). Although the extent of the ablation varied for each cat, with (A) being the largest ablation and (C) being the smallest, the recognized auditory areas (Fig. 1) were removed in each subject.
Fig. 5 Coronal 2-deoxyglucose (2DG) autoradiograms of the midbrain to show diminished 2DG uptake in the superficial layers of the superior colliculus (SC) during cooling of a cryoloop to 10°C (B). (A) 2DG uptake in the SC when the cooling loop was not operational. Compare high levels of 2DG uptake (dark) in the superficial layers of the SC (A) to low uptake levels in the cooled SC (B). Circles indicate position of the cryoloop over the dorsal surface of the SC. Scale bar = 1mm. PAG - periaqueductal gray; SGI - stratum griseum intermediale; and SGS - stratum griseum superficiale.
Fig. 6. Orienting responses to an acoustic stimulus from each of the three cats (i-iii). A) Control data collected prior to cryoloop implantation (Pre-Implant) and auditory cortex ablation (Pre-Lesion). B) Data collected prior to auditory cortex ablation (Pre-Lesion), but after implantation of the superior colliculus cryoloop (Post-Implant). Note that the presence of the collicular cryoloop did not alter performance. C) Data collected during cooling of the collicular cryoloop to 2°C. Note that deactivation of the right superior colliculus resulted in a complete neglect of acoustic stimuli in the left (contracooled) hemifield. Dorsal view icons of the cat brain indicate the presence or absence of an auditory cortex ablation, cryoloop implantation (stippled oval) and cryoloop operational status (black = operational). In this and subsequent data graphs, the two concentric semicircles represent 50% and 100% response levels and the length of each bold line corresponds to the percentage of responses at each location tested. For each experimental condition (A–C) and each locus tested, data from at least 100 stimulus presentations are shown.
Fig. 7. Acoustic orienting responses during cooling of the right superior colliculus cryoloop to decreasing temperatures. Right cryoloop at A) 38°C, B) 11°C, C) 8°C, D) 5°C, E) 2°C. For conventions, see Fig. 6. Note progressive reduction of auditory responses as cryoloop temperature was lowered, until orienting to the acoustic stimuli presented in the left (contracooled) hemifield was abolished. Data from Cat SEA 2. For each experimental condition (A-E) and each locus tested, data from at least 24 stimulus presentations are shown.
Fig. 8. Orienting responses to an acoustic stimulus from each of the three cats (i-iii). A) Data collected prior to auditory cortex ablation (Pre-Lesion), but after implantation of the superior colliculus cryoloop (Post-Implant). B) Data collected following the auditory cortex ablation (Post-Lesion) in the left hemisphere and after implantation of the superior colliculus cryoloop (Warm). Note that the left auditory cortex ablation eliminated acoustic orienting responses in the right hemifield. C) Data collected following the auditory cortex ablation (Post-Lesion) and during cooling deactivation of the right collicular cryoloop to 2°C (Cool). Note that deactivation of the right superior colliculus resulted in a restoration of auditory orienting responses into the right hemifield. For conventions, see Fig. 6. i-iii) show the data collected from each of the three cats. For each experimental condition (A-C) and each locus tested, data from at least 100 stimulus presentations are shown.
Fig. 9. Acoustic orienting responses during cooling of the right superior colliculus (SC) cryoloop to different temperatures in a cat with an ablation of auditory cortex in the left hemisphere. SC cryoloop at A) 38°C, B) 14°C, C) 11°C, D) 8°C, E) 5°C and F) 2°C. Data from Cat SEA2. For conventions, see Fig. 6. Note progressive restoration of auditory orienting responses as cryoloop temperature was lowered below 14°C. Restoration progressed from the midline into the periphery as cryoloop temperature decreased to 2°C. For each experimental condition (A–F) and each locus tested, data from at least 24 stimulus presentations are shown.
Fig. 10. Graph illustrating the mean percent correct responses into either the right (filled symbols and solid line) or left (open symbols and dashed line) hemifield during progressive cooling of the cryoloop in contact with the right superior colliculus (circle). Note that responses into the right hemifield begin at zero as a consequence of the auditory cortex ablation in the left hemisphere. Each symbol represents data from ten or more testing blocks. Circles, squares, and triangles represent data from Cats SEA1, SEA2, and SEA3, respectively. The results were very similar for all three animals.
Fig. 11. Visual orienting data collected from each cat following the removal of auditory cortex in the left hemisphere. Note that for each cat (i-iii), the left auditory cortex ablation eliminated acoustic orienting responses into the right hemifield (Fig. 8B) while not changing visual orienting responses into the same hemifield. For conventions, see Fig. 6.