

THE ROLE OF THE CAT'S ANTERIOR ECTOSYLVIAN CORTEX IN  
UNISENSORY AUDITORY AND VISUAL ORIENTATION BEHAVIORS

By

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# THE ROLE OF THE CAT'S ANTERIOR ECTOSYLVIAN CORTEX IN UNISENSORY AUDITORY AND VISUAL ORIENTATION BEHAVIORS

Thesis under the direction of John McHaffie, Ph.D., Professor, Department of  
Neurobiology and Anatomy.

Behavioral studies have revealed that regions along the anterior ectosylvian sulcus (AES) of the cat cortex are critical for orientation to multisensory stimuli. However, whether AES also plays a role in orientation to unisensory auditory stimuli is not yet clear. Some studies have shown that AES deactivation does not produce unisensory (visual or auditory) orientation deficits, consistent with physiological studies in the superior colliculus. More recently, however, AES deactivation has been shown to have a significant negative impact on sound localization. It is unknown why such similar studies show such different results. We hypothesized that the differences in auditory orientation behaviors following AES deactivation may be related to differences in the spectral characteristics of the auditory stimuli used in these experiments. To test this notion, we employed an auditory orientation task using two distinct auditory test stimuli that would mimic, in part, those used previously. Thus, cats were trained to orient to both broadband (200-20,000 Hz) and low (800-5000 Hz) frequency noise pulses, and their auditory localization capabilities were evaluated following unilateral AES lesions. To determine if AES lesions also effected movements to unisensory visual stimuli, cats also were trained in a standard visual orientation task. During the first post-lesion week, AES lesioned animals failed to orient to both

broadband and low frequency auditory stimuli presented in the contralesional auditory field, except for occasional movements to stimuli in the more central target locations. Orientation in ipsilesional auditory space was unaffected. By the second post lesion week, however, orientation to broadband stimuli began to improve in a central to peripheral fashion. By the third week post-lesion, orientation to broadband stimuli was back at pre-lesion values. In contrast, the accuracy of orientation to low frequency stimuli remained substantially impaired. These same lesions had no effect on contralesional visual orientation behaviors other than a transient 1-2 day impairment.

These data reveal that lesions of the caudal AES, that presumably disrupt both its auditory and visual subdivisions, produce enduring deficits in an animal's ability to accurately orient to low frequency but not broadband noise pulses. They also show that visual orientation is unaffected by such lesions.

## INTRODUCTION

Regions in walls and fundus along the cat's anterior ectosylvian sulcus (AES) have long been known to receive inputs from various sensory modalities (Imig and Reale, 1980; Mucke et al., 1982; Reinoso-Suarez and Roda, 1985; Norita et al., 1986; Olson and Graybiel, 1987; Clarey and Irvine, 1990a, 1990b; Norita et al., 1991) and traditionally was referred to as a polysensory region. More recently, AES was subdivided into three individual unisensory subdivisions: visual (AEV) (Mucke et al., 1982; Olson and Graybiel, 1987; Benedek et al., 1988; Jiang et al., 1994), auditory (FAES) (Clarey and Irvine, 1986; Meredith and Clemo, 1989) and somatosensory (SIV) (Clemo and Stein, 1982, 1983). One of its major efferent targets of these areas is the midbrain superior colliculus (SC), where this input is thought to be important for multisensory integration. These, and other issues, are expanded upon below.

### Visual Input to AES

Anatomical evidence shows that AES receives projections from various visual sensory areas. Mucke and colleagues originally suggested that visual input to AES was derived mainly from the lateral suprasylvian (LS) cortex, which receives its principal projections from the extrageniculate thalamus (Mucke et al., 1982). This notion was supported by retrograde and anterograde tracing studies that showed that the most substantial cortical afferents to the AES arose from LS (Mucke et al., 1982; Miceli et al., 1985; Reinoso-Suarez and Roda, 1985; Norita et al., 1986; Olson and Graybiel, 1987). These studies have also revealed that

the connections between the LS and AEC are reciprocal and topographically organized. Based on their anatomical connectivity, the corresponding LS cortical area was defined by Heath and Jones (Heath and Jones, 1971a) as sitting along the middle and caudal suprasylvian sulcus. According to electrophysiological studies, this cortical region is further divided into six subregions, each of them containing a complete and independent representation of the contralateral visual hemifield (Palmer et al., 1978). Anatomically, two of these six subregions occupy the rostral one-third of the middle suprasylvian sulcus (anteromedial, AMLS; anterolateral, ALLS); two other subregions are located in the caudal two-thirds of the middle suprasylvian sulcus (posteromedial, PMLS; posterlateral PLLS) while the remaining two subregions are situated around the fundus of the caudal suprasylvian sulcus (dorsal, DLS; ventral, VLS). The cortex of the rostral third of the AES dorsal bank receives projections from the ALLS; The caudal part of the AES receives projections from the AMLS; the fundal region of anterior AES receives its projections mainly from the ALLS and the AMLS with only modest input from PLLS and PMLS; the ventral bank of the AEC receives heavy projections from PLLS and PMLS as well as from DLS and VLS (Mucke et al., 1982; Reinoso-Suarez and Roda, 1985; Olson and Graybiel, 1987).

The reciprocal fiber projections between AEC and LS are asymmetrical in terms of the cortical cells-of-origin. Thus, the projections from LS originate almost exclusively from the cell bodies in layer III (Mucke et al., 1982; Miceli et al., 1985) and terminate in a broad band centered layers V and VI of AES. In contrast, the



return pathways originate predominantly from layer V and VI of AES and terminate in layer I of LS (Miceli et al., 1985; Olson and Graybiel, 1987). In the view of transcortical connection patterns, intracortical ascending projections can be distinguished from the descending projections by the cortical layers from which they originate and terminate (Jones and Wise, 1977; Tigges et al., 1977; Jones et al., 1978; Wong-Riley, 1978; Rockland and Pandya, 1979; Tigges et al., 1981; Friedman, 1983). Ascending projections, for example, transmitting information away from primary sensory areas, arise primarily in the superficial cortical layer and terminate primarily in layer IV and the lower part of layer III. Descending projections, e.g. those conveying signals back towards the primary sensory areas, originate largely from neurons in the deep layers (layers Vb and VI) and end primarily in the superficial layer I. Thus, LS is known to receive bilateral cortico-cortical projections directly from visual areas 17, 18 and 19 (Graybiel, 1972b; Ferrer et al., 1992), and therefore is the major relay between the AES and the lower-order visual cortical areas (17, 18, 19) to which AES is not directly linked (Olson and Graybiel, 1987). Apart from receiving projections from areas 17, 18 and 19, LS area also receives projections from tecto-thalamic visual areas. A direct retino-thalamic input to LS via the medial interlaminar nucleus (MIN) of the dorsal lateral geniculate body (LGN) has also been reported (Rosenquist et al., 1974). These retino-thalamic-LS connections involve the posterior nucleus (PN), the lateral posterior (LP), the pulvinar (P), the posterior nuclear group (PO), and the lateral dorsal and ventral anterior (VA) nuclei of the thalamus (Rosenquist et al., 1974; Tong et al., 1982).

In addition to receiving input from the LS, AES also receives visual input from other cortical regions, such as the posterior suprasylvian sulcus areas (PS, including DLS, VLS, area 21 and area 20: (Mucke et al., 1982; Cavada and Reinoso-Suarez, 1983; Kuchiiwa et al., 1985; Reinoso-Suarez and Roda, 1985; Norita et al., 1991)). Area PS is known to contain neurons representing primarily the lower visual hemi-fields (Updyke, 1986) and to project principally to the posterior part of the ventral bank of the AES (Reinoso-Suarez and Roda, 1985).

Apart from receiving projections from the cortical visual areas, AES also receives visual input from some thalamic visual structures such as the lateral posteromedial nucleus (LPm) and the lateralis medialis-suprageniculate nuclei (LM-Sg). The LPm receives input from the superficial layers of the SC (Graybiel and Berson, 1980) and contains visual responsive cells (Chalupa et al., 1983). The LM-Sg, which is connected with the intermediate and deep layers of the SC (Graham, 1977; Hicks et al., 1986), also contains visually responsive neurons that are organized in a rather loose retinotopic fashion (Hicks et al., 1984). Fiber projection from the LM-Sg to the AES is organized topographically with extensive overlapping. The anterior portions of the AES receive LM-Sg projections from the ventral territory, while the posterior portions of the AES receive afferents from the dorsal part of the nucleus LM-Sg (Norita et al., 1986). AES also receives projections from ventral region of the presylvian sulcus and the lateral bank of the rhinal sulcus (Scannell et al., 1995), both of which have been shown to process visual information.

### Auditory Input to AES

Auditory afferents to the fAES arise from the insular cortex, primary auditory cortex (AI, in the middle ectosylvian gyrus), the secondary auditory cortex (AII, in the medial sylvian gyrus), and the anterior auditory fields (AAF, in the posterior portion of the anterior ectosylvian gyrus; (Clarey and Irvine, 1990b)), as well as from the auditory suprasylvian fringe cortex (in the middle suprasylvian sulcus and posterodorsal part of the posterior ectosylvian gyrus; (Heath and Jones, 1971a; Imig and Reale, 1980; Reinoso-Suarez and Roda, 1985; Norita et al., 1991)) and the fourth somatosensory area IV (SIV) (Meredith et al., 2006). Reinoso-Suarez and Roda (Reinoso-Suarez and Roda, 1985) observed that HRP injections into the fundus or dorsal bank of AES of cats resulted in retrograde labeling in the auditory suprasylvian fringe cortex (in the middle suprasylvian sulcus and posterodorsal part of the posterior ectosylvian gyrus) and in the primary auditory area in the adjacent middle ectosylvian gyrus. The ventral bank and the fundus of the AES receive abundant connections from the dorsal and the posterior parts of the suprasylvian fringe cortex (Heath and Jones, 1971a; Norita et al., 1991). The ventral bank of the AES also receives afferents from the ventral auditory area (Reinoso-Suarez and Roda, 1985). In addition, a few reciprocal projections were observed between the caudal part of AES and secondary auditory area (Imig and Reale, 1980).

Using combined single-cell recording and anterograde tracing techniques to study the pattern of cortical connections related to tonotopic maps in cat auditory

cortex, Imig and Reale (Imig and Reale, 1980) found that the caudal AES receives projections from both fields AI and AII. Little correspondence is seen, however, between the best frequencies represented in the area of the caudal bank of the AES (where the injection was made) and the best frequencies represented in the AI or AII where labeling was obtained. The best frequencies are considerably correspondence between the injection zone in the AI and the labeling in the AII, or vice versa.

It is, nevertheless, a common observation that injections of tracers in the AES result in heavy labeling in the MG, including both the dorsal principal and the magnocellular portions, especially, the caudal parts of these structures (Roda and Reinoso-Suarez, 1983; Norita et al., 1986; Niimi et al., 1987; Clarey and Irvine, 1990b; Norita et al., 1991). The dorsal principal portion is a major relay of auditory input to the auditory cortices. MG is, therefore, regarded as the most important auditory afferent to the AES.

#### Somatosensory Input to AES

Somatosensory input to AES is known to arise mostly from the primary (SI), second (SII) and third (SIII) somatic sensory cortices. By injecting HRP in the dorsal bank of the AES, Reinoso-Suarez and Roda (Reinoso-Suarez and Roda, 1985) found that retrogradely labeled neurons were most abundant in cortical areas of SI (in the posterior sigmoid gyrus and the coronal gyrus), SII (in the anterior ectosylvian gyrus) and SIII (corresponding to area 5a, in the rostral end

of the lateral gyrus and ansate sulcus). Each of these three areas contains a complete topographic somatosensory map (Dykes et al., 1980; Burton et al., 1982; Garraghty et al., 1987). The rostral third of the AES dorsal bank receives somatic input from the anterior part of SII; the rostral part of the middle third of the AES dorsal bank receives somatic input from the SI with more abundant projections from the posterior sigmoid gyrus, the adjoining area 5a and the dorsal bank of the cruciate sulcus of area 4 (Reinoso-Suarez and Roda, 1985; Avendano et al., 1988; Norita et al., 1991). The dorsal bank of the AES receives additional projections from the lateral bank of the anterior suprasylvian sulcus (Reinoso-Suarez and Roda, 1985), an area that receives somatosensory, auditory and vestibular projections (Landgren et al., 1967). Input from area 5, an association area, has been found to be important for conveying information about spatially-organized somatosensory input of different submodalities (Tanji et al., 1978; Dykes, 1983) and for integrating visuomotor behavior (Fabre and Buser, 1981).

Using anterograde and retrograde tracing techniques to study the connections between the thalamus and the somatosensory areas of the anterior ectosylvian gyrus in the cat, Burton and Kopf (Burton and Kopf, 1984) reported that injections made within the lips and the depth of the upper (dorsal) bank of the AES, heavily labeled the central and the posterior portions of the medial subdivision of the posterior nuclei (Pom) of the thalamus. Substantial labeling also was seen in the lateral (Pol) and the intermediate (Poi) divisions of the

posterior nuclear group (PO) when the injections involved the posterior part of both banks of the AES. The suprageniculate nucleus (SG) was labeled from the lower bank of the AES. Similar projections were reported by Graybiel (Graybiel, 1972a, 1973) using anterograde degeneration techniques.

### Multisensory Input

Multisensory afferents to AES are believed to arise from the orbito-insular cortex (Reinoso-Suarez and Roda, 1985; Norita et al., 1991) whose neurons are driven by both visual and auditory stimuli (Loe and Benevento, 1969). Cats with lesions of the insular cortex have problems discriminating temporal patterns and spatial sequences of different stimuli (auditory, tactile, visual: (Colavita and Weisberg, 1978, 1979)). Multisensory cortical input to AES also has been suggested to come from the perirhinal cortex, principally area 36 that receives converging projections from different modality-specific neocortical areas (Heath and Jones, 1971a). The afferents from insular and perirhinal cortex reach all parts of the AES (Reinoso-Suarez and Roda, 1985; Norita et al., 1986; Norita et al., 1991) and thus may provide AES neurons with pre-determined multimodal inputs.

In addition to the cortical projections, the AES receives multisensory input from a variety of subcortical structures, such as the posterior thalamic group (PO) and the lateralis medialis-suprageniculate nuclear complex (LM-Sg complex). All these structures are known to receive multisensory input (Poggio and

Mountcastle, 1960; Heath and Jones, 1971b). Both the PO and LM-Sg complex include a certain number of sensory thalamic nuclei, and both are major retrograde targets for AES. These thalamic structures are sites of multimodal integration (Huang and Lindsley, 1973). The posterior nuclear group of the cat's thalamus contain neurons sensitive to polysensory auditory and somatosensory stimulation (Poggio and Mountcastle, 1960) to. later, Huang and Lindsley (Huang and Lindsley, 1973) described bimodal and trimodal cells in the pulvinar-lateral posterior (Pul-LP) complex. Avanzini (Avanzini et al., 1980) confirmed the predominately visual-somesthetic convergence in this structure. The suprageniculate nucleus (SGn) is one of the three member nuclei comprising the ventrally located zone of the posterior nuclear group of the thalamus. The LM-Sg is innervated from the intermediate and deep layers of the superior colliculus (Graham, 1977; Hicks et al., 1986) where multisensory cells have frequently been found (Stein and Meredith, 1990). These areas are generally known to possess cells of multisensory properties dealing with acoustic, somatosensory, and visual input (Berkley, 1973).

The connectivity between AES and MG suggests that the MG also may relay multisensory information to AES (Roda and Reinoso-Suarez, 1983). It was found that the AES receives heavy projections from the MG. Although the MG is more relevant to auditory input, single neurons of the magnocellular division of the MG were found to respond also to somatosensory, auditory and vestibular stimulation,

as well as to nociceptive stimuli. Cross-modality interactions also has been reported (Poggio and Mountcastle, 1960).

#### AES Projections to Other Cortical Regions

Using anterograde tracing techniques, Norita (Norita et al., 1986) found that the cortical areas surrounding the posterior rhinal sulcus, the bottom region of the presylvian sulcus, the lower bank of the cruciate sulcus, and the rostral half of the lower bank of the splenial sulcus are targets of AES efferents (Norita et al., 1986). Nakai (Nakai et al., 1987) demonstrated that oculomotor areas of frontal cortex, including the medial wall of the cruciate sulcus, the fundus of the coronal sulcus, and both banks of the presylvian sulcus receive fibers from the ipsilateral ventral bank and the fundus of AES. These efferent pathways also were physiologically identified by Nakai. AES sends feed-back projections to LS and the ventral portion of area 20 (Norita et al., 1986). AES also is reciprocally connected with area 4 and 6 (the primary motor and premotor areas), respectively.

#### AES Projections to Subcortical Structures

Reciprocal connections between AES and thalamic nuclei are well organized with a dense overlap of anterograde and retrograde labeling (Norita et al., 1986; Segal and Beckstead, 1989). By injecting tritiated leucine in the anterior-dorsal bank of the AES, Stein (Stein et al., 1983) reported that dense terminal labeling was apparent in the posterior group of thalamic nuclei (PO) where thalamo-cortical afferents to the AES originate. AES also projects to the LP-pulvinar and



the LM-Sg complex (Norita et al., 1986). The rostral part of the AES connects with the ventral part of the LM-Sg complex, and the caudal AES connects with the medial part of the LPm and with more dorsal portions of the LM-Sg complex (Norita et al., 1986). The caudate nucleus, the putamen and the lateral amygdaloid nucleus also are connected reciprocally with AES (Norita et al., 1986).

AES has been defined as one of the cortical regions that projects most abundantly to the deep layers of the SC (Tortelly et al., 1980; Stein et al., 1983; Clemo and Stein, 1984; Meredith and Clemo, 1989; Segal and Beckstead, 1989). The SC is a laminated midbrain structure that is traditionally divided into superficial and deep layers (Stein and Arigbede, 1972). The superficial layers are purely visual and receive direct retinal afferents; it sends efferents to regions of the visual thalamus that project, in turn, to extraprimary visual cortex, such as LS and AES, and to the basal ganglia (Harting et al., 2001a, 2001b; McHaffie et al., 2005). By contrast, the deep layers of SC respond to a variety of sensory cue are multisensory. They receive converging visual, auditory, and somatosensory projections from many subcortical and cortical sources including AES (Edwards et al., 1979). The convergence of these sensory inputs has been studied at the single unit level (Meredith and Stein, 1983), and this multisensory population constitutes ~50-60% of sensory responsive neurons (Gordon, 1973; Meredith and Stein, 1985, 1986b). The axons of deep layer neurons form the output pathway of the SC and access the motor areas of the brain stem and spinal cord

to facilitate orientation of the head and eyes toward salient sensory stimuli (Grantyn and Grantyn, 1982; Meredith and Stein, 1985; Wallace et al., 1993). Early studies have shown that the receptive fields of multisensory neurons are in spatial registration, which allows multisensory neurons to be responsive to the same area of space across modalities (Meredith and Stein, 1986a). This characteristic suggests a possible role in the coordination of spatial information across sensory modalities (Meredith and Stein, 1986a). Moreover, the SC multisensory neurons are not just passive relays of sensory information, but they can produce different neuron responses from unisensory neurons (Meredith and Stein, 1986b). The difference is that they can integrate the multisensory information from many subcortical and cortical sources of various sensory modalities. The integration can be subdivided into two types: response enhancement and response depressions (Meredith and Stein, 1986b). In the case of response enhancements, the multisensory response is significantly greater than the best unisensory response. For example, the combining visual and auditory stimuli can evoke responses in SC deep layers multisensory neurons which are stronger than the visual and auditory stimulus presented alone and which can even exceed the sum of two modality-specific responses. In the case of response depressions the multisensory response is significantly less than the best unisensory response. In summary, the superficial layers are parts of visual information pathway, however, the deep layers are the route in which the sensory information (mainly from AES) can be transformed into motional response.

Injections of HRP into the SC produce retrogradely-labeled cells along the entire rostro-caudal extent of AES (Clemo and Stein, 1983). Labeled cells were located in both the ventral and dorsal banks of AES and were restricted almost exclusively to lamina V. A topographic organization between AES and deep SC was suggested by Segal and Beckstead (Segal and Beckstead, 1989). A component of the cortico-tectal projection originating from the rostro-dorsal part of AES is considered to be the primary descending somatosensory projection to the SC (Stein et al., 1983). The cortico-tectal projections arising from the caudal AES are referred to as auditory efferents to the SC (Meredith and Clemo, 1989). Further more, visual, auditory, and somatosensory influences from different subregions surrounding AES were reported to converge onto individual multisensory neurons in the cat's SC (Wallace et al., 1993).

In addition, intrinsic connections have been reported to exist between different subregions of AES along the full extent of the sulcus (Reinoso-Suarez and Roda, 1985). Following a small amount of HRP injected into the dorsal bank, the fundus or the ventral bank of the posterior AES, labeled cells were found throughout both banks of the greater part of AES (Clarey and Irvine, 1990b). Guldin and Mardowitsch (Guldin and Markowitsch, 1984) also demonstrated that reterogradely labeled cells are distributed along the dorsal bank following a small-dose HRP injection into the rostral of middle-ventral bank of AES.

## Sensory Representation within AES

AES has been subdivided into three sensory distributions, shown in Fig. 1.

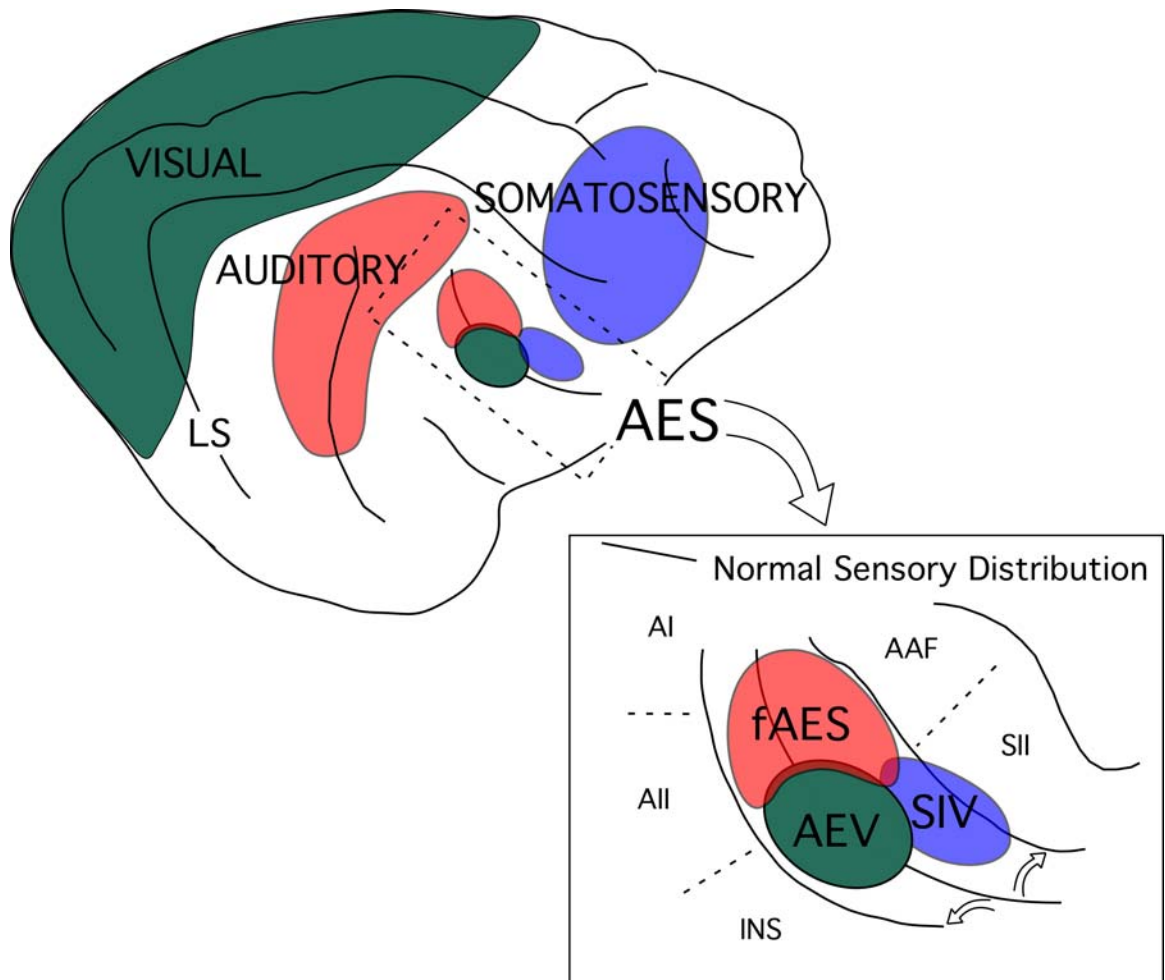
### Anterior Ectosylvian Visual Area (AEV)

Because of its high density of visually responsive neurons in the posterior two-thirds of the ventral bank of AES, this area has been referred to as the anterior ectosylvian visual area (AEV) (Mucke et al., 1982). Visual neurons in AEV have unique characteristics that distinguish AEV from other cortical visual areas. For example, the receptive fields (RFs) diameters of some AEV neurons range from 10-60° of visual space while others encompass the entire contralateral hemifield (Nagy et al., 2003a, 2003b). In addition, the receptive fields of AEV neurons are bias towards the inferior hemifield. No obvious topographic organization has been discerned in AEV. Although AEV neurons respond to binocular stimuli, they have a preference for stimuli presented to the contralateral eye. The neurons show a preference for small ( $<2^\circ$ ) rapidly moving (70-120 deg/sec) stimuli moving from central to peripheral space (Norita et al., 1986; Olson and Graybiel, 1987; Scannell et al., 1996).

### Field Anterior Ectosylvian Auditory (fAES)

Clarey and Irvine (Clarey and Irvine, 1986) reported an distinct auditory representation in the caudal aspect of AES called fAES that was adjacent to All and the anterior auditory field (AAF) but with distinct auditory response properties. The border between fAES and AAF has been determined by three characteristic

Figure 1. The location of the anterior ectosylvian sulcus (AES) is shown on a drawing of the cat cortex (upper left). Shown in the box on the lower right is the normal unisensory distributions found in the gray matter along the banks of AES: anterior ectosylvian visual area (AEV-green), anterior ectosylvian auditory field (fAES - red), and the fourth somatosensory representation (SIV - blue).



differences (Clarey and Irvine, 1986, 1990a, 1990b). First, there was a shift from responses elicited to low frequencies with a sharp tuning curve (in AAF) to responses that were broad tuned or had multiple best frequencies (in fAES). Second, there was an increase in response to noise in fAES in contrast to the preference for tones seen in AAF. Third, there also were visually responsive neurons deep within ventro-caudal aspect of the sulcus. However, the border between fAES and AII was more difficult to determine because transitions in responsiveness to noise were less obvious than those between AAF and fAES (Clarey and Irvine, 1990a; Clarey et al., 1994). Most neurons in fAES have broad and irregular tuning curves, with only a few having an obvious best frequency. Tuning curves of most fAES neurons showed multiple peaks over a range of 20-40 kHz (Clarey and Irvine, 1986, 1990a). The majority of fAES neurons showed simple onset responses to auditory stimuli. The majority of fAES neurons showed response latencies of <20 ms, with only a minority had latencies >30 ms (Clarey and Irvine, 1986). A large proportion of fAES neurons prefer binaurally presented stimuli (Clarey and Irvine, 1986; Meredith and Clemo, 1989).

#### Somatosensory Area IV (SIV)

In 1982, Clemo and Stein reported a novel somatotopic representation within the dorsal bank of AES sulcus called SIV (Clemo and Stein, 1982, 1983). The majority of somatosensory neurons in SIV were activated by low-threshold cutaneous stimuli, with only a few requiring distortion of subcutaneous tissue (Clemo and Stein, 1983). Receptive fields in SIV vary in size and are similar to

those found in dorsally adjacent SII. Some neurons are responsive to stimuli presented to a single digit whereas others response to stimuli of the entire hind limb (Clemo and Stein, 1983). In addition, detailed examination of SIV revealed that the cortico-tectal projections from SIV to SC are topographically organized with stimulation of a given cortical locus affecting only those SC cells with overlapping receptive fields (Clemo and Stein, 1983).

The three subdivisions of AES are separated by transition zones that contain multisensory neurons matching the sensory modalities of adjacent subdivisions. For example, multisensory neurons responsive to visual and auditory are found between AEV and fAES. Interestingly, these multisensory neurons do not seem to project to the SC (Wallace et al., 1992; Wallace et al., 2006).

These three unisensory AES subdivisions are not static entities but are subject to neuroplastic alterations. Rauschecker showed that AES subdivisions can change their sensory modality specificity as a result of selective early experience. For example, visual deprivation during early postnatal periods can lead to a profound reorganization whereby AEV neurons, normally responsive to visual stimuli, become dominated by auditory inputs (Rauschecker and Korte, 1993; Rauschecker, 1995, 1996) . This colonization and capture of AEV by the neighboring auditory representation (fAES) has striking functional consequences: auditory localization capabilities of these animals are markedly enhanced (Rauschecker and Kniepert, 1994), reflecting the enhanced auditory tuning of



neurons in the colonized region (Korte and Rauschecker, 1993). Accompanying these changes is a marked increase in the incidence and distribution of AES multisensory neurons, reflecting a broader region in which neurons that retain visual responsiveness now share auditory information. Presumably, the decrement in unisensory visual neurons and the increment in visual-auditory neurons reflect an increase in auditory information in the remaining pool of visually-responsive neurons.

#### The Role of AES in Subcortical Processing and Behavior

A region of associational cortex along the anterior ectosylvian sulcus (AES) of the cat is intimately associated with the deep layers of the midbrain superior colliculus (SC). This region contains three individual unisensory subdivisions: visual (AEV) (Mucke et al., 1982; Olson and Graybiel, 1987; Benedek et al., 1988; Jiang et al., 1994), auditory (FAES) (Clarey and Irvine, 1986; Meredith and Clemo, 1989) and somatosensory (SIV) (Clemo and Stein, 1982, 1983). Each unisensory subdivision sends projections to the SC (Stein et al., 1983; Norita et al., 1986; McHaffie et al., 1988; Meredith and Clemo, 1989; Fuentes-Santamaria et al., 2008; Fuentes et al., 2009 in press) where they contact SC output neurons (Fuentes et al 2009 in press) that mediate orientation behaviors via descending projections to brainstem regions involved in the control of head and eye movements (Meredith and Stein, 1985; Sparks, 1986; May, 2006). The ability of neurons in the cat SC to integrate multisensory stimuli is dependent upon cortical influences from AES (Wilkinson et al., 1996; Jiang et al., 2001; Jiang et al., 2002).

Jiang have shown that when AES is functionally deactivated, the characteristic multisensory responses of SC neurons are eliminated, rendering the responses of these neurons no different than those evoked by one of these stimuli presented individually (Jiang et al., 2001). Taken together, this data indicate that the cortical projection from AES has a specific influence on the way in which SC is able to integrate information from different sensory cues to effect multisensory orientation behaviors.

Behavioral approaches have revealed that AES deactivation has a significant influence on the animal's ability to orient to multisensory stimuli. Both thermal (cooling coils) and pharmacological (lidocaine injections) deactivation techniques have been used to reversibly deactivate AES (Wilkinson et al., 1996; Jiang et al., 2002). In these studies, animals first were trained to orient and approach a visual or auditory stimulus. The effectiveness of the stimulus then was degraded until the probability of the animal producing a correct orientation response to the stimulus was reduced to 45%. The concurrent presentation of a stimulus of a second modality facilitated orientation behavior. This behavioral facilitation parallels the enhanced neural responses found in the SC (Jiang et al., 2001). Deactivation of AES resulted in a loss of this behavioral facilitation. These behavioral changes parallel the loss of multisensory integration in individual SC neurons when AES is deactivated (Jiang et al., 2001).

### Does AES Mediate Orientation to Unisensory Auditory Stimuli?

Although previous evidence has shown that AES renders animals capable of multisensory orientation (Jiang et al., 2001; Jiang et al., 2002), whether AES plays a role in orientation to auditory stimuli is still not clear. Stein and colleagues (Jiang et al., 2002) and Lomber and colleagues (Malhotra and Lomber, 2007) trained cats to orient and approach stimuli while reversibly deactivating AES in an attempt to determine its role in these behaviors. While they used similar methods, these two groups reported conflicting results. For example, Jiang et al. showed that there were no unisensory behavioral orientation deficits to either visual or auditory stimuli after reversible thermal deactivation of AES (Jiang et al., 2002). In this study, animals were trained to orient and approach both visual and auditory stimuli. After reversible deactivation of AES, orientation to unisensory stimuli (visual target alone or auditory target alone) was unaffected, suggesting that AES is not involved in orientation to unisensory stimuli. These findings are similar to prior studies by Wilkinson who used a similar behavior paradigm but deactivated AES pharmacologically with lidocaine injections (Wilkinson et al., 1996). Thus, while AES is important for orientation to multisensory stimuli, deactivation of AES has no effect on orientation to unisensory visual or auditory stimuli.

More recently, however, Lomber and colleagues demonstrated that AES deactivation had a significant negative impact on sound localization following cryogenic cooling of the caudal aspect of AES (Malhotra and Lomber, 2007). In

this case, a deficit in turning toward and approaching auditory stimuli was observed for stimuli in the auditory field contralateral to the deactivated AES. Thus, in contrast with the conclusions of Stein and colleagues, these data indicate that AES may be important for orientation to unisensory auditory stimuli.

#### What Experimental Variables May Contribute to These Differing Results?

In principle, a variety of factors, including the method for AES deactivation or differences in the behavioral task itself, could potentially contribute to the differing results described by Stein et al. (Jiang et al., 2002) and Lomber (Malhotra and Lomber, 2007) and their respective conclusions that AES does, or does not, play a role in auditory localization. While early experiments by Stein and colleagues used pharmacological deactivation by lidocaine injections (Wilkinson et al., 1996), subsequent experiments relied on thermal deactivation of AES (Jiang et al., 2002), a technique identical to that employed by Lomber and colleagues (Malhotra and Lomber, 2007). Furthermore, minor differences in task requirements and testing procedures might also contribute, as they do in visual orientation experiments (Hardy and Stein, 1988; Lomber and Payne, 2004).

However, important clues as to the potential cause of these conflicting data may come from consideration of the nature of the auditory stimuli used by these two groups. While Stein and colleagues (Jiang et al., 2002) and Lomber and colleagues (Malhotra and Lomber, 2007) both indicated that broadband white noise pulse were generated with similar intensities (Stein's group: 15 dB SPL

above background; Lomber's group: 20 dB SPL above background), only Stein and colleagues reported the actual spectral characteristics of computer generated auditory signal (800-20,000 Hz). However, a critical feature in auditory studies is the frequency response of the specific speakers used to deliver the computer generated broadband noise pulses. While the reports from Stein and colleagues do not specify the particular speakers used or their response characteristics, Lomber and colleagues used speakers with a frequency response of 800-5000 Hz. This suggests that the high frequency components of their broadband noise pulses would have been severely attenuated by the poor frequency response of such speakers. Given that cats have different sound localization capabilities at different frequency and bandwidth of orientation stimuli (Huang and May, 1996), this factor alone may account for the auditory orientation deficits observed by Lomber and colleagues following deactivation of AES.

### A Hypothesis

These factors led us to speculate that the differences in auditory orientation behaviors following AES deactivation is related to differences in the spectral characteristics of the auditory stimuli used by these two groups. To test this notion, we employed a similar auditory orientation task using two distinct auditory test stimuli that would mimic, in part, those used previously by these two groups. Thus, cats were trained to orient to both broadband (200-20,000 Hz) and low (800-5000 Hz) frequency noise pulses, and their auditory localization capabilities were evaluated following manipulations of AES cortex. Because we also were

interested in determining if AES lesions have any effect on visual orientation behaviors (see Discussion), we chose to make permanent lesions of AES rather than use reversible deactivation techniques. We hypothesize that animals would have a persistent contralesional auditory orientation deficit when tested with low frequency, but not broadband, noise pulses. In contrast, visual orientation behaviors would remain intact, consistent with previous observations (Wilkinson et al., 1996; Jiang et al., 2002; Malhotra and Lomber, 2007).

## MATERIALS AND METHODS

Three mature domestic male cats, obtained from a USDA-licensed commercial animal breeding facility (Liberty Labs, Waverly, NY), were used in the present study. All experimental procedures were performed in compliance with the National Institutes of Health "Guide for the Care and Use of Laboratory Animals" (NIH Publications No. 80- 23, revised 1996) and approved by the Institutional Animal Care and Use Committee at Wake Forest University School of Medicine. All efforts were made to minimize the number of animals used and to alleviate any discomfort through the use of appropriate anesthetics and analgesics (see below).

### Auditory Orientation Testing Procedures

Auditory orientation was evaluated using procedures similar to those described previously (Jiang et al. 2002; Lomber et al. 2007). Testing was conducted in a matte black semi-circular perimetry arena, 116 cm in diameter and bounded by 60 cm high walls. This arena was subdivided into 15 sectors by intersecting guidelines, extending from 105° left to 105° right. Speakers were mounted in the wall at each 15° interval. The speakers (Kobitone part #25CE500-RO; Mouser Electronics, Mansfield, TX) were 3.8 cm in diameter with a frequency response ranging from 20 Hz to 20 KHz. The speakers were located 58 cm from the animal's start position and vertically positioned at 27.5 cm to approximate the cat's pinna height. The speakers emitted noise bursts of 100ms in duration. Stimuli were computer generated using custom designed software

that could generate both broadband white noise (200-20,000 Hz) and low frequency (800-5000 Hz) noise. Acoustic calibration was conducted with a Model 1800 sound level meter (SLM) of Quest Technologies (Model 1800, Quest Technologies, Oconomowoc, WI) with a microphone placed equidistant between the left 90° and right 90° speakers. Before any training or testing, the mean ambient noise intensity was determined (~50 dB), and auditory test stimuli were presented 20 dB above this background. All testing was conducted in a dimly lit room. A schematic drawing of the auditory arena is shown in Figure 2.

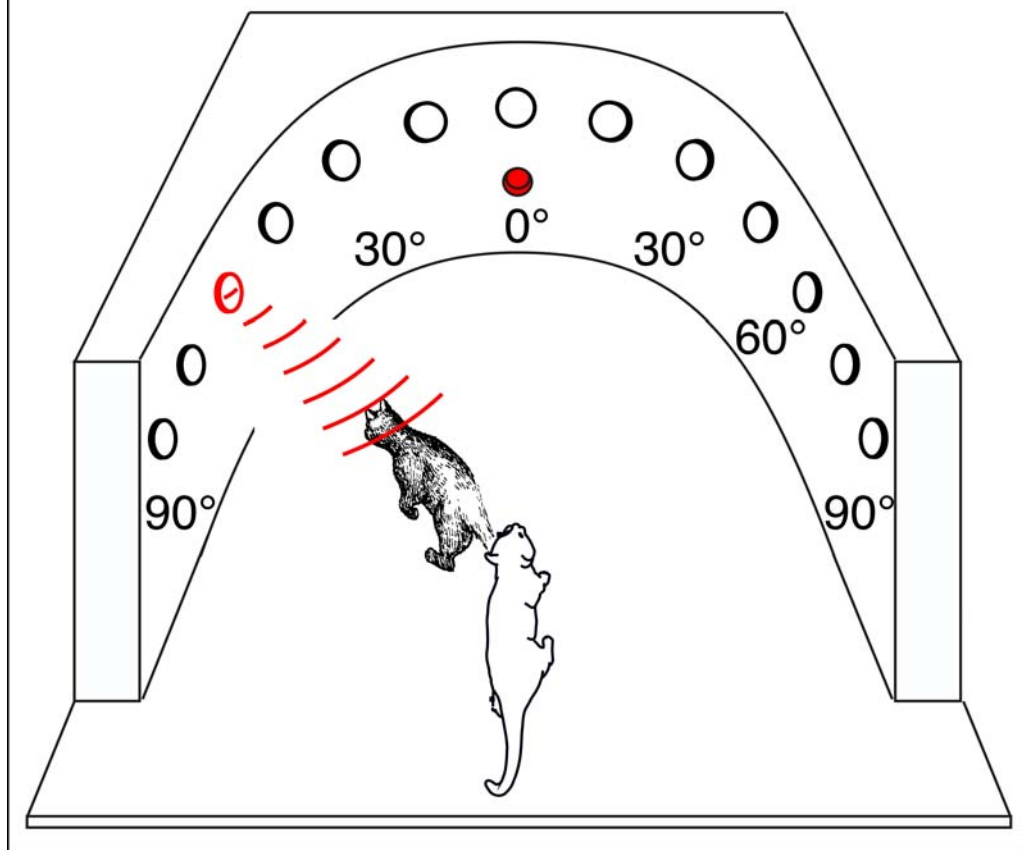
Two individuals conducted the experiments: an experimenter and the observer. The experimenter, standing behind the auditory arena, maintained the animal's position in the center of the apparatus, controlled the stimulus delivery, and recorded the behavioral responses. The observer, positioned in front of the apparatus, was responsible for helping to monitor the behavioral responses and for determining the accuracy of the orienting response, as well as manually delivering the food reward.

Food-deprived cats were gently restrained by the experimenter so that the eyes and heads were directed ahead. Animals were trained to fixate on a red LED located at the 0° mark, 58 cm from the animal's nose. A trial began when the experimenter pressed a foot control pedal. At that point, the LED was extinguished, and an auditory stimulus (either broadband noise or 800-5000 Hz low frequency noise) was delivered to one of the 15 speakers. Stimulus location



Figure 2. For auditory orientation testing, cats were trained to fixate directly ahead at a red LED and were rewarded for approaching the source of an auditory stimulus delivered via a wall-mounted speaker. If no stimulus was presented (or detected), they moved straight ahead to receive a food reward at the 0° position. Auditory stimuli were computer generated and consisted of broadband white noise (200-20,000 Hz) or low-frequency noise (800-5000 Hz) pulses, 100 ms duration. Auditory stimuli intensity was approximately 70 dB, 20 dB higher than mean ambient background noise intensity. The location of the test stimuli was randomly determined by custom designed software at one of 15 target locations of eccentricity from 105° left to 105° right in 15° increments. Food rewards were delivered at the location of stimulus delivery. After normative data (100 stimulus presentations/eccentricity) were gathered, AES was removed unilaterally. Following recovery, animals were re-tested for auditory orientation behaviors.

## AUDITORY ORIENTATION TESTING



was randomly assigned to one of the 15 speakers throughout the field, extending from 105° left to 105° right. The cat then was immediately released from restraint and moved toward the activated speaker to obtain a food reward. In some instances, no auditory stimulus was presented (catch trials). The catch trials required the cat to move directly ahead to the fixation point to receive a food reward if no sound was presented (or detected). Any response other than a prompt direct approach to the appropriate stimulus was scored as an incorrect. Premature responses were not scored and went unrewarded. Both correct and 'wrong' movements were recorded.

During the final stages of training and during testing, behavioral procedures remained the same. For each speaker target, four trials at each stimuli eccentricity were collected daily. Testing typically was conducted for five weeks before and after surgical removal of AES. Thus, pre and post-lesion testing consisted of more than 100 trials for each speaker location. If normative testing revealed that a particular cat had a tendency toward better performance in one hemifield (generally reflected as greater accuracy in the periphery of that field), the AES contralateral to that hemifield was selected to be removed. Following cortical extirpation and surgical recovery, the presence, duration, and magnitude of any spontaneous circling and/or head deviation was noted (see Neurological testing, below). Once any post-surgical motor asymmetries had resolved, animals were retested on the auditory orientation task.

Prior to each session, cats were food-restricted for 24 hours to facilitate training but had free access to water at all times. For their performance, cats received 40 gms of food each day in the auditory perimetry arena and, following each session, were allowed to feed to satisfaction in the arena. Body weight was monitored daily and recorded. Food consumption was such that no excessive weight loss occurred (>20% of initial weight).

After collecting a minimum of 100 normative tests at each eccentricity, an animal was prepared for unilateral AES ablation. If normative testing revealed a particular cat had a tendency toward better performance in one hemifield (generally reflected as greater auditory orientation accuracy in one hemifield), the AES subserving that hemifield (i.e., contralateral) was selected for removal. Following AES extirpation and surgical recovery, the presence, duration, and magnitude of any spontaneous circling and/or head deviation was noted (see Neurological testing, below). Once any post-surgical motor asymmetries had resolved, animals were retested on the auditory orientation task.

### Visual Orientation Testing Procedures

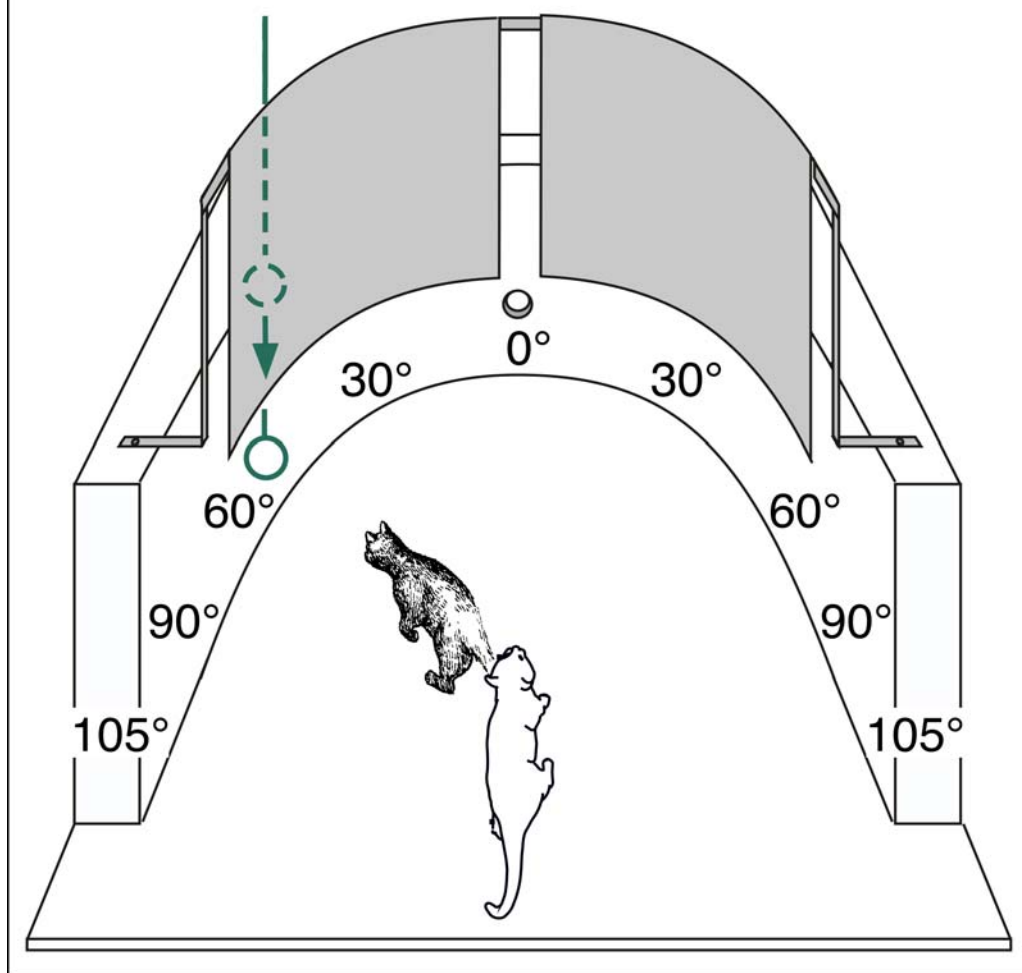
Visual orientation was evaluated using previously applied methods (Hardy and Stein, 1988). A matte black semi-circular perimetry arena, 116 cm in diameter and bounded by 60 cm high walls, was marked off into 15° sectors by intersecting guidelines, extending from 105° left to 105° right. Visual test stimuli (a white ping-pong ball on the end of a wand) were delivered manually, emerging

from behind a black curtain suspended parallel to the arena walls. This arrangement minimized extraneous visual cues associated with stimulus delivery and eliminated anticipatory movements. The apparatus was housed in a standard laboratory environment with normal ambient light and sound levels (50 dB, SPL). A schematic drawing of the visual perimetry arena is shown in Figure 3.

A food-restricted cat was gently restrained by an animal handler so that its head and eyes were directed to the 0° fixation mark, 58 cm away. The handler was blind to the location of test stimuli in order to preclude him from inadvertently providing the animal with target-related cues. Each animal was trained to fixate directly ahead at a food reward (commercial solid cat food) held with forceps by the experimenter and protruding through a hole in the forward wall of the apparatus. This experimenter was behind that wall holding the forceps and would tap the forceps on the side of the hole to initiate fixation when necessary. This experimenter also monitored the animals' eye position to verify fixation. A trial began when the experimenter determined that the animal was fixating and gave the verbal command "Go". At that time, the animal was released and could move toward to receive the food reward. On select trials, the visual test stimuli emerged from behind the curtain coincident with the Go command. If the animal oriented briskly toward the test stimulus, it received a food reward at that position. If the animal failed to orient to the test stimuli, or if no test stimuli were delivered (i.e., "catch" trials), it could move ahead to receive a food reward at the

Figure 3. For visual orientation testing, cats were trained to fixate directly ahead and were rewarded for approaching a visual stimulus (ping-pong ball on a wand) delivered from behind a curtain. If no stimulus was presented (or detected), they moved straight ahead to receive a food reward at the 0° position. Stimuli were introduced pseudo-randomly at one of 14 target positions of eccentricity from 105° left to 105° right in 15° increments. Food rewards were delivered at the location of stimulus delivery. After normative data (100 stimulus presentations/eccentricity) were gathered, AES was removed unilaterally. Following recovery, animals were re-tested for visual orientation behaviors.

## VISUAL ORIENTATION TESTING



0° fixation mark. These quasi- randomly presented catch trials effectively minimized "scanning" or spontaneous orientations (Wallace et al, 1989). Thus, the cat was rewarded regardless of its response and made few spontaneous responses. Test stimulus locations were assigned quasi-randomly at each of 15 eccentricities along the horizontal meridian throughout the field. Typically, orientation to stimuli at each eccentricity was delivered 4 times during a daily testing session. After a variable period of training, intact cats responded to stimulus delivery on nearly every trial, albeit with lowered accuracy at peripheral locations. Criterion performance was 95% correct responses, averaged throughout the field.

Prior to each daily testing session, cats were food restricted for 24 hrs but had free access to water at all times. As a reward during training and testing, cats received 40 g of high caloric value food (Science Diet Kitten Original, Hill's Pet Nutrition, Topeka, KS) in the orientation arena and, following each session, were allowed to feed on the remainder of their daily ration while in the testing area. Body weight was monitored daily during the week, with no excessive weight loss noted. No testing was conducted on weekends, when the cats were permitted to feed ad lib on a daily ration of standard animal chow.

After collecting a minimum of 100 normative tests at each eccentricity, an animal was prepared for unilateral AES ablation. If normative testing revealed a particular cat had a tendency toward better performance in one hemifield



(generally reflected as greater accuracy in the periphery of that field), the AES subserving that hemifield (i.e., contralateral) was selected for removal. Following AES extirpation and surgical recovery, the presence, duration, and magnitude of any spontaneous circling and/or head deviation was noted (see Post-operative Neurological Testing, below). Once any post-surgical motor asymmetries had resolved, animals were retested on the visual orientation task.

### Surgical Procedures

All surgery was conducted aseptically. Animals were food-deprived for 24 hrs prior to surgery and administered a corticosteroidal anti-inflammatory (dexamethasone; 1 mg/kg, im) preoperatively to minimize cerebral edema. Sedation was induced with pentobarbital (22-30 mg/kg, i.p. or i.v.), and a pre-operative dose of an analgesic (butorphanol, 0.1-0.4 mg/kg, im) was given. An endotracheal tube was inserted, and a surgical plane of anesthesia was induced with isoflurane (1-4%). Core body temperature, expiratory CO<sub>2</sub>, blood pressure, and heart rate were continuously monitored (VSM7, VetSpecs, Canton, GA) and maintained within normal physiological bounds. Animals were placed in a stereotaxic head-holder, wrapped in a heating pad, and the saphenous vein was catheterized. A lateral incision was made in the scalp and a part of temporalis muscles were removed. A craniectomy exposed the cortical areas to be removed. The dura was reflected, and the cortical blood vessels were heat-coagulated to minimize bleeding. The gray matter along the caudal two-thirds of the anterior ectosylvian sulcus then was extirpated by subpial aspiration. Moist

gelfoam was placed within the aspiration defect, the cranial bone plate was replaced, and the scalp closed with sutures. An antiseptic agent was applied topically around the sutured wound margin. Physiological saline (50-200 ml, sq or iv) was given to compensate for fluid loss. The animal then was removed from the stereotaxic frame and placed in a darkened recovery cage. Observations were made every 30 min for the duration of the recovery period, which lasted 4-6 hrs. During this time, the animals' posture was adjusted, and appropriate notations, including all measured physiological variables, were entered into the animals' surgical charts. Once alert and ambulatory, they were given a prophylactic dose of analgesic (butorphanol tartrate; 0.1-0.4 mg/kg, im) and antibiotic (cefazolin, 20 mg/kg, im) and returned to the home cage. Analgesics were continued for 18-24 hrs, or until no longer deemed necessary. Dexamethasone was administered, in progressively lower doses, for 2 days, bid.

#### Post-Operative Neurological Testing

Post operative neurological testing was performed daily for seven consecutive days after surgery and at less frequent intervals thereafter. The following visuomotor capacities were qualitatively assessed: open field visual following, visual placing, blink-to- threat, ability to localize stationary stimuli, eye movements, pupillary symmetry and responsiveness, and open field visually guided behavior (jumping to floor, etc). The following auditory capacities were qualitatively assessed: startle response, accuracy to auditory localization. In

addition, any spontaneous motor behavior was observed for postural asymmetries, circling, ataxia, etc.

#### Histological Evaluation of Cortical Lesions

After all data were collected, animals were sedated with ketamine (20 mg/kg, im) and, following the loss of pinna reflexes, injected with lethal doses of pentobarbital (100 mg/kg; ip). They then were exsanguinated by transcardial perfusion with 0.9% saline followed by an aldehyde fixative. Brains were removed and photographed.

The nomenclature used to define AES subdivisions and SC lamination was in accordance with previous studies. Briefly, AES is located at the juncture of the frontal, parietal and temporal regions of the cortex. The somatosensory subregion, SIV, is located in the anterior dorsal bank (Clemo and Stein, 1983) while the anterior ectosylvian auditory field (FAES) (Clarey and Irvine, 1986; Meredith and Clemo, 1989) and the anterior ectosylvian area (AEV) (Mucke et al., 1982; Olson and Graybiel, 1987) are located in the anterior dorsal and posterior ventral banks.

#### Data Analysis

On each day, a performance profile was collected. This consisted of percent correct and incorrect responses for each stimulus condition, perimetric position, AES treatment condition (before or after removal AES). For auditory and visual

orientation testing, stimuli were presented four times at each target position, and all the orienting responses of the animals were noted including the correct and incorrect responses. Once we had collected at least 100 responses to stimuli at each target position, which took approximately five weeks, all the data were entered into a computer. The accuracy percentage of orienting responses was calculated and plotted using the Excel and Canvas software. Accuracy percentage = incidence of correct response to one target / all trials for that target. In addition, during auditory test, the incorrect response percentage also was calculated.

## RESULTS

After a training period, all three animals were able to orient to both broadband white noise (200-20,000 Hz) pulses and low-frequency noise (800-5000 Hz) pulses delivered from each of the 15 speakers positioned from 105° left to 105° right in auditory space. For each trial, the accuracy of each orientation response was determined by noting the cats' final head and body position with respect to the activated speaker location. Following normative data collection, all three animals received lesions targeting AES, and daily post-operative neurological examinations were made following post-surgical recovery.

### Post-Operative Neurological Testing

All cats displayed similar post-operative neurological signs and had similar time courses for recovery of transient lesioned-induced deficits. The pupils of both eyes were approximately symmetrical and exhibited a normal consensual pupillary light reflex. Immediately following recovery from anesthesia, lesioned animals displayed a tendency to turn their heads and veer towards the ipsilesional side when walking although no obvious ipsilesional circling or ataxia was observed. None were responsive to stationary visual objects in the contralesional hemifield, and all were unable to following visual stimuli moving into the contralesional hemifield. All appeared to have decreased mobility of the contralateral pinna and decreased auditory start response of contralateral auditory space. All of the gross motor deficits noted gradually resolved over the

ensuing 1-2 post-operative days at which point auditory and visual orientation testing was resumed.

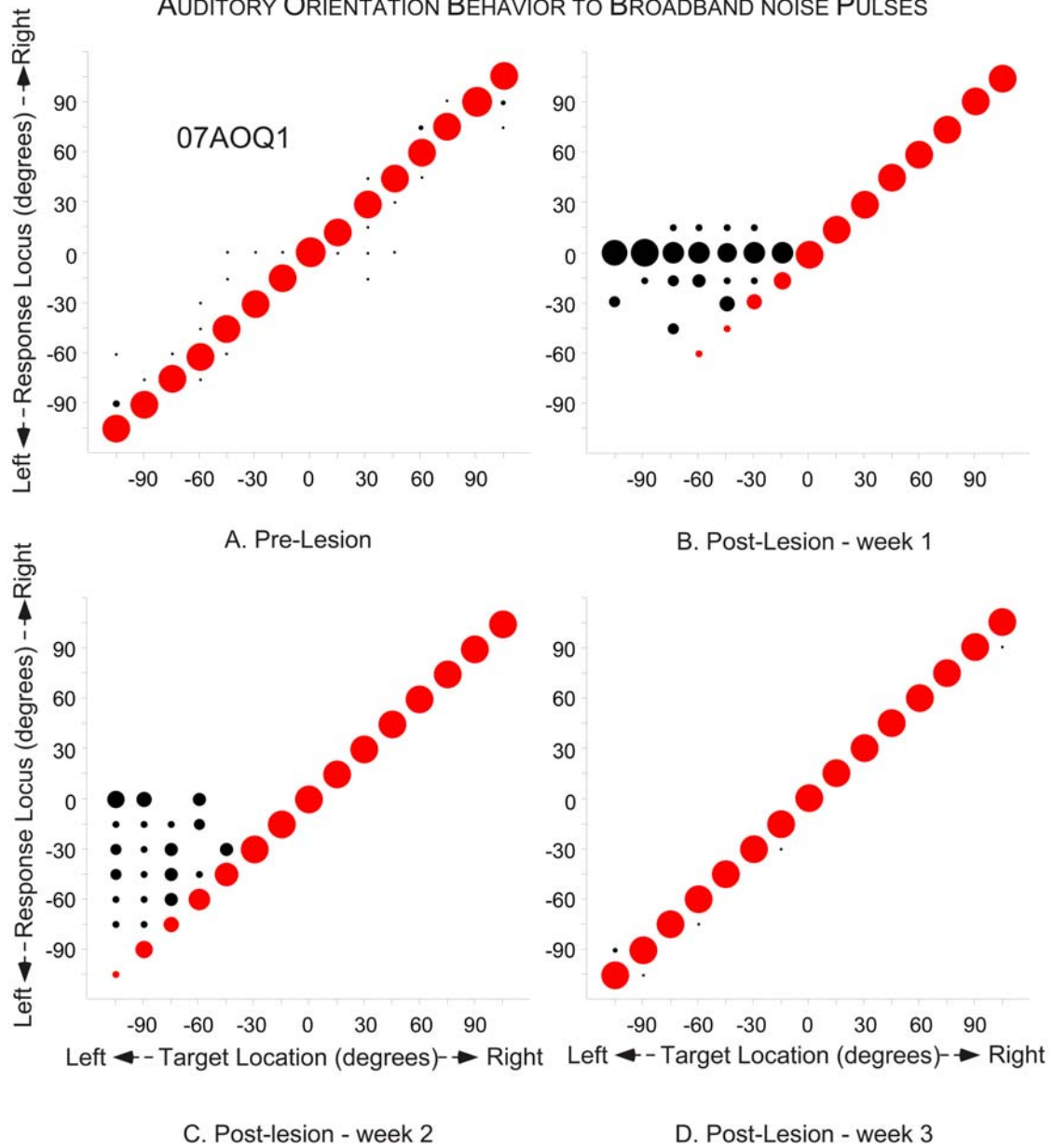
#### Auditory Orientation Behaviors to Broadband White Noise (200-20,000 Hz)

##### Pulses

The auditory orienting behavior of cat 07AOQ1 to broadband white noise (200-20,000 Hz) pulses is shown in Figure 4. Prior to lesioning, cat 07AOQ1 was able to orient to broadband white noise pulses at both left and right auditory space with a high degree of accuracy (Fig. 4A). The orienting accuracy to each speaker location at left auditory space was between 97% and 99%, except for the most peripheral speaker location ( $105^\circ$ ) which was 92%. The orienting accuracy to each speaker location in right auditory space was between 96% and 100%. Following cortical lesions and surgical recovery, auditory orientation testing was resumed once the transient motor deficits had resolved. During the first week post-lesion, orientation to broadband white noise pulses was significantly impaired to targets at the contralateral auditory space (Fig. 4B). Cat 07AOQ1 failed to orient to the target locations in contralateral auditory space and instead moved to the central target location ( $0^\circ$ ), especially when the targets were at more peripherally located targets (i.e., from  $30^\circ$  to  $105^\circ$  left). By contrast, orientation to broadband stimuli in ipsilateral auditory space was unimpaired and even was somewhat more accurate. The accuracy pre-lesion was between 96% and 100% and the accuracy post-AES lesion was 100% (Fig. 4B). During the second week post-lesion, orientation to broadband stimuli in contralateral

Figure 4. Pre- and post-operative behavioral data for cat 06AOQ1 in the auditory orientation task with broadband white noise (200-20,000 Hz) pulses. Target location is indicated on the x-axis (negative values indicate left hemifield); orienting response is indicated on the y-axis. Red circle at each location indicates the percentage of correct responses. Black circle at each location indicates the location of incorrect responses. The size of each circle is proportional to the percentage. A. Pre-operative data demonstrated normal auditory orienting behaviors at both auditory space (top left); B. By the first week post lesion, cat 07AOQ1 failed to orient to the target locations at contralateral auditory space and instead moved to the central target location ( $0^\circ$ ), especially when the targets were at more peripherally located targets (i.e., from  $30^\circ$  to  $105^\circ$  left). However, the ipsilesional orienting behavior was not impaired (top right); C. By the second week post lesion, although auditory orienting behavior at the contralateral auditory space was better than the first week post-AES lesion, it was still worse than normal behavior (bottom left); D. By the third week post lesion, the cat showed no impairment in contralateral auditory orientation capabilities (bottom right).

# AUDITORY ORIENTATION BEHAVIOR TO BROADBAND NOISE PULSES



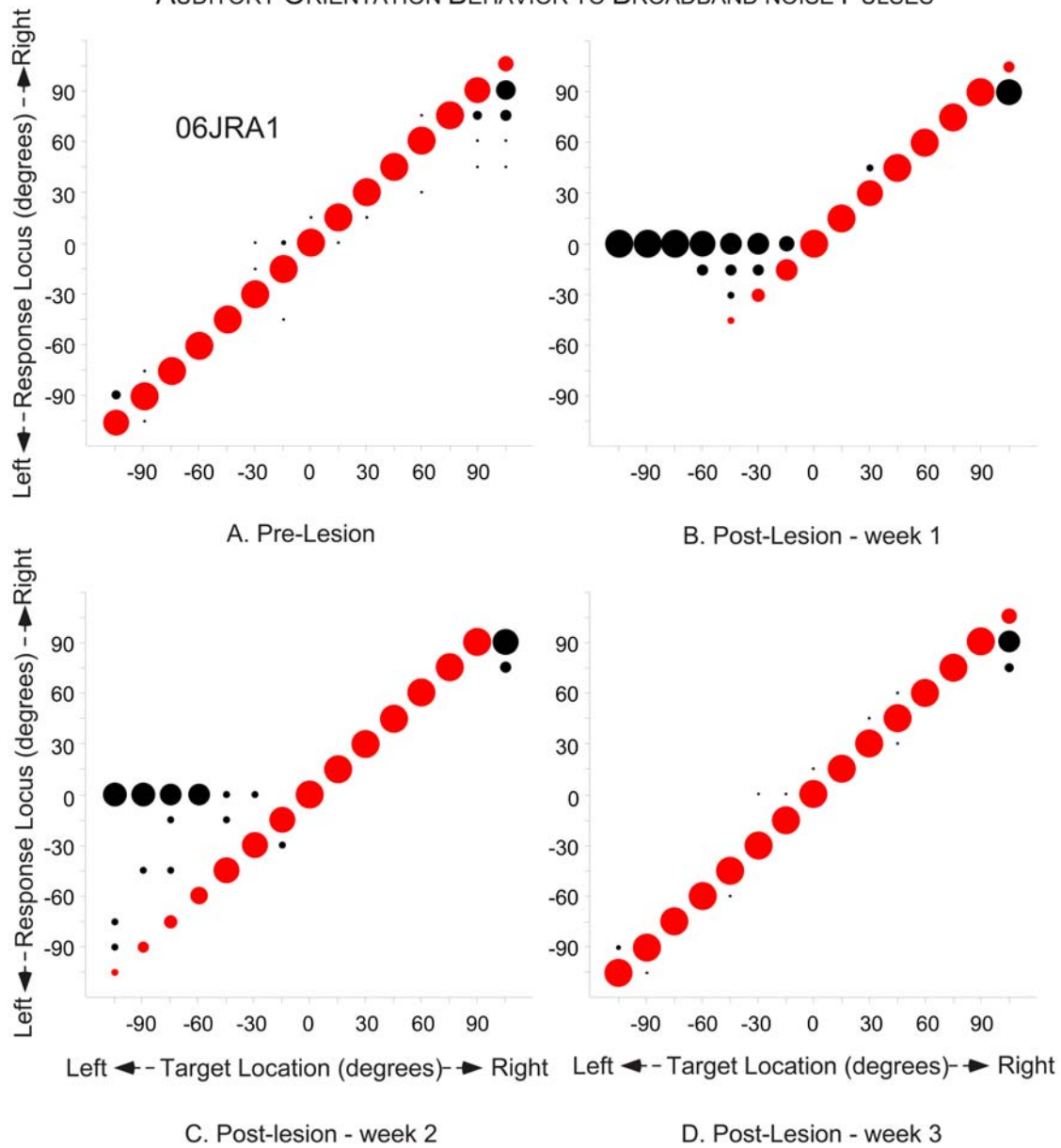


auditory space had greatly improved (Fig. 4C). The cat now was able to orient to broadband stimuli in contralateral auditory space, although more peripheral stimuli were still far less accurate. After the third week post-lesion, the accuracy of orientation to targets in contralesional auditory space had largely return to pre-lesion capabilities (Fig. 4D).

A second animal (06JRA1) displayed similar auditory orienting behavior changes following cortical lesions (Fig. 5). Prior to lesioning, cat 06JRA1 was able to orient to broadband white noise pulses in both left and right auditory space with a high degree of accuracy (Fig. 5A). The orienting accuracy to each speaker location in left auditory space was between 97% and 100%, except for the most peripheral speaker location ( $105^{\circ}$ ) which was 90%. The orienting accuracy to each speaker location at right auditory space was between 96% and 100%, except for the most two peripheral speaker locations ( $90^{\circ}$  and  $105^{\circ}$ ) which were 91% and 30% respectively. During the first week post-lesion, orientation to broadband white noise pulses was significantly impaired to stimuli in contralateral auditory space (Fig. 5B). Cat 06JRA1 failed to orient to the target locations in contralateral auditory space and instead oriented to the central target location ( $0^{\circ}$ ), especially when the stimuli were delivered at more peripheral speaker locations (i.e.,  $30^{\circ}$  to  $105^{\circ}$  left). By contrast, orientation to broadband auditory stimuli at the ipsilesional auditory space for the cat 06JRA1 was largely unchanged. The pre-lesion accuracy was between 96% and 100%, and the post-lesion accuracy was between 95% and 100%, except for target location  $105^{\circ}$

Figure 5. Pre- and post-operative behavioral data for cat 06JRA1 in the auditory orientation task with broadband white noise (200-20,000 Hz) pulses. As was the case in the animal show previously (Fig. 4), the cat showed no long-term enduring orienting deficit following AES lesions. See Fig. 4 for details.

# AUDITORY ORIENTATION BEHAVIOR TO BROADBAND NOISE PULSES



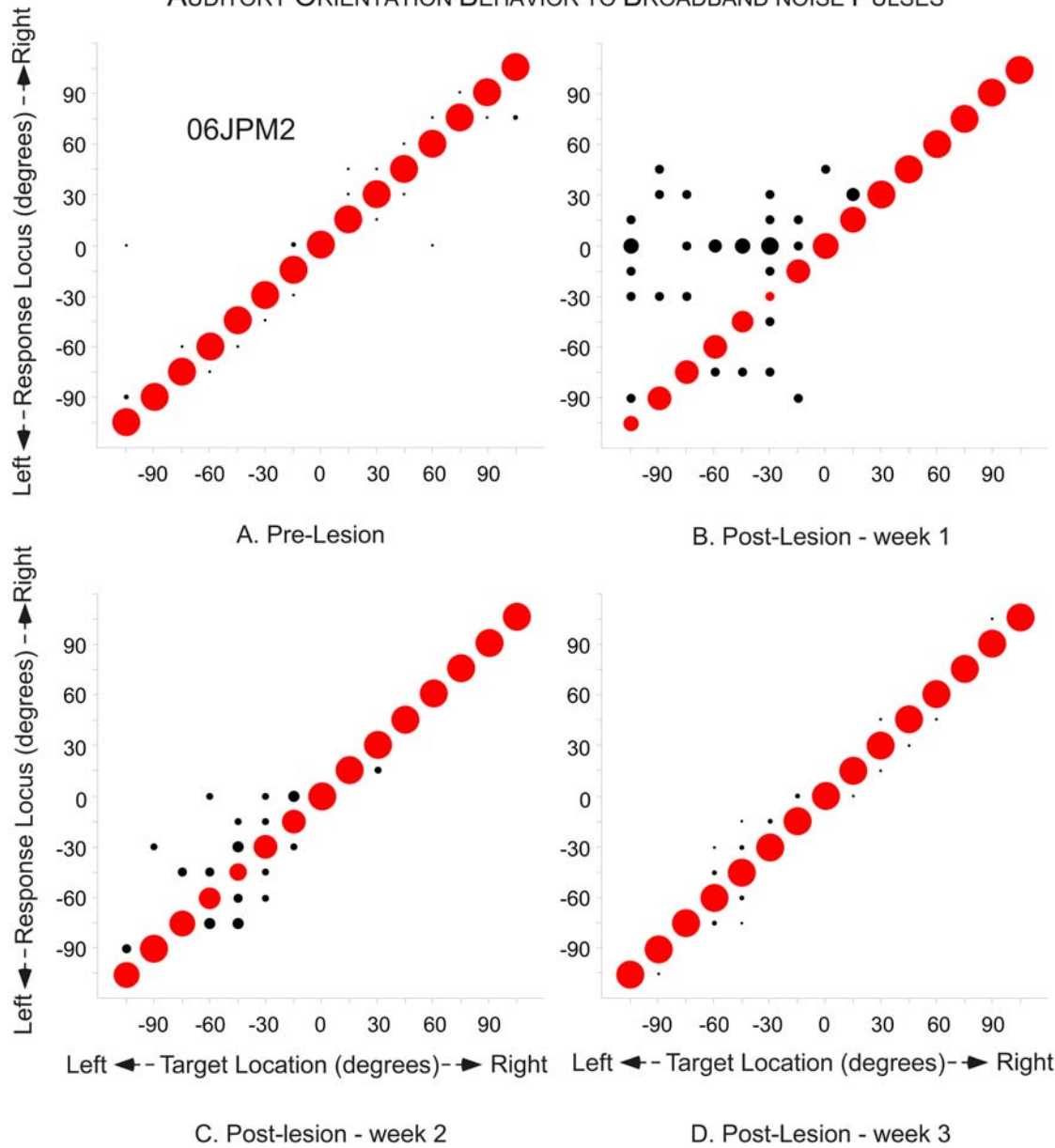
which fell to 24% (Fig. 5B). During the second week post-lesion, auditory orientation to broadband white noise pulses to targets at the contralateral auditory space had greatly improved (Fig. 5C). The cat now was able to orient to the target location at contralateral auditory space. However, the accuracy was less than that seen prior to lesioning. After the third week post-lesion, the accuracy of orientation to targets in contralesional auditory space had largely return to pre-lesion capabilities (Fig. 5D).

In summary, although there was a short-term auditory orienting deficit to broadband noise pulses in contralateral auditory space during the first two weeks post-lesion, these two animals showed no enduring impairments in contralateral auditory orientation capabilities. Moreover, recovery proceeded in a similar central to peripheral fashion. In addition, the incorrect orienting responses tended to stay within the same auditory space as the auditory target location and were composed of both undershoots and overshoots of the target position, with the majority of the errors being undershoots (see Fig. 4B&D and Fig. 5B&D).

In contrast, cat 06JPM2 showed different post-operative auditory orientation deficits. Prior to lesioning, this animal was able to orient to broadband white noise pulses at both left and right auditory space correctly (Fig. 6A). The orienting accuracy to stimuli in left auditory space was between 95% and 100%. The orienting accuracy to stimuli in right auditory space also was between 95% and 100%. In contrast to the two animals described above, this animal's

Figure 6. Pre- and post-operative behavioral data for cat 06JPM2 in the auditory orientation task with broadband white noise (200-20,000 Hz) pulses. Target location is indicated on the x-axis (negative values indicate left auditory space); orienting response is indicated on the y-axis. Red circle at each location indicates the percentage of correct responses. Black circle at each location indicates the percentage of incorrect responses. The size of each circle is proportional to the percentage. A. Pre-operative data demonstrated normal auditory orienting behaviors to the broadband white noise pulses at both auditory space (top left); B. By the first week post-lesion, the auditory orienting behavior was not as severely impaired to stimuli at the contralateral auditory space. Cat 06JPM2 was still able to orient to the target location at contralateral auditory space, although the accuracy is lower than normal auditory orienting behaviors. The ipsilesional orienting behavior was not impaired too (top right); C. By the second week post-lesion, although auditory orienting behavior at the contralateral auditory space was better than the first week post-AES lesion, it was still worse than normal behavior (bottom left); D. By the third week post-lesion, the cat showed no impairment in contralateral auditory orientation capabilities (bottom right).

# AUDITORY ORIENTATION BEHAVIOR TO BROADBAND NOISE PULSES



orientation to broadband white noise pulses during the first week post-lesion was not as severely impaired to stimuli in the contralateral auditory space (Fig. 6B). Cat 06JPM2 was still able to orient to the target location at contralateral auditory space although the accuracy of orientation was reduced from between 95% and 100% to between 10% and 70%. Orientation to broadband auditory stimuli in ipsilesional auditory space was largely unchanged. The pre-lesion accuracy was between 95% and 100%, and the post-lesion accuracy was between 80% and 100% (Fig. 6B). During the second week post-lesion, the accuracy of auditory orientation to broadband stimuli in contralesional auditory space had improved to between 50% and 92% (Fig. 6C). The most peripheral stimuli were accurately localized while the more central were mislocalized. By the third week post-lesion, the accuracy of orientation to targets at contralesional auditory space had largely return to pre-lesion capabilities (Fig. 6D).

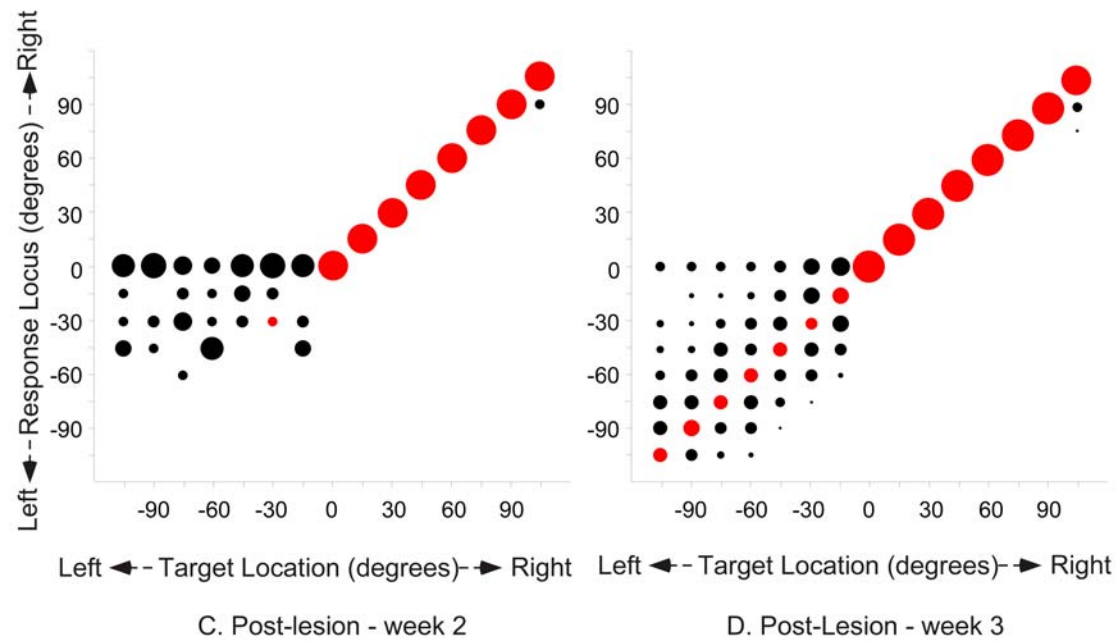
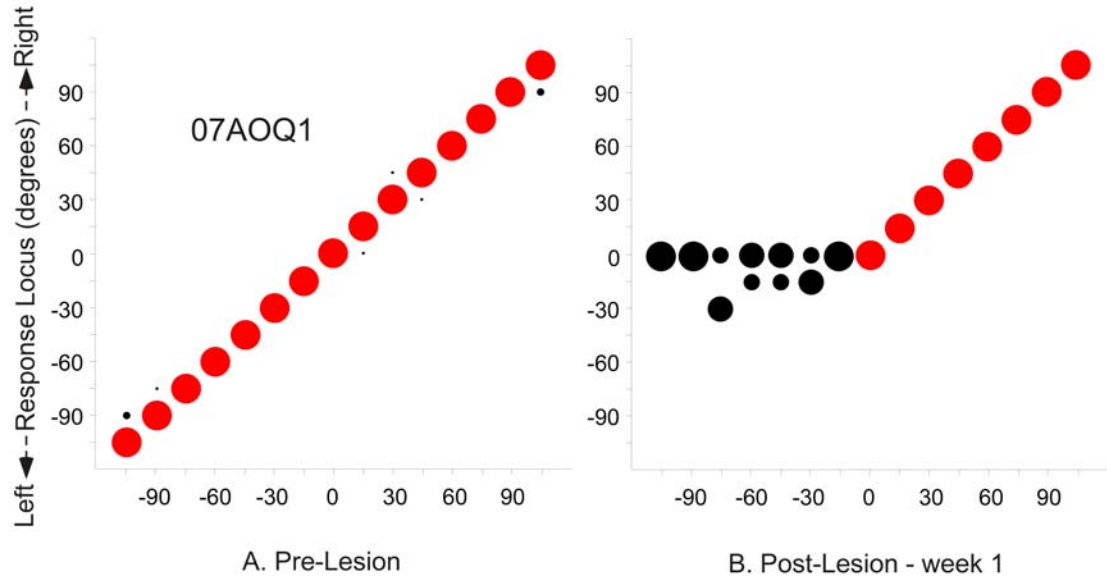
#### Auditory Orientation Behaviors to Low-Frequency Noise (800-5,000 Hz) Pulses

The auditory orienting behavior of the cat 07AOQ1 to low-frequency (800-5,000 Hz) noise pulses is shown in Figure 7. Prior to lesioning, cat 07AOQ1 was able to orient to low-frequency noise pulses at both left and right auditory space correctly (Fig. 7A). The orienting accuracy to each speaker location at left auditory space is between 97% and 100%, except for the most peripheral speaker location (105°) which was 93%. The orienting accuracy to each speaker location at right auditory space is between 97% and between 100%, except for the most peripheral speaker location (105°) which was 92%. -During the first week

Figure 7. Pre- and post-operative behavioral data for cat 06AOQ1 in the auditory orientation task with low-frequency noise (800-5000 Hz) pulses. Target location is indicated on the x-axis (negative values indicate left hemifield); orienting response is indicated on the y-axis. Red circle at each location indicates the percentage of correct responses. Black circle at each location indicates the percentage of incorrect responses. The size of each circle is proportional to the percentage. A. Pre-operative data demonstrated a normal auditory orienting behavior at both sides of auditory space (top left). Following two weeks post lesion (B, top right, and C, bottom left), cat 06AOQ1 failed to orient to the target locations at contralateral auditory space although it was able to orient to low-frequency noise pulses at contralateral auditory space. In contrast to broadband stimuli, the accuracy of orientation to low-frequency stimuli in contralateral auditory space remained significantly lower than the pre-lesion capabilities and showed a long term orienting deficit to the low-frequency noise pulses at the contralateral auditory space (D, bottom right).



# AUDITORY ORIENTATION BEHAVIOR TO LOW-FREQUENCY NOISE PULSES

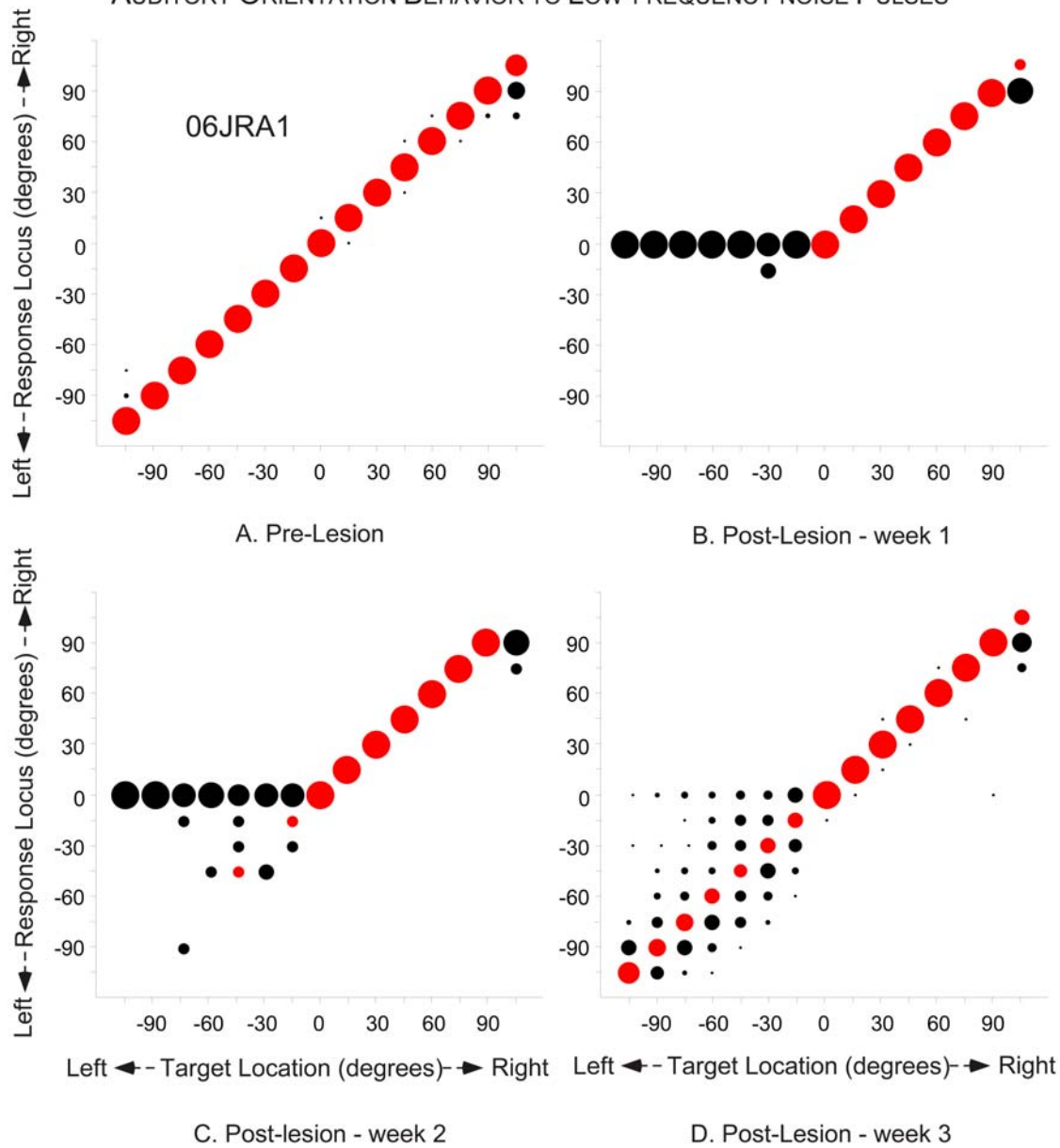


post-lesion, orientation to low-frequency noise pulses was significantly impaired to targets in contralateral auditory space (Fig. 7B). The cat failed to orient to the target location at contralateral auditory space and instead moved to the central target location ( $0^\circ$ ), especially when the targets were at more peripherally located targets (i.e.,  $30^\circ$  to  $105^\circ$  left). By contrast, orientation to low-frequency auditory stimuli at the ipsilesional auditory space was largely unchanged and even slightly improved. The accuracy pre-lesion was between 96% and 100%, and the accuracy post-lesion was 100% (Fig. 7B). During the second week post-lesion, the auditory orientation to low-frequency noise pulses in contralesional auditory space was still impaired. Although the tendency to orient to the central target location ( $0^\circ$ ) was reduced, the animal was still not able to orient to target locations correctly (Fig. 7C). By the third week post-lesion (Fig. 7D), the animal began to orient to low-frequency noise pulses, but in contrast to broadband stimuli, the accuracy of orientation to low-frequency stimuli in contralateral auditory space remained significantly lower than the pre-lesion capabilities. The accuracy was reduced to between 16% and 28%. The inaccurate responses tended to stay within the same auditory space as the auditory target location and were composed of both undershoots and overshoots of the target position with the majority of the errors being undershoots.

A second animal (06JRA1) displayed similar auditory orienting behavior changes following cortical lesions (Fig. 8). The normative data for the 06JRA1 is shown in panel A of Figures 8. Prior to cortical lesioning (Fig. 8A), cat 06JRA1

Figure 8. Pre- and post-operative behavioral data for cat 07JRA1 in the auditory orientation task with low-frequency noise (800-5000 Hz) pulses. As was the case in the animal show previously (Fig. 7), this cat showed a long-term enduring orienting deficit following AES lesions. See Fig. 7 for additional details.

# AUDITORY ORIENTATION BEHAVIOR TO LOW-FREQUENCY NOISE PULSES



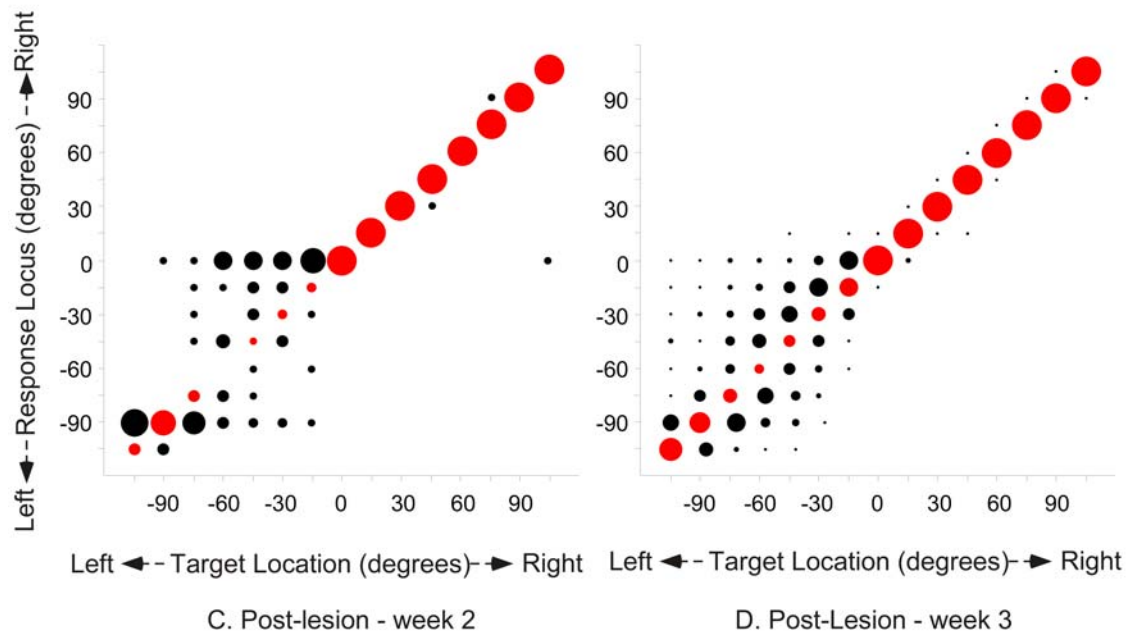
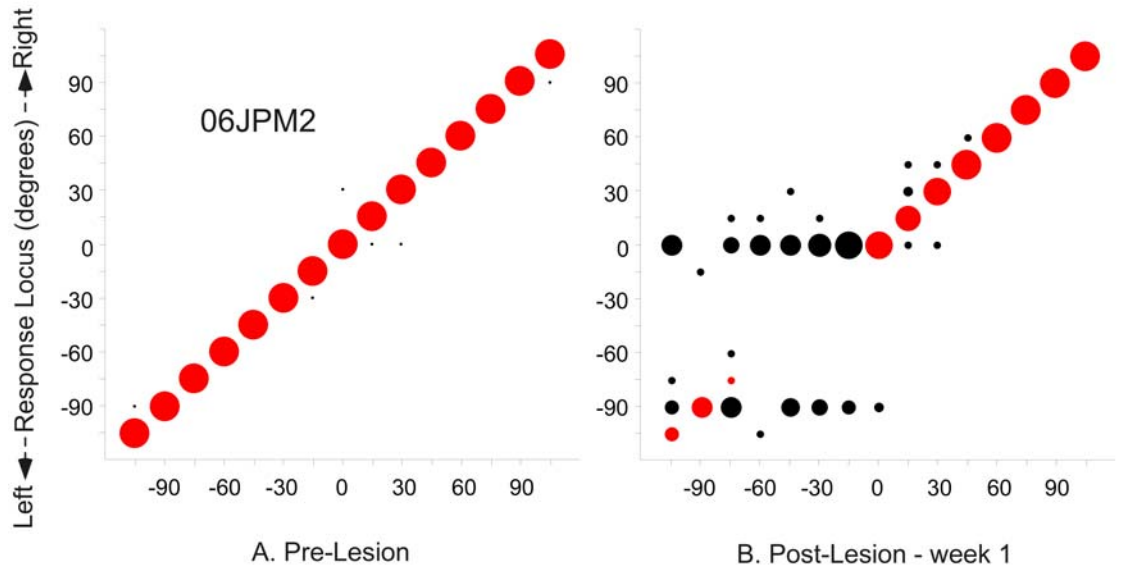
was able to orient to low-frequency pulses at both left and right auditory space with a high degree of accuracy. The orienting accuracy to each speaker location at left auditory space was between 95% and 100%. The orienting accuracy to each speaker location at right auditory space was between 95% and 100%, except for the most peripheral speaker location ( $105^\circ$ ) which was 60%. During the first week post-lesion, orientation to low-frequency stimuli was significantly impaired to targets at the contralateral auditory space (Fig. 8B). The cat failed to orient to the target location at contralateral auditory space and instead moved to the central target location ( $0^\circ$ ). By contrast, orientation to low-frequency stimuli at ipsilateral auditory space was largely unchanged. The accuracy pre-lesion is between 95% and 100%, except for the most peripheral speaker location ( $105^\circ$ ) which was 60%. The accuracy post-AES lesion was 100%, except for the very peripheral speaker location ( $105^\circ$ ) which was 30% (Fig. 8B). During the second week post-lesion, the auditory orientation to low-frequency stimuli in contralateral auditory space was still impaired. Although the tendency to orient to the central target location ( $0^\circ$ ) was reduced, the animal was still not able to orient to target locations correctly (Fig. 8C). By the third post-lesion week (Fig. 8D), the animal began to orient to low-frequency noise pulses correctly, but in contrast to broadband white noise, the accuracy of orientation to low-frequency stimuli in contralateral auditory space was greatly less than the accuracy pre-lesion. The accuracy was reduced to between 19% and 44%. The inaccurate responses tended to stay within the same auditory space as the auditory target location and

were composed of both undershoots and overshoots of the target position with the majority of the errors being undershoots.

A third animal (06JPM1) displayed similar auditory orienting behavior changes following cortical lesions (Fig. 9). The normative data for the cat 06JPM2 is shown in panel A of Figures 9. Prior to cortical lesioning (Fig. 9A), cat 06JPM2 was able to orient to low-frequency pulses at both left and right auditory space with a high degree of accuracy. The orienting accuracy to each speaker location at left auditory space is between 97% and 100%. The orienting accuracy to each speaker location at right auditory space is also between 97% and between 100%. During the first week post-lesion, orientation to low-frequency stimuli was significantly impaired to targets at the contralateral auditory space (Fig. 9B). The cat failed to orient to the target location at contralateral auditory space and instead moved to the central target location ( $0^\circ$ ). By contrast, orientation to low-frequency auditory stimuli at ipsilateral auditory space was largely unchanged. The accuracy pre-AES lesion is between 97% and 100%; and the accuracy post-AES lesion is between 82% and 100% (Fig. 9B). During the second week post-AES lesion, the auditory orientation to low-frequency stimuli in contralateral auditory space was still impaired. Although the tendency to orient to the central target location ( $0^\circ$ ) was reduced, the animal was still not able to orient to target locations correctly (Fig. 9C). By the third post-lesion week (Fig. 9D), the animal began to orient to low-frequency noise pulses correctly, but in contrast to broadband white noise, the accuracy of orientation to low-frequency

Figure 9. Pre- and post-operative behavioral data for cat 07JPM2 in the auditory orientation testing with low-frequency noise (800-5000 Hz) pulses. As was the case in the animal show previously (Fig. 7), the cat showed a long-term enduring orienting deficit following operation. See Fig. 7 for additional details.

# AUDITORY ORIENTATION BEHAVIOR TO LOW-FREQUENCY NOISE PULSES





stimuli in contralateral auditory space was greatly less than the accuracy pre-AES lesion. The accuracy was reduced to between 17% and 60%. The inaccurate responses tended to stay within the same auditory space as the auditory target location and were composed of both undershoots and overshoots of the target position with the majority of the errors being undershoots.

Thus, in contrast to the recovery from contralateral trauma-induced auditory orientation deficits seen with broadband stimuli, animals failed to regain pre-lesion auditory orientation capabilities when tested with low frequency stimuli.

#### Histological Evaluation of AES Lesions

After all data of post-operative auditory and visual testing were collected, animals were sacrificed, and brains were removed to determine the location and extent of cortical damage. The location and extent of the AES lesion of cats 07AOQ1 and 06JRA1 was shown in panel A of Figures 10 and 11. In both animals, the lesion was correctly placed in AES with tissue along the caudal two-thirds of the sulcus having been removed. However, the lesion in cat 06JPM2 was incorrectly placed in more caudal auditory areas. These regions include the primary (AI), the secondary (AII) auditory fields and the posterodorsal part of the posterior ectosylvian gyrus, all of which send afferent to AES (Heath and Jones, 1971a; Imig and Reale, 1980; Reinoso-Suarez and Roda, 1985; Norita et al., 1991). This lesion was shown in figure 12. It is likely that the incorrect lesion location placement accounts for the made the different auditory orienting

Figure 10. Post mortem verification of AES lesion in cat 07AOQ1. Shown is the location and extent of the AES lesions. Removal of the caudal 2/3's of the AES (shown at higher magnification in B and C) had no effect on visual orientation but compromised auditory orientation in a stimulus dependent fashion.

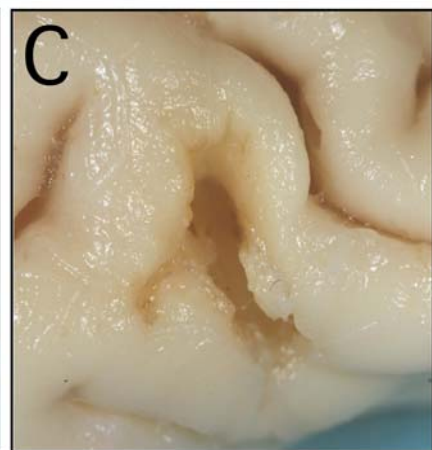
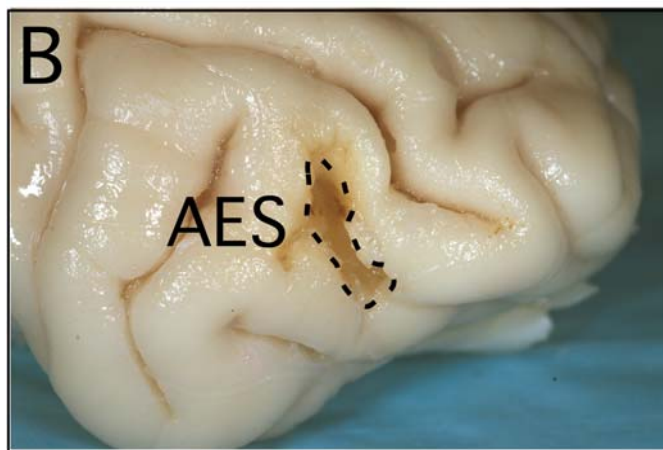
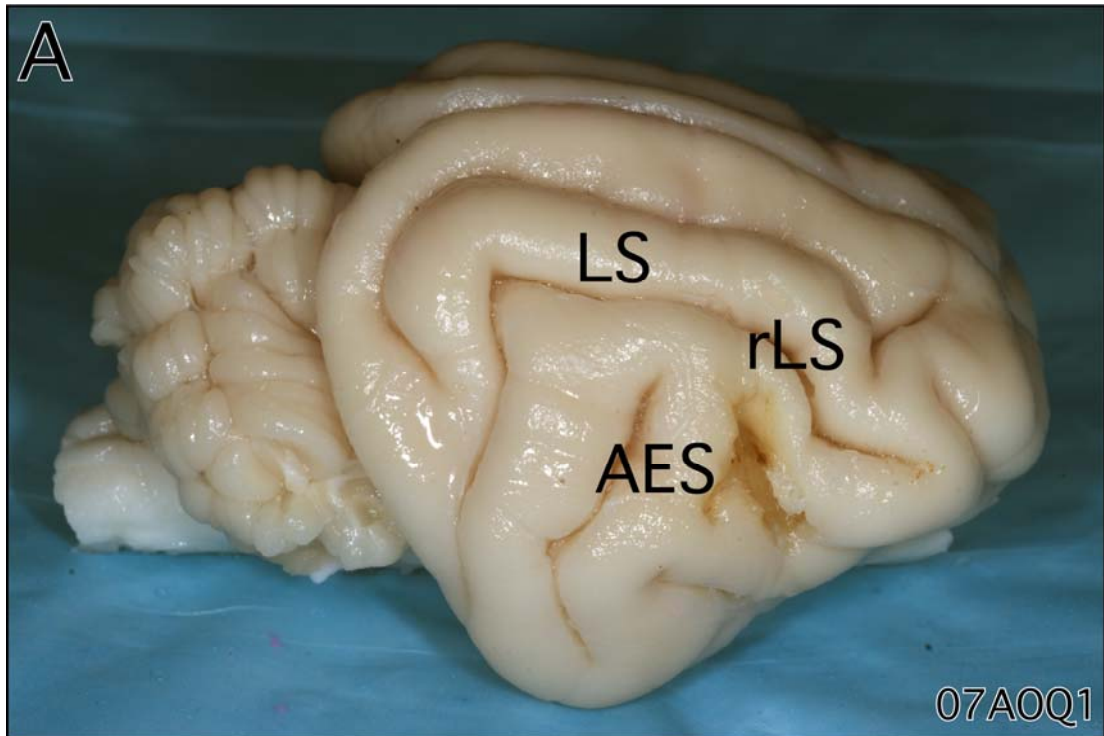


Figure 11. Post mortem verification of AES lesion in cat 06JRA1. Shown is the location and extent of the AES lesions. Removal of the caudal 2/3's of the AES (shown at higher magnification in B and C) had no effect on visual orientation but compromised auditory orientation in a stimulus dependent fashion.

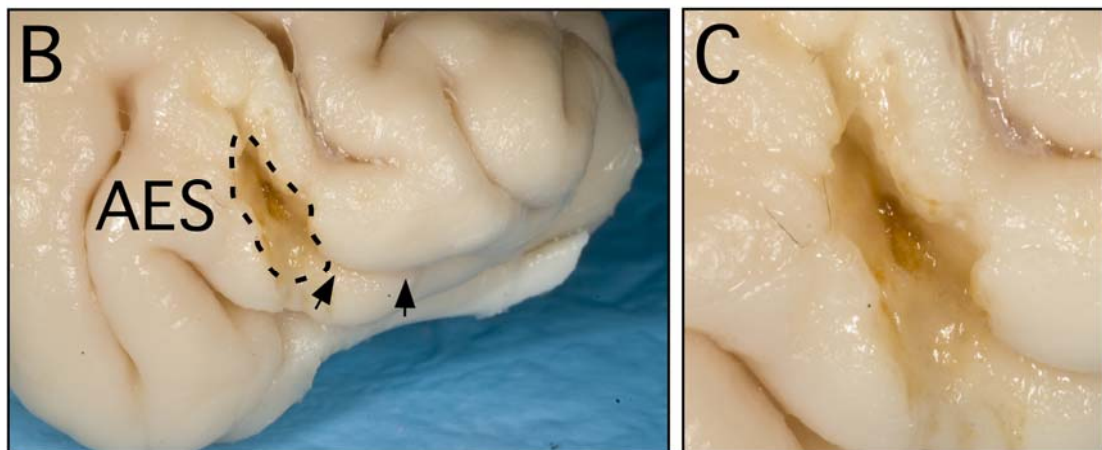
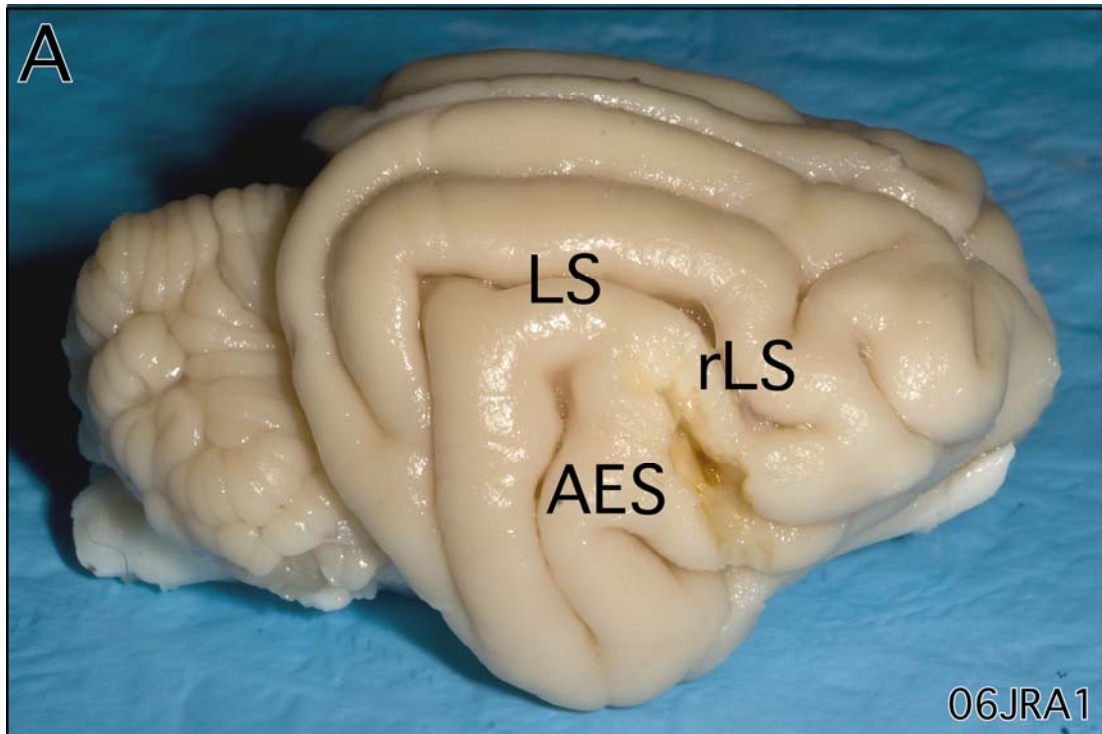
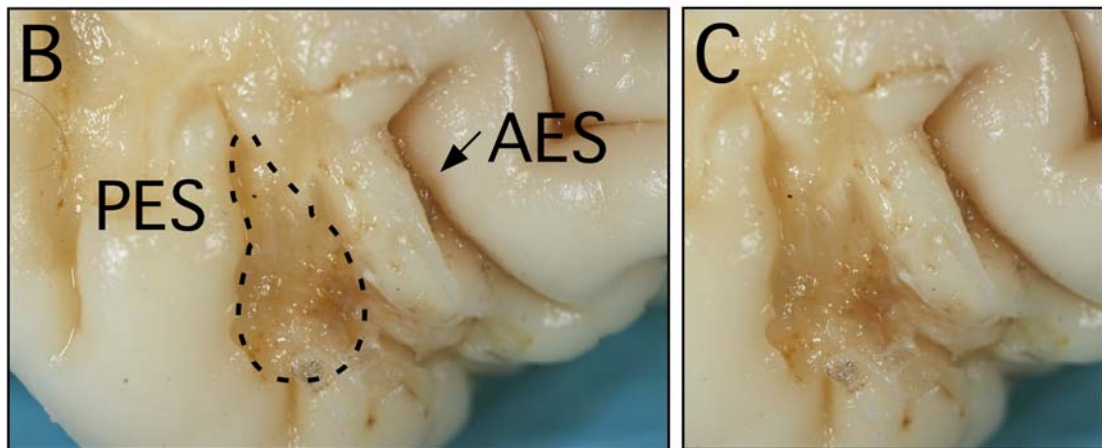
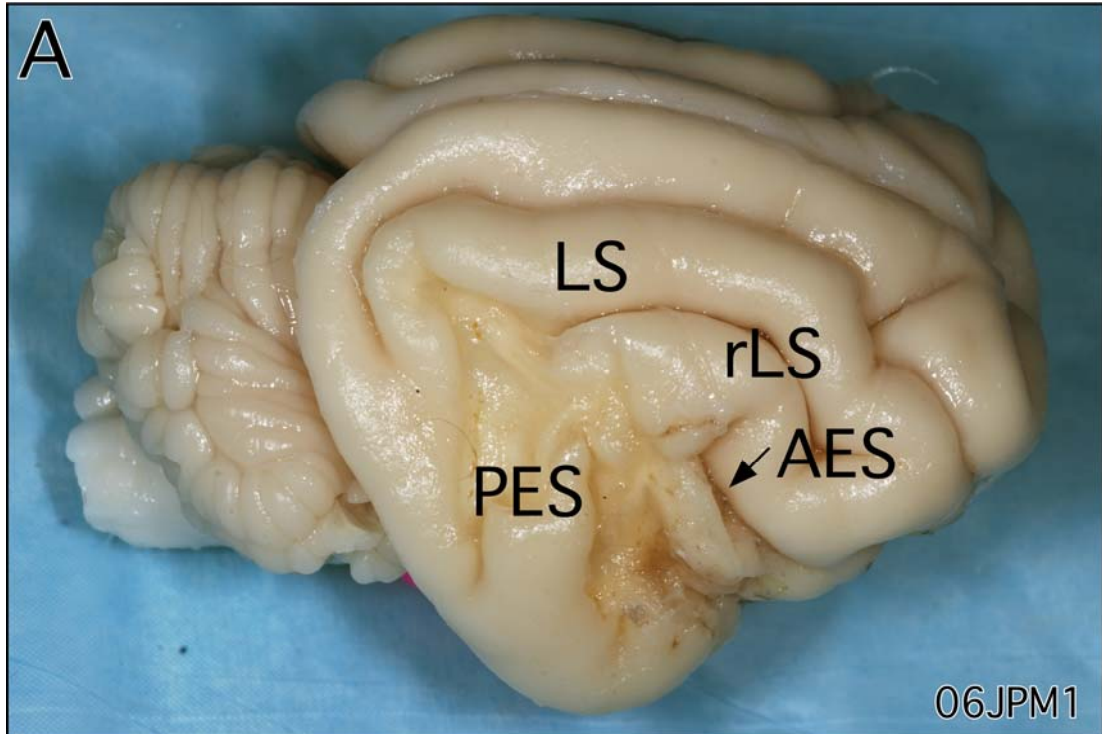


Figure 12. Post mortem verification of a misplaced lesion in cat 06JPM1. Shown is the location and extent of the lesion in more caudal auditory areas. Removal of this area (shown at higher magnification in B and C) had no effect on visual orientation but compromised auditory orientation in a stimulus dependent fashion.



behaviors observed between the cat 06JPM2 and the other two animals in which the lesion was restricted to AES.

#### Normal Visual Orientation Behaviors

After a pre-operative training period, all three animals were able to orient to visual stimuli (a ping-pong ball on a wand) delivered at each of the 14 target locations of eccentricity from 105° left to 105° right in visual space. The normative data for each cat is shown in top left panels of Figures 13, 14, and 15. For each trial, if the animal was able to orient briskly toward the visual stimulus, this trial was recorded as a correct orienting response. If the animal failed to orient to the visual stimulus, this trial was recorded as an incorrect orienting response. Prior to cortical lesions, all animals could orient to each target location correctly greater than 95%, with the exception of the most peripheral target locations (90°, 105°) where performance was slightly less accurate. Following collection of control data, animals were prepared for cortical ablation (see Methods).

#### Post-Operative Visual Capabilities:

Following AES removal and surgical recovery, visual orientation testing was resumed on the cats 07AOQ1 and 06JRA1 once the transient motor deficits had resolved. On the first day post-lesion, the visual orientation was significantly impaired to targets delivered at the contralesional hemifield, with both animals displaying a profound contralesional hemineglect (Figs. 13 & 14, right middle



Figure 13. Pre- and post-operative behavioral data for cat 07AOQ1 in the visual orientation task. Pre-operative data demonstrated a normal visual orienting behavior in both visual hemifields (top left perimetry plot). Following a brief transient 1-2 day post-operative contralateral deficit (middle three perimetry plots), the cat showed no impairment in contralateral visual orientation capabilities (bottom right). The location of the ablated AES part (red area) is shown at top right. See Figure 10 for photograph of this animal's brain. Green areas of perimetry plots indicate correct responses pre- (top left) and post (bottom right) lesion. The grey areas of perimetry plots indicate incorrect responses. The outer circle of the perimetry diagram is 100%. The ping-pong ball target locations are shown surrounding the outer circle of the perimetry diagram from 105° left to 105° right.

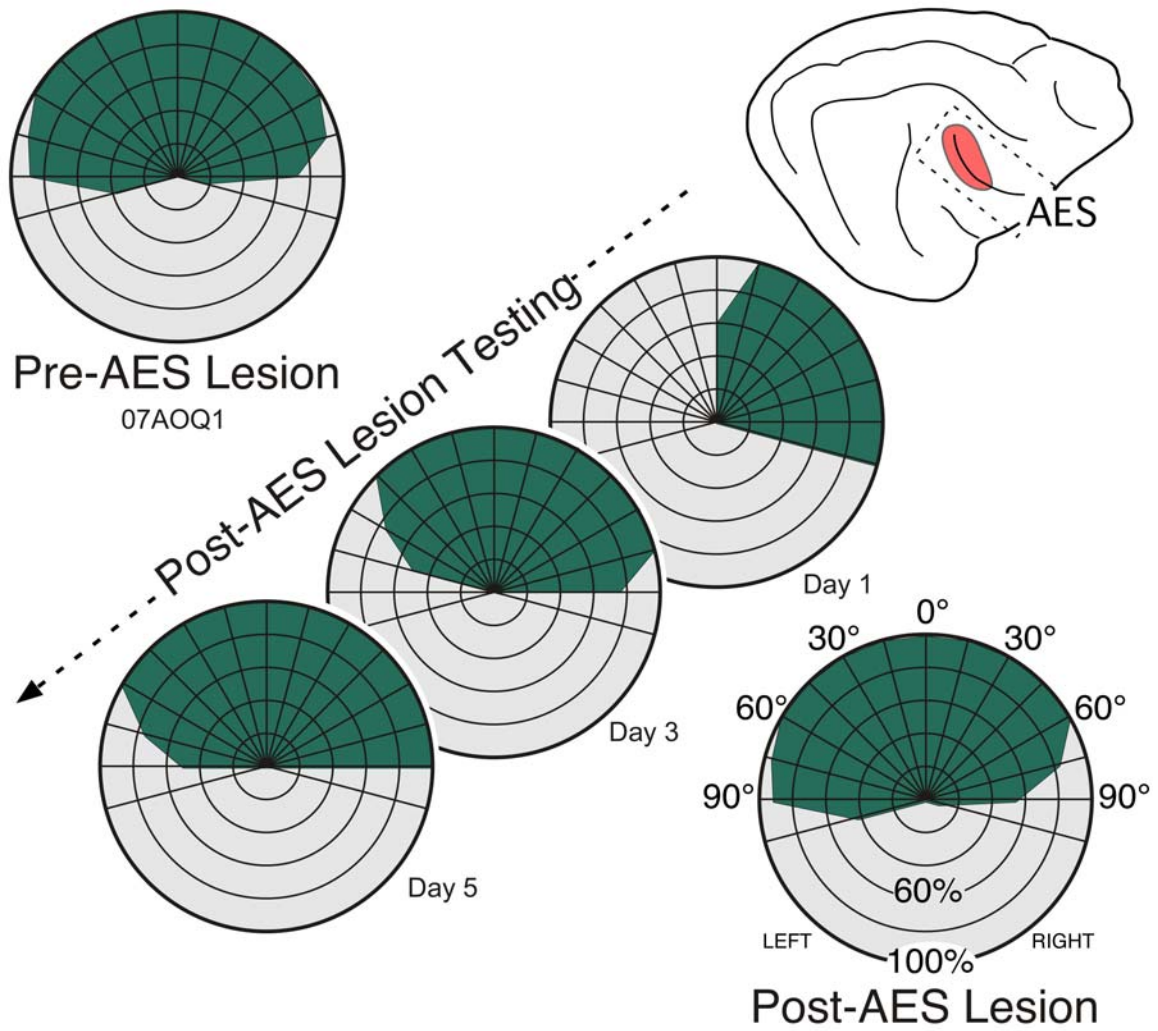


Figure 14. Pre- and post-operative behavioral data for cat 06JRA1 in the visual orientation testing. As was the case in the animal show previously (Fig. 13), this cat did not display an enduring orienting deficit following AES lesions. See Figure 11 for photograph of this animal's brain. See Figure 13 for additional details.

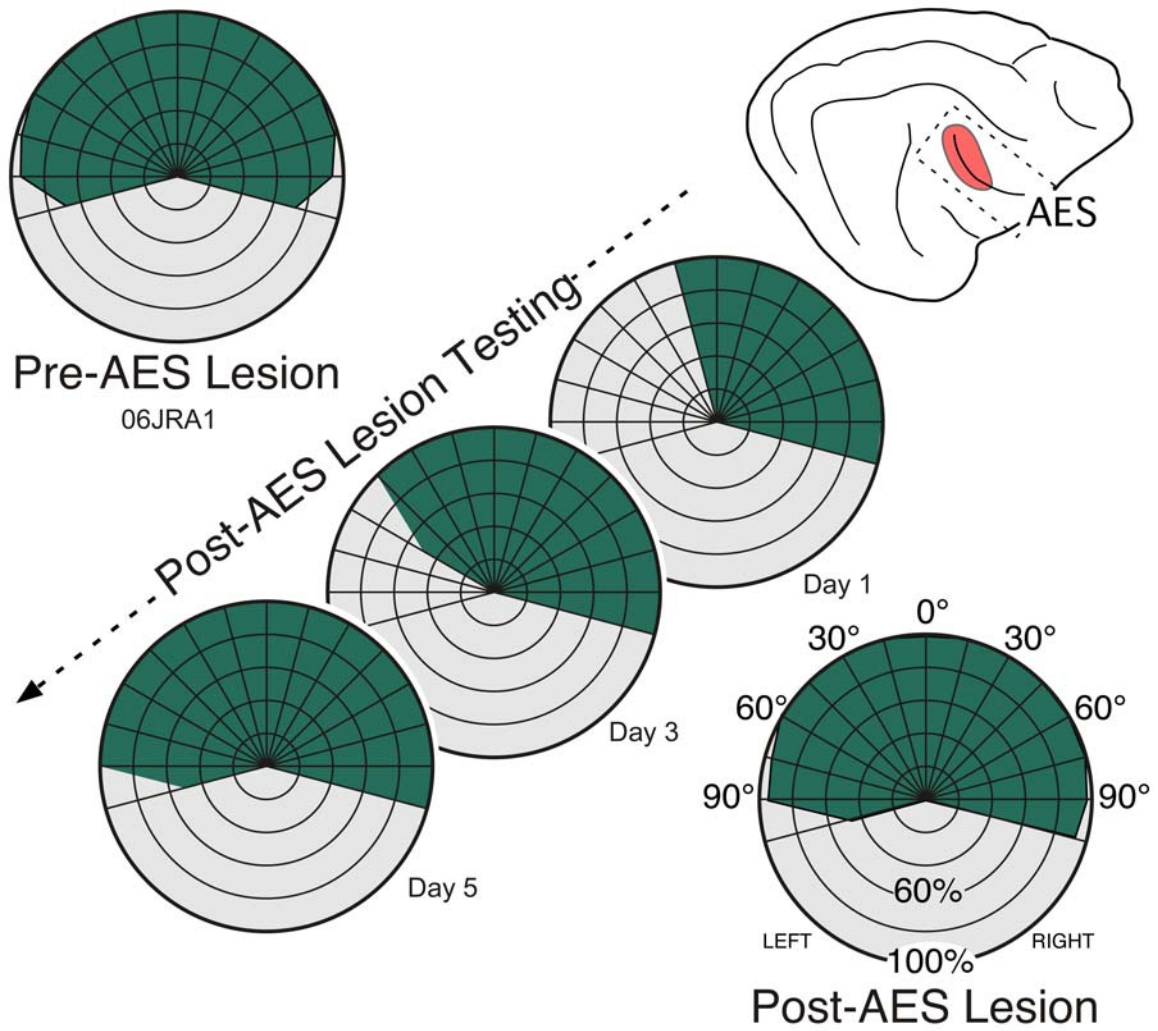
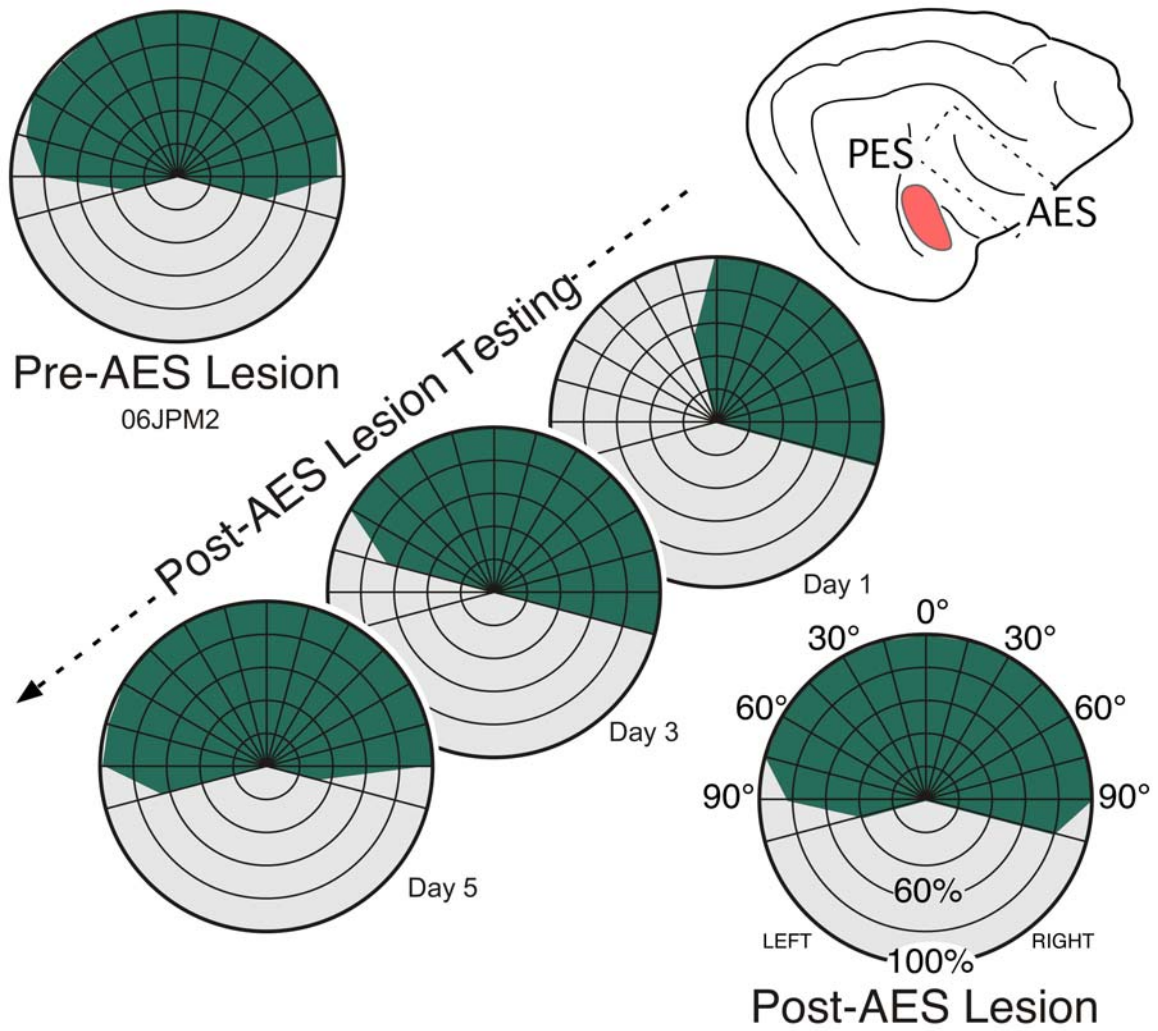


Figure 15. Pre- and post-operative behavioral data for cat 06JPM2 in the visual orientation testing. Pre-operative data demonstrated a normal visual orienting behavior at both visual hemifields (top left perimetry plot). Following a brief transient day post-operative contralateral deficit (middle three perimetry plots), the cat showed no enduring impairment in contralateral visual orientation capabilities (bottom right). The location of the ablated auditory part (red area) is shown at top right. See Figure 12 for photograph of this animal's brain. Green areas of perimetry plots indicate correct responses pre- (top left) and post (bottom right) lesion. The grey areas of perimetry plots indicate incorrect responses. The outer circle of the perimetry diagram is 100%. The ping-pong ball target locations are shown surrounding the outer circle of the perimetry diagram from 105° left to 105° right.



panels). However, by third post-lesion day, orientation to targets in the previously neglected hemifield had greatly improved. The animals now were able to orient to visual stimuli delivered between 0° and 60° left at the contralateral hemifield (Fig 13 & 14, center middle panels). By the fifth post-lesion day, the animals showed no impairment in contralateral visual orientation capabilities (Fig 13 & 14, left middle panel). After three months of testing, the animals were display normal visual orienting behavior at the contralateral hemifield (Fig 13 & 14, bottom right). Thus, despite a very brief transient post-operative contralateral neglect, the cats showed no enduring impairment in contralateral visual orientation capabilities. Similar results were observed in cat 06JPM2, whose lesion was misplaced in the posterior ectosylvian region.

## DISCUSSION

### Summary

Orientation behaviors to unisensory auditory and unisensory visual stimuli were examined in cats prior to, and following unilateral AES lesions. For the auditory localization task, two different types of auditory stimuli (broadband white noise stimuli [200-20,000 Hz]; low frequency noise stimuli [800-5000 Hz]) were used. Visual orientation was studied with a standard visual task (Hardy and Stein, 1988). Before making the cortical lesion, animals showed remarkably accurate auditory localization abilities to both types of stimuli. During the first post-lesion week, animals failed to orient to both types of auditory stimuli presented in the contralesional auditory field, except for occasional correct movements to more central target locations (i.e.,  $<30^\circ$ ). Orientation to both types of stimuli in ipsilesional auditory space was unaffected. By the second post lesion week, orientation to broadband stimuli began to improve in a central to peripheral fashion. By the third week post-lesion, orientation to broadband stimuli was back at pre-lesion values. In contrast, orientation to low frequency stimuli remained substantially impaired, by both over- and undershooting the actual target position. These data reveal that lesions placed along the caudal aspect of the AES that presumably disrupt its auditory and visual subdivisions produce enduring deficits in an animal's ability to accurately orient to low frequency pulses but not to broadband noise pulses. By contrast, these same unilateral AES lesions had no effect on contralesional visual orientation behaviors other than a brief transient 1-2 day impairment. These data reveal that lesions of the caudal AES, that



presumably disrupt both its auditory and visual subdivisions, produce enduring deficits in an animal's ability to accurately orient to certain types of auditory. They also show that visual orientation is unaffected by such lesions. We suggest that the re-appearance of auditory capabilities following AES lesions may be the result of neuroplastic changes.

### Relationships with Previous Studies

Stein and colleagues (Jiang et al., 2002) trained cats to orient to visual cues in the presence or absence of a neutral auditory cue. When the two (visual and auditory) stimuli were spatially coincident, the number of correct responses were substantially increased. However, when the two stimuli were spatially disparate, the number of correct responses was markedly diminished. However, when AES was deactivated, both the enhanced performance produced by spatially coincident cross-modal cues and diminished performance produced by spatially disparate cues was eliminated whereas orientation to visual stimuli alone was unchanged. They also trained the animals to orient to both visual and auditory stimuli. In this case, they noted results similar to those that occurred with a neutral auditory stimulus: the spatially coincident cross-modal stimulus pair evoked consistently higher performance than did either of the individual modality cues presented alone. Once again, this multisensory enhancement to the spatially coincident cross-modal targets was eliminated by cryogenic deactivation of AES. Importantly, AES deactivation had no significant effect on the number of correct responses to visual or auditory targets when they were presented alone.

This suggests that AES is not critical for unisensory orienting and approach behaviors to visual or auditory stimuli.

Stein and colleagues (Wilkinson et al., 1996) had previously used a similar behavior paradigm where the AES was pharmacologically deactivated with lidocaine injections. Animals were trained to orient and approach a near-threshold visual stimulus while ignoring a brief, low-intensity auditory stimulus presented simultaneously. Following AES deactivation, the normal response enhancement to coincident visual and auditory stimuli was significantly decreased and the depressed response induced by disparate visual and auditory stimuli was also apparently degraded. However, AES deactivation did not alter responses to a visual stimulus alone, nor did it affect responses to the auditory cue alone that signaled the animal to return to the start position, suggesting that deactivation of AES does not affect the unisensory orientation.

In contrast, Lomber and colleagues (Malhotra and Lomber, 2007) reported that cryogenic deactivation of caudal aspect of AES of cats had a significant impact on auditory localization. The major impact was the failure of animals to orient and approach auditory stimuli presented in the auditory space contralateral to the deactivated AES. They also deactivated AI, the Posterior Auditory Fields (PAF), and found that the unilateral deactivation of any region of these three areas (AI, PAF, or AES) was sufficient to produce a deficit in auditory localization at the contralateral hemifield. These cats were generally able to turn toward the

side where the auditory stimulus was presented but could not accurately orient to the location of the auditory stimulus. In contrast, cooling of these auditory cortical areas (AI, PAF, and AES) produced no deficit in the orientation and approach behaviors to visual stimuli. This control experiment provided evidence that the cooling coil placement was effectively deactivating the auditory representation in AES and not visual or motor representations. Thus, the results Lomber and colleagues (Malhotra and Lomber, 2007) contradict the studies of Stein and colleagues (Wilkinson et al., 1996; Jiang et al., 2002) who found that AES deactivation had no affect on the unisensory orientation to the auditory stimuli.

#### What is the Potential Cause of this Discrepancy?

Although both Stein and colleagues and Lomber and colleagues used a broad band noise pulse as the auditory stimulus, the frequency response range of the speakers used by Lomber had a frequency response 800 Hz to 5000 Hz, suggesting that the auditory stimuli provided did not contain high frequency components. Therefore, we postulated that the difference of spectral frequency of the auditory stimuli between the experiments of Stein and colleagues and Lomber and colleagues accounts for the difference of their experiment results.

In the present study, intact animals were trained to orient and approach both broadband and low frequency ranges an auditory stimuli as well as visual stimuli. After removal of AES, we observed that animals showed no impairment in contralesional auditory orientation capabilities to broadband white noise.

However, they showed a long term contralateral auditory orienting deficit to low-frequency noise. In addition, following a brief transient day post-operative contralateral deficit, the cats showed no enduring impairment in contralateral visual orientation capabilities (see Results).

In the present study, no attempt was made to evaluate how altering the auditory stimulus parameters might influence the magnitude of the lesion-induced deficits. For example, one possibility is that as the stimulus becomes more salient, and presumably easier to detect, less of a behavioral deficit would be present than was demonstrated here. Thus, increasing either stimulus duration or intensity of the low-frequency stimulus might enhance orientation accuracy in AES lesioned animals exhibiting a persistent deficit to the low-frequency stimuli that were used in these experiments. The influences of manipulating stimulus parameters on the accuracy of contralesional auditory orientation deficits will be an important goal in future studies.

#### Neuroplastic Changes Following AES Lesions?

We noticed that after approximately weeks following AES lesion, the animals' capability to orient to auditory stimuli at contralateral auditory space had more or less recovered to pre-lesion levels, with a complete return of orientation to broadband white noise pulses but only a partially recover to. When low-frequency noise pulses were presented, the animals turned to the correct region of auditory space but the accuracy was much less than previously observed. This contrasts

to the previous post-lesion weeks when animals always tended to move to the central position ( $0^\circ$ ) like they did during catch trials when stimuli were in more peripheral locations. Some orientation was possible near the more central regions (i.e.,  $0^\circ$  to  $\sim 30^\circ$ ). Therefore, we suggest some auditory cortex remodeling occurred following the lesion to allow auditory orientation to both stimuli. However, in contrast to broadband stimuli, the accuracy of orientation to low-frequency stimuli at contralateral auditory space remained significantly lower than the pre-lesion capabilities. The time course for this cortical remodeling process occurs during the 2-3 weeks following the lesion. During the first two weeks post-AES lesion, because the auditory cortical remodeling process was not finished, animals were not able to orient to both broadband white and low-frequency auditory stimuli at the contralateral auditory space. By the third week post-AES lesion, since the auditory cortical remodeling had finished, animals were able to orient to auditory stimuli again.

This compensation is consistent with previous studies. Auditory cortical representations can be remodeled according to the behavioral significance of the stimuli (Buonomano and Merzenich, 1998). This remodeling follows Hebbian principles as well as homosynaptic and heterosynaptic rules (Bailey et al., 2000; Dalley et al., 2001; Gu, 2002; Schultz, 2002). Moreover, it may depend on diffusely released modulatory neurotransmitters (Gu, 2002). Dopamine is the most prominent neuromodulator associated with reinforcement learning (Schultz, 2000, 2002). Consistent with this notion, regions along the AES cortex of the cat

is rich in both dopamine D1 and dopamine D2 receptors (Markowitsch and Irle, 1981; Richfield et al., 1989). In addition, HRP injections into AES labels neurons in the midbrain dopaminergic nucleus (VTA) (Foote and Morrison, 1987) that are likely to be activated when the animal experiences a food reward (Hollerman and Schultz, 1998) or experiences novel stimuli (Dommett et al., 2005). Interesting, auditory stimuli are known to be particularly effective in activating VTA neurons (Horvitz et al., 1997; Horvitz, 2000). Dopamine reinforcement signals are thought to act via D<sub>1</sub> receptors such that D<sub>1</sub>-NMDA interactions represent a coincidence detector of sensory events that serves as the molecular basis for synaptic changes involved in associative or stimulus-response learning (Baldwin et al., 2002). For example, pairing of a 9K tone with electrical stimulation of VTA in adult rats results in an increased representation of that tone within primary auditory cortex (AI) but also induces a new representation outside AI, in the multisensory area immediately adjacent to AI (Bao et al., 2001). Giving the D1 antagonist before the experiment blocks the pairing-induced alterations (Bao et al., 2001).

In summary, our study reveals that lesions of the caudal AES, that presumably disrupt both its auditory and visual subdivisions, produce enduring deficits in an animal's ability to accurately orient to certain types of auditory. They also show that visual orientation is unaffected by such lesions. We suggest that the re-appearance of auditory capabilities following AES lesions may be the result of neuroplastic changes.

### Does AES Affects Unisensory Visual Orientation in the Sprague Task?

Visual hemineglect is a disorder characterized by a loss of awareness to stimuli in one hemifield (Mesulam, 1999; Driver and Vuilleumier, 2001) and a loss of ability to detect and respond to visual events in the contralesional hemifield induced by visual cortex injury, such as stroke and trauma. Currently, there are no effective rehabilitative strategies for visual hemineglect (Luaute et al., 2006). Therefore, providing an effective rehabilitative way for the visual hemineglect is very necessary.

Unilateral visual cortex lesions in cats produce a stable and enduring visual hemineglect that can be ameliorated by removal of the contralesion SC or substantia nigra pars reticulata (Sprague and Meikle, 1965; Sprague, 1966; Sherman, 1974, 1977; Wallace et al., 1989, 1990). Recently, our lab has developed a rehabilitative training strategy involving repetitive orientation to cross-modal auditory and visual stimuli presented in the neglected hemifield (McHaffie et al., 2008). After one month such training, animals display normal orientation to visual stimulus throughout the previously neglected hemifield when they were re-evaluated with the standard visual orientation testing. It was hypothesized that another region of cortex assumes the role of the lost visual cortex (McHaffie et al., 2008). As a test of this hypothesis, regions along the caudal two thirds of ipsilesional AES (includes the visual and auditory regions-AEV and fAES) removed. Post-AES lesion testing revealed that the reinstated visuomotor behaviors had been eliminated.

Taken together, this hypothesis suggests that cross-modal rehabilitative training facilitates functional recovery in the deep SC via training induced alterations in the AES-SC projection, which normally plays no role in visual orientation. In short, AES appears to be one very crucial part in the circuitry modified by the rehabilitative process that reinstates visual orientation.

AES was thought to have no role in unisensory visual orientation in the intact animal (Jiang et al., 2002). However, prior studies have used deactivation techniques (Jiang et al., 2002) rather than ablations. In addition, these studies also have used different testing procedures. Therefore, in the present thesis, we used identical testing and ablation techniques to verify that AES has no role in visual orientation.



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