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# The cat's meow: A high-field fMRI assessment of cortical activity in response to vocalizations and complex auditory stimuli

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#### ABSTRACT

Sensory systems are typically constructed in a hierarchical fashion such that lower level subcortical and cortical areas process basic stimulus features, while higher level areas reassemble these features into object-level representations. A number of anatomical pathway tracing studies have suggested that the auditory cortical hierarchy of the cat extends from a core region, consisting of the primary auditory cortex (A1) and the anterior auditory field (AAF), to higher level auditory fields that are located ventrally. Unfortunately, limitations on electrophysiological examination of these higher level fields have resulted in an incomplete understanding of the functional organization of the auditory cortex. Thus, the current study uses functional MRI in conjunction with a variety of simple and complex auditory stimuli to provide the first comprehensive examination of function across the entire cortical hierarchy. Auditory cortex function is shown to be largely lateralized to the left hemisphere, and is concentrated bilaterally in fields surrounding the posterior ectosylvian sulcus. The use of narrowband noise stimuli enables the visualization of tonotopic gradients in the posterior auditory field (PAF) and ventral posterior auditory field (VPAF) that have previously been unverifiable using fMRI and pure tones. Furthermore, auditory fields that are inaccessible to more invasive techniques, such as the insular (IN) and temporal (T) cortices, are shown to be selectively responsive to vocalizations. Collectively, these data provide a much needed functional correlate for anatomical examinations of the hierarchy of cortical structures within the cat auditory cortex. © 2015 Elsevier Inc. All rights reserved.

Introduction

Sensory systems are typically arranged in a processing hierarchy that begins with the coding of basic stimulus features at the sensory epithelium and leads to full-scale object representation in secondary and associative cortical areas. At each level of this ascending pathway, more complex features are represented. For example, in the visual system, neurons in primary visual cortex (V1) are most responsive to simple stimuli like spots or bars of light (Drager, 1975; Hubel and

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Wiesel, 1959, 1968; Singer et al., 1975). Ascending from V1, more complex stimuli are required for best activation, eventually leading to two parallel streams processing either spatial location ("where") dorsally. or identification ("what") ventrally (Haxby et al., 1991; Ungerleider and Mishkin, 1982). These streams are comprised of individual areas specialized for specific actions or stimuli such as visually-guided reaching (Karnath and Perenin, 2005; Singhal et al., 2013) in the dorsal stream, or faces (Collins and Olson, 2014; Kanwisher et al., 1997; Liu et al., 2010) in the ventral stream. Auditory cortex is not understood in the same level of detail as the visual cortex. However, Chevillet et al. (2011) demonstrated that the core, belt, and parabelt regions within human auditory cortex can be delineated using pure tones, band-passed noise bursts, or vocalizations, respectively. Thus, an understanding of the way in which hierarchies of cortical fields are arranged has significant consequences for our interpretation of how stimuli in the world around us are encoded and reconstructed in the brain.

Rouiller et al. (1991) first proposed a hierarchical organization within auditory cortex of the cat that was based on anatomical connections (Figs. 1A,B). This study focused on the second auditory cortex (A2) and the four areas of the auditory cortex known to be organized by







Abbreviations: A1, primary auditory cortex; A2, second auditory cortex; AAF, anterior auditory field; *aes*, anterior ectosylvian sulcus; BBN, broadband noise; dPE, dorsal posterior ectosylvian; DZ, dorsal zone; FAES, auditory field of the anterior ectosylvian sulcus; FM, frequency modulated; fMRI, functional magnetic resonance imaging; IN, insular cortex; iPE, intermediate posterior ectosylvian; NBN, narrowband noise; PAF, posterior auditory field; *pes*, posterior ectosylvian sulcas; PSC, percent signal change; ss, suprasylvian sulcus; T, temporal cortex; V1, primary visual cortex; VAF, ventral auditory field; VPAF, ventral posterior auditory field; vPE, ventral posterior ectosylvian.



Fig. 1. Hierarchy of auditory cortex. A) Lateral view of the cat cortical surface with the thirteen acoustically responsive areas outlined as defined by electrophysiological and anatomical investigations. Core (red), tonotopic non-core (orange), non-tonotopic (green), and multisensory (blue) areas are also indicated. B) Hierarchy of cat auditory cortex as originally proposed by Rouiller et al. (1991) including only 5 of the 13 cortical areas. C) More recent hierarchy of cat auditory cortex as proposed by Lee and Winer (2011) including all 13 areas. D) Auditory cortex of the old world monkey with core (red), tonotopically organized belt (orange), and non-tonotopic para-belt (green) areas indicated. E) Most recent hierarchy within old world monkey auditory cortex as proposed by Hackett (2015).

frequency (i.e. those with tonotopic organization); primary auditory cortex (A1), the anterior auditory field (AAF), the posterior auditory field (PAF), and the ventral posterior auditory field (VPAF). Based on anatomical connectivity, Rouiller et al. placed A1 and AAF at the base of the hierarchy, with A2, VPAF, and PAF at increasingly higher levels. More recent anatomical investigations have confirmed the separation between low-level (A1 and AAF) and higher-level (A2, VPAF, PAF) cortical areas (Fig. 1C; see Lee and Winer, 2011 for review). In addition, anatomical evidence suggests that there are parallel processing streams in the auditory cortex (Lee et al., 2004; Lee and Winer, 2011) that may be analogous to the separate ventral and dorsal streams of visual cortex (Ungerleider and Mishkin, 1982; Lomber et al., 1996). While these studies have been critical to establishing a proposed hierarchy within the auditory cortex of the cat, complementary functional data are necessary to provide a complete understanding of perception within the auditory system.

Electrophysiological (Harrington et al., 2008; Carrasco et al., 2013; Carrasco and Lomber, 2009a, 2011) and functional imaging (Hall and Lomber, 2015) studies have confirmed that A1 and AAF are at a similar, low level of cortical processing (Fig. 1). Collectively, these fields appear to be analogous to the auditory core of old world monkeys (Figs. 1D,E; Carrasco et al., 2013, 2015; Hackett, 2011, 2015; Hall and Lomber, 2015; Ma et al., 2013; Petkov et al., 2006; Schönwiesner et al., 2014), which also consists of multiple areas. Beyond core areas, it has been proposed that information flow within auditory cortex of the cat proceeds postero-ventrally (Carrasco and Lomber, 2011; Hackett, 2011). Latencies within individual areas are increasingly longer moving ventrally with AAF and A1 having similar, shorter latencies and A2 and PAF having longer latencies (Harrington et al., 2008; Carrasco and Lomber, 2011). Also, there is some anatomical (Andersen et al., 2004) electrophysiological evidence (Carrasco and Lomber, 2009a, 2009b) to support parallel processing streams within auditory cortex of the cat while behavioral studies have identified areas that are selective for localization but not for discrimination, and vice versa (Lomber and Malhotra, 2008; Malhotra et al., 2004; Malhotra and Lomber, 2007). Indeed, functional evidence for dual-stream processing in auditory cortex has also been observed in humans (DeWitt and Rauschecker, 2012, 2013; Rauschecker, 1997) and monkeys (Rauschecker, 1997; Rauschecker and Tian, 2004; Rauschecker et al., 1995, 1997). However, functional investigations of cortical processing in the cat have provided only a limited glimpse of the hierarchy of cortical processing due to three major limitations: 1) electrophysiological studies often focus on only one or two cortical areas per animal, 2) the position of the external auditory meatus typically limits investigations to the more dorsal fields of auditory cortex, and 3) these studies have traditionally relied on simple acoustic stimuli which may not be well-suited to evoking activity in higher-level cortical areas.

While electrophysiological methods may be limited to dorsal auditory cortex, functional magnetic resonance imaging (fMRI), which has been used extensively with human and non-human primate subjects, provides the ability to observe activity throughout cortex. Recently, fMRI has also been used to image sound processing in the auditory cortex of the cat. Differential patterns of activity have been observed in response to broadband noise and tonal stimuli (Hall et al., 2014). Moreover, responses to pure tones of different frequencies have been employed to illustrate the capacity of fMRI to represent tonotopic gradients in A1, AAF, PAF, and VPAF in accordance with those measured electrophysiologically (Hall and Lomber, 2015). Finally, fMRI has also been shown to be capable of measuring higher-level feature extraction in the cat (Butler et al., 2015). Thus, fMRI is well suited to investigate the function of ventral auditory cortex in the cat, including the ventral auditory field (VAF), insular cortex (IN), and temporal cortex (T). In addition, the present investigation employs a variety of more complex stimuli including conspecific vocalizations, narrowband noise (NBN), frequency modulated (FM) sweeps, harmonics, and broadband noise (BBN) that are better suited to elicit activity from higher-level auditory cortical areas. We hypothesize that these complex stimuli will most effectively activate areas outside of core auditory cortex. Also, static stimuli will be presented with no location information, such that the functional stream dedicated to discrimination or identification, will be preferentially activated.

#### Methods

Ten adult (>6 month) domestic shorthair cats were selected for this project. All animals were housed as a clowder and obtained from a commercial breeding facility (Liberty Labs, Waverly, NY). The University of Western Ontario's Animal Use Subcommittee approved all procedures. All procedures were also in accordance with the National Research Council's *Guidelines for the Care and Use of Mammals in Neuroscience* 

*and Behavioral Research* (Van Sluyters et al., 2003) and the Canadian Council on Animal Care's *Guide to the Care and Use of Experimental Animals* (Olfert et al., 1993).

#### Anesthesia and recovery

Anesthetic and recovery procedures have been reported in detail previously (Brown et al., 2013, 2014; Hall et al., 2014). Briefly, each animal was pre-medicated with an intramuscular injection of atropine (0.02 mg/kg) and acepromizine (0.02 mg/kg), then anesthesia was induced by intramuscular injection of a mixture of ketamine (4 mg/kg) and dexdomitor (0.025 mg/kg). Once anesthetized, the animal was intubated and an indwelling feline catheter was placed in the cephalic vein for the maintenance of anesthesia. Body temperature and vital signs were continuously monitored. Each cat was then placed, in a sternal position, inside a custom made plexiglass apparatus with the head in a custom-built RF coil (Fig. 2). MRI-compatible ear inserts were placed in each ear and the head was stabilized with sound-attenuating foam padding. The animal and apparatus were then inserted into the bore of the magnet. Anesthesia was maintained through continuous administration of ketamine (0.6-0.75 mg/kg/h, i.v.) and spontaneous inhalation of isofluorane (0.4–0.5%). Each session lasted approximately 2 h.

Following each session, anesthesia was terminated and the animal was monitored closely until fully recovered. The cat was then returned to the clowder. Generally, animals exhibited normal behavior within 1 h of anesthesia cessation.

#### Image acquisition

All data were acquired on an actively shielded 68 cm 7-Tesla horizontal bore scanner with a DirectDrive console (Agilent, Santa Clara, California) equipped with a Siemens AC84 gradient subsystem (Erlangen, Germany) operating at a slew rate of 300 mT/m/s. An in-house designed and manufactured 10 cm cylindrical 8-channel transceiver RF coil was used for all experiments. Magnetic field optimization (B0 shimming) was performed using an automated 3D mapping procedure



Fig. 2. Photograph of the eight channel RF coil. The anesthetized animal's head, enveloped in foam to minimize movement and attenuate scanner noise, is inserted inside an eight-channel RF transceiver. The animal is intubated (plastic tube ventral to nose) to permit administration of isofluorane anesthesia.

# (Klassen and Menon, 2004) over the specific imaging volume of interest.

For each cat, functional volumes were collected using a single-shot EPI acquisition with grappa acceleration (R = 3) and the following scanning parameters: TR = 2000 ms; TE = 19 ms; flip = 70°; slices =  $26 \times 1$  mm; matrix =  $96 \times 96$ ; FOV =  $84 \times 84$  mm; acquisition voxel size = 0.88 mm × 0.88 mm × 1.0 mm; acquisition time (TA) = 2 s/volume; BW = 3719 Hz/px. Images were corrected for physiological fluctuations using navigator echo correction. A high-resolution PD-weighted anatomical reference volume was acquired along the same orientation and field-of-view as the functional images using a FLASH imaging sequence (TR = 750 ms; TE = 8 ms; matrix =  $256 \times 256$ ; acquisition voxel size =  $281 \ \mu\text{m} \times 281 \ \mu\text{m} \times 1.0 \ \text{mm}$ ).

#### Stimulus presentation

Eleven stimuli were generated including: four, quarter octave narrowband noises (NBN; Fig. 3A) centered at 1 kHz, 10 kHz, 17 kHz, or 20 kHz; one broadband white noise (BBN; Fig. 3F); two frequencymodulated (FM) sweeps (Fig. 3B), one swept from 1 kHz to 25 kHz (upsweep) and the other from 25 kHz to 1 kHz (downsweep); two conspecific vocalizations of similar duration (Figs. 3C,D) recorded in a sound attenuating chamber from two separate animals who were not participants in the present experiment; and two harmonic stimuli (Fig. 3E), generated using the fundamental frequency from each of the vocalizations (0.75 kHz and 1 kHz) and three additional harmonics. All stimuli, with the exception of vocalizations and harmonics, were presented in 400 ms bursts with a 100 ms gap for the entire (30 s) block. Vocalizations were 750 and 850 ms long which necessitated a slower presentation rate (1 Hz) for the entire (30 s) block. Harmonics were durationmatched to the vocalizations and were also presented at a rate of 1 Hz.

With the exception of the vocalizations, all stimuli were generated using MatLab (MathWorks). All stimuli were presented using custom programming in C + (Microsoft visual studio) on a Dell laptop through an external Roland Corporation soundcard (24-bit/96 kHz; Model UA-25EX), a PylePro power amplifier (Model PCAU11) and Sensimetrics MRI-compatible ear inserts (Model S14). Inserts were calibrated separately to the same sound pressure level, and stimuli were presented diotically. Sound card and amplifier output levels were the same for all stimuli. All stimuli were calibrated to 85 dB SPL using an ear simulator (Bruel & Kjaer, model # 4157), an ear plug simulator (model # DP 0370), and microphone (model # 4134) all mounted on a sound level meter (model #2250).

All scanning was done using the continuous method, which has been evaluated to be more sensitive than sparse acquisition for fMRI of the cat auditory cortex (Hall et al., 2014). A block design (Fig. 4A) was used for all runs using blocks of 15 volumes (Fig. 4B; TR and TA = 2 s) collected every 30 s. Each block of auditory stimulation was interleaved with equal duration blocks during which no stimulus was presented. Thirteen blocks (6 stimuli and 7 baseline; 195 volumes) were collected every run (Fig. 4A). Two stimuli were presented alternately during each run for a total of 3 blocks (45 volumes) of each stimulus per run.

At the beginning of every session a structural MRI was collected followed by two runs using only the BBN stimulus. This enabled online analysis to confirm that the anesthetic depth permitted cortical activity before continuing. Following this, regular runs commenced. Each session included a minimum of 6 runs and 3 sessions were conducted for each animal.

#### Data analysis

#### Pre-processing

Data from each animal were processed and analyzed using SPM8 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK) and MatLab (MathWorks) software. All images were reoriented, corrected for motion (movements in all 6 directions were <0.5 mm) and co-

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Fig. 3. Stimulus spectrograms. Spectrograms for the 1 kHz NBN (A), upward FM sweep (B), each of the vocalizations (C,D), 1 kHz Harmonic (E), and BBN (F) stimuli.

registered to the structural image acquired at the beginning of each session. Data were then normalized to an anatomical template image and smoothed using a 2 mm Gaussian full width at half maximum (FWHM) kernel.

#### Anatomical template

All data were normalized to an anatomical template generated inhouse. A manuscript detailing the specifics of this template is in preparation. In short, 12 feline anatomical scans collected on a 7 T high-field MRI scanner were preprocessed using SPM8 (Wellcome Trust Centre for Neuroimaging, UCL, London) and MatLab (Mathworks) software to



**Fig. 4.** Acquisition design. A) Schematic of the block design. Stimuli were presented in blocks (Stim) interleaved by blocks during which no stimulus was presented (Base). B) Schematic of volume acquisition relative to stimulus presentation. Two blocks, a stimulus presentation (shaded) and baseline (white), are diagramed. Stimuli were presented during acquisition allowing fifteen volumes of data to be collected every 30 s.

align them to a common coordinate system. In a two-phase process, these reoriented images were then normalized and averaged, first to a reference scan chosen from the group, then to the average generated by the first pass processing. Finally, this second pass average was smoothed and provided for group analysis.

#### Regions of interest

Hand drawn (MRIcron, McCausland Center, Columbia, SC) region of interest (ROI) masks were generated to be used during pre-processing and analysis. One ROI mask which encompassed the cerebrum and excluded the skull, soft tissues and cerebellum was generated using the anatomical scan from each animal and scanning session, and for the template to be used for normalization during pre-processing. A second ROI was generated using the anatomical template which encompassed all of auditory cortex. The suprasylvian (ss) sulcus was used as the dorsal and posterior limits of auditory cortex as all thirteen acoustically responsive areas can be found within these bounds (Mellott et al., 2010). The ventral border of the auditory cortex mask encompassed the ventral limits of the suprasylvian sulcus and the anterior and posterior ectosylvian sulci. This ROI was used during data analysis as a mask to isolate activations within auditory cortex. The template was also used to generate an ROI for each of the thirteen auditory areas using a combination of anatomical landmarks and reversals in tonotopic organization, where applicable. The cortical landmarks used have been shown to provide an accurate and stable delimitation of auditory cortical areas, as confirmed by SMI-32 staining (e.g. Mellott et al., 2010; Chabot et al., 2015; Wong et al., 2015). These masks were used during analysis to

examine blood-oxygen level-dependent (BOLD) activity within and between different areas.

#### Data analysis

Data were initially analyzed independently for each animal with motion parameters included in each model as regressors. Models were built using a restricted maximum likelihood (ReML) estimation and a correlational AR(1) model with high pass filter of 128 s. Following model estimation, contrasts were generated for each of the stimuli in individual runs. A cluster forming threshold of p < 0.01 uncorrected was applied initially. Inclusion of an individual animal in further analysis depended on two criteria: 1) at least a single run which produced a cluster of activation passing a familywise error (FWE) threshold of p < 0.05for each of the BBN, harmonics, vocalization, and sweep stimuli and, 2) at least a single run which produced clusters of activation passing a FWE threshold of p < 0.05 for three of the four NBN stimuli. Unlike humans and some other animal species, fMRI in the domestic cat requires that the animal be imaged under general anesthetic. While the drug protocol outlined above has been shown to allow for the observation of stimulus-evoked cortical activity, there are between-animal and between-run effects that may result in the absence of activity in response to a given stimulus. Thus, the above described inclusion criteria ensure that only runs free from such effects were included in the analysis.

In order to make fair comparisons between activations, a single run containing 45 volumes was identified for each animal for each NBN stimulus, to be included in further analysis. For the remaining stimulus categories, individual stimuli did not consistently result in clusters of activity which satisfied the FWE threshold; thus, stimuli were analyzed by category (e.g. vocalizations were combined). Therefore, individual runs for each of the remaining stimulus categories (BBN, sweeps, vocalizations and harmonics) contained 90 volumes of stimulus-evoked data (45 upsweeps + 45 downsweeps, 45 vocalization #1 + 45 vocalization #2, etc.). These runs were then incorporated into a model with all animals for group analysis.

#### Average timecourses

Timecourses for all voxels within clusters passing the FWE (p < 0.05) threshold were extracted. A mean percent signal change (PSC) from baseline was calculated for every volume within a block collapsed across animals and hemispheres. A one-way analysis of variance (ANOVA) and Tukey's honestly significant difference criteria were used to evaluate significant differences from baseline values. This evaluation was performed for every stimulus separately.

#### Average PSC

The average PSC for each animal, cortical area, and stimulus type, was extracted using the MarsBaR (Brett et al., 2002) region of interest toolbox and the individual mask for each cortical area. These numbers were then averaged across animals, a 95% confidence interval was calculated, and a paired t-test was performed to determine significant differences between stimuli within each area. Using the same cortical masks, timecourses for only active voxels across all animals were extracted and average PSC values and block timecourses were calculated.

#### Results

Clusters of BOLD activity in response to NBN, FM sweeps, harmonics, BBN, and vocalizations were analyzed for their strength and location within auditory cortex. It was hypothesized that: 1) areas outside of the presumptive core auditory cortex (A1 and AAF) would be preferentially activated by complex stimuli like vocalizations versus stimuli with fewer complex features; 2) the static stimuli presented will preferentially activate areas that are specialized for auditory identification (presumptive "what" pathway areas) rather than those involved in sound localization ("where" areas); and 3) vocalizations would preferentially activate areas of the auditory cortex that lie ventral to A2.

Individual animals that did not demonstrate clusters of activity which satisfied the FWE (p < 0.05) threshold for at least three of the four NBN stimuli were excluded from further analysis. This standard resulted in four animals being excluded while the remaining six were analyzed further for lateralization of activity, the location of peak activity within the thirteen areas of auditory cortex (Fig. 1A), and the strength of activation within each of those areas.

#### Lateralization

Lateralization of auditory activations, specifically for the processing of speech, has been well documented in human subjects (Hickok and Poeppel, 2015). Previously, lateralization of function in the cat has been technically difficult to analyze because of the inability to assess activity throughout cortex. However, in the present study, analysis of lateralization was made possible as fMRI enables analysis of the whole of auditory cortex, and the addition of a cortical template enables the normalization and analysis of group data.

A contrast for each stimulus was created across all animals against baseline levels. For each stimulus type, this resulted in a single cluster of activity in each of the left and right hemispheres, with the exception of the 1 kHz NBN stimulus which elicited a unilateral cluster of activity in the right hemisphere (Table 1). Most stimuli resulted in a cluster consisting of a larger number of voxels in the left hemisphere. The two exceptions were the 1 kHz NBN stimulus, which elicited a unilateral cluster of activity in the right hemisphere, and the FM sweep stimuli which elicited a greater number of active voxels in the right hemisphere. The statistical strength at the peak voxels within these clusters echoed the results of the cluster size with all but the 1 kHz NBN and FM sweep stimuli showing a left hemisphere bias.

In summary, most cortical activity was lateralized, both in size and statistical strength, to the left hemisphere with the exception of 1 kHz NBN and FM sweeps.

#### Cortical activity

One of the many advantages of fMRI is the ability to observe activation throughout auditory cortex. Previous electrophysiological investigations of auditory cortex in the cat have largely focused on dorsal areas including A1, AAF, PAF, the dorsal zone (DZ), and the auditory field of the anterior ectosylvian sulcus (FAES). The use of fMRI afforded the capability to investigate neural function within all cortical areas.

Across animals, BOLD activity in response to NBN stimuli was observed in both hemispheres except to the 1 kHz NBN stimulus (Fig. 5A). NBN stimuli centered at 1 kHz were only observed in the

#### Table 1

Lateralization of activations. Number of voxels (top) in clusters found in either the left (L) or right (R) hemispheres. Also, T-statistic values (bottom) for the peak voxel in the left or right hemispheres. Blue shading indicates a larger number of voxels or statistically stronger activation in the left hemisphere. Red shading indicates a larger number of voxels or statistically stronger activation in the right hemisphere.

		Narrowband noise				Swoon	Vocal	Uarmonio	DDN
		1 kHz	10 kHz	17 kHz	20 kHz	Sweep	voCal	naimonic	DDIN
Number of voxels	L		596	531	485	183	676	404	397
	R	65	66	385	183	502	112	113	56
Peak T-statistic*	L		9.15	10.89	7.54	8.85	7.05	7.03	7.92
	R	3.77 (0.269)	5.03 (0.001)	7.75	4.72 (0.004)	9.5	5.18	5.25	3.99

\*All statistics have a p-value < 0.001 unless specified otherwise.



Fig. 5. Narrowband noise (NBN) activations. A) 1 kHz (red), 10 kHz (blue), 17 kHz (green), and 20 kHz (yellow) NBN stimuli contrasts across animals. The coronal and axial sections correspond to those indicated in the inset above. White arrowheads indicate the anterior ectosylvian sulcus and posterior ectosylvian sulcus. B–E) Average percent signal change for blocks of each NBN stimulus. Shading indicates significant difference (p < 0.05) from baseline.

right hemisphere in AAF (Fig. 5A). NBN stimuli centered at 10, 17, and 20 kHz elicited bilateral activity with peak activations observed in A1 and along the posterior ectosylvian sulcus (pes) in areas such as PAF and the VPAF. Significantly active voxels were observed in all cortical areas with the exception of the insular (IN) and dorsal posterior ectosylvian (dPE) areas. In addition, a tonotopic progression along the pes was observed (Fig. 5A). Additional, voxelwise analyses were undertaken to better visualize this tonotopy. The auditory cortex mask described above was used to extract the response estimate coefficients for the group-level responses to each of the NBN stimuli. The coefficients for these contrasts were compared, and the frequency to which each voxel was maximally responsive was determined and plotted (Fig. 6B). Additionally, to illustrate the slow progression along the tonotopic axis, the response estimate coefficient of each voxel to the 10 kHz NBN stimulus was subtracted from the 20 kHz stimulus (Fig. 6C). Responses to the 10 kHz NBN are represented at the dorsal and ventral extents of *pes* (the blue patches near the upper and lower limit of the bounding box in Fig. 6B), with higher frequencies represented in between. It should be noted that these illustrations represent data from 4 NBN stimuli (6B; no voxel was maximally responsive to 1 kHz) or a contrast between NBN stimuli centered on 2 different frequencies (6C); while they lack the frequency resolution of typical tonotopic gradients obtained electrophysiologically, the patterns presented are in accordance with well documented patterns observed for abutting cortical fields.

In response to the 1 kHz NBN, average timecourses for all significantly active voxels, across animals were highly variable and were only intermittently greater than baseline activity levels (Fig. 5B). In response to the remaining NBN stimuli, average timecourses for significantly active voxels showed a typical hemodynamic response and were significantly different from baseline (p < 0.05) throughout the block (Figs. 5C–E).



Fig. 6. Voxelwise tonotopic analyses. A) The coronal section from Fig. 5 with NBN response clusters overlaid. The white box in panel A represents the fields surrounding the posterior ectosylvian sulcus, and corresponds to the areas enclosed by the black boxes in panels B and C. B) Map of the frequency band eliciting the strongest BOLD response in each voxel. C) Subtraction map of BOLD responses to 20 kHz and 10 kHz NBN stimuli. Changes toward red indicate increasing dominance of high frequencies.

BOLD responses to FM sweeps, across animals, were robust and bilateral (Fig. 7A). Active voxels were observed in all cortical areas except the most ventral areas: temporal cortex (T), IN, VPAF, or the ventral posterior ectosylvian (vPE) area. Peaks of activity were located on the posterior bank of *pes* in the left hemisphere, and anterior bank of the right hemisphere. The average timecourse for active voxels in response to FM sweeps (Fig. 7B), although at lower percent signal change (PSC) levels than those resulting from NBN stimuli, were significantly different from baseline throughout the block.

Activity in response to vocalizations, across animals, was also bilateral (Fig. 8A). Active voxels were observed in all cortical areas, with no exceptions. Peak activations occurred within the *pes* in the left hemisphere and on the lateral bank of the suprasylvian sulcus (*ss*) in the right hemisphere. The average timecourse for active voxels in response to vocalizations (Fig. 8B) showed low PSC levels but maintained a significant difference from baseline throughout the block.

Activity in response to harmonics, across animals, was bilateral (Fig. 9A). Active voxels were observed in all cortical areas except T and IN. Peaks of activity were observed in the *pes* in the left hemisphere and on the middle ectosylvian gyrus in the right hemisphere. The average timecourse for active voxels in response to harmonics (Fig. 9B) showed low PSC levels, started significantly below baseline level, and took 6 s to rise significantly above baseline, maintaining this level to the end of the block.

Activity in response to BBN across animals was bilateral (Fig. 10A). Active voxels were observed in all cortical areas except IN and the intermediate posterior ectosylvian (iPE) area. The average timecourse for active voxels in response to BBN (Fig. 10B) was only significantly greater than baseline after 6 s but maintained this level to the end of the block.

Average PSC levels across all voxels within each cortical area were calculated for the NBN stimuli. The 1 kHz NBN stimulus was only significantly above baseline levels in AAF (Fig. 11A). The 10, 17 and 20 kHz NBN stimuli were most effective at eliciting activity from A1 and areas along the *pes*, namely PAF, VPAF, and the ventral auditory field (VAF). There were very few significant differences between NBN stimuli within each area. Where significant differences (p < 0.05) did exist within an area, they involved the 1 kHz stimulus.

Average PSC levels across all voxels in each area were also calculated for the more complex stimuli. FM sweeps resulted in the largest average PSC in every area except IN (Fig. 11B), and these changes were significantly greater than those elicited by vocalizations, harmonics, or BBN stimuli in A1, PAF, VPAF, VAF, and vPE. Vocalizations elicited a significant BOLD response in A1, AAF, PAF, VPAF, A2, and FAES. The harmonic and BBN stimuli failed to elicit a signal that was significantly greater than baseline activity in any area.

#### Vocalization specific activation

Within the visual cortex of multiple species, cortical areas have been discovered that appear to be specialized for the identification of faces (Taylor and Downing, 2011). Similarly, cortical fields which process language have been identified in the auditory cortex of humans, and this network appears to be largely lateralized (Hickok and Poeppel, 2015). A homologue of these areas in the cat has yet to be identified and was the focus of the next set of analyses.

In the present study, it was noted that no active voxels are observed in IN except to vocalization stimuli. Area T appeared less functionally specialized, and contained significantly active voxels in response to all stimuli except the 1 kHz NBN and FM sweep stimuli. However, average time courses within area T revealed that vocalizations are the only stimuli for which the BOLD signal remained significantly (p < 0.05) above baseline levels for the majority of the stimulus block (data not shown). The average timecourse in area IN was much more variable than that of T in response to vocalizations (Fig. 12) such that area T was more consistently responsive to vocalizations than IN. It should be noted that Fig. 11B shows a very small mean PSC in both areas IN and T in response to vocalizations. However, both of these ventral auditory fields occupy a large volume of cortex; since Fig. 11 shows the mean PSC across all voxels in a given field, a small but robust response is washed out in these areas.

The harmonic stimuli used in the current study were designed to have similar spectral qualities as the vocalizations, but without temporal variance. Therefore a contrast between blocks of vocalization stimuli and those of harmonic stimuli was performed to elucidate potential cortical areas specific to vocalizations. This contrast resulted in a cluster (p < 0.05 FWE) of 59 voxels in the left hemisphere, at the ventral end of *pes*, which included VPAF and VAF and spread anteriorly across the gyrus corresponding to area T (Fig. 13).

# A. FM Sweep Activations



**Fig. 7.** Frequency modulated (FM) sweep activations. A) Contrast for FM sweep stimuli across all animals. Statistically strongest peak for each cluster is indicated by blue crosshairs for either the left (L) or right (R) hemisphere. B) Average percent signal change for blocks of the FM sweep stimuli. Anterior and posterior arrow heads indicate the anterior ectosylvian sulcus (*aes*) and posterior ectosylvian sulcus (*pes*), respectively. Shading indicates significant difference (p < 0.05) from baseline.

#### Discussion

This current investigation represents the first comprehensive fMRI study to examine responses of auditory cortical areas in the cat to a variety of auditory stimuli ranging from simple noise stimuli to complex conspecific vocalizations. fMRI provides the unique opportunity to gain access to cortical areas that are inaccessible to electrophysiological examination, and the current study extends the functional hierarchy to include the more ventral, higher-level cortical fields. With few exceptions, analyses reveal a general left hemisphere lateralization. While responses to more complex stimuli were also observed, FM sweeps were most effective across auditory cortex. Finally, using a contrast against



# A. Vocalization Activations





**Fig. 8.** Conspecific vocalizations activations. A) Contrast for vocalization stimuli across all animals. Statistically strongest peak for each cluster is indicated by blue crosshairs for either the left (L) or right (R) hemisphere. (Note: the two nodes of activity present in the left hemisphere of the right hand panel are part of a single cluster and are connected in more dorsal slices). B) Average percent signal change for blocks of the vocalization stimuli. Anterior and posterior arrow heads indicate the anterior ectosylvian sulcus (*aes*) and posterior ectosylvian sulcus (*pes*), respectively. Shading indicates significant difference (p < 0.05) from baseline.

frequency-matched harmonic complexes, vocalizations were found to be selectively processed in area T.

#### Cortical lateralization

Within human auditory cortices, lateralization of function, especially with respect to language, is a commonly accepted principle (Hickok and Poeppel, 2015; Kolb and Whishaw, 1996). This lateralization has been attributed to differences in temporal or spectral change (for a review see (Scott and McGettigan, 2013), or attention and sensorimotor interactions (Mottonen et al., 2014), and can be enhanced for self-generated sounds, relative to externally generated stimuli (Reznik et al., 2014). Investigations of lateralization of auditory cortex processing in nonhuman species are limited. Joly et al. (2012) noted that activations in rhesus monkeys in response to intact conspecific vocalizations were lateralized to the right hemisphere. Specifically, lateral belt and parabelt

areas of the right hemisphere. Conversely, scrambled vocalizations were lateralized to auditory cortex in the left hemisphere.

In the present investigation, a cerebral template was used which enabled group analysis across animals as well as analysis of hemispheric lateralization which was not previously possible. It should also be noted that, as described above, ear inserts were calibrated to ensure that stimuli were presented diotically at the same loudness, and images were acquired in the transverse orientation sampling left and right hemispheres simultaneously. Therefore differences in stimulus presentation or slice timing cannot account for the observed lateralization.

Lateralization of function, both in size and strength, was observed for all stimuli in the auditory cortices of the cat. BOLD signals were larger and stronger in the left hemisphere for all stimuli with the exception of 1 kHz NBN, which elicited unilateral activity in the right hemisphere, and FM sweeps which elicited a larger, stronger signal in the right hemisphere.

## A. Harmonics Activations





**Fig. 9.** Harmonics activations. A) Contrast for harmonic stimuli across all animals. Statistically strongest peak for each cluster is indicated by blue crosshairs for either the left (L) or right (R) hemisphere. B) Average percent signal change for blocks of the harmonic stimuli. Anterior and posterior arrow heads indicate the anterior ectosylvian sulcus (*aes*) and posterior ectosylvian sulcus (*pes*), respectively. Shading indicates significant difference (p < 0.05) from baseline.

Stimuli in the current study can be grossly divided into those that change in frequency over time, and those that remain static. For example, the vocalizations employed are comprised of multiple harmonics over several segments including rising and falling phases, similar to formant transitions in human speech, and a plateau (Figs. 3C,D). Additionally, FM sweeps were included which rise or fall in frequency at a fast rate, across a large frequency spectrum (Fig. 3B). Conversely, all NBN (Fig. 3A), BBN (Fig. 3F), and harmonic (Fig. 3E) stimuli used were of constant frequency across their duration. The fact that BOLD activity for FM sweeps was right-lateralized while vocalization-evoked activity showed left-lateralization similar to the static stimuli begs the question — how are FM sweeps unique? While the vocalizations used here do have sweep-like phases, they did not occur at the same rate and do not span the same frequency range as the FM sweep stimuli.

Interestingly, sweep rate and frequency range have been shown to effect lateralization in humans (for a review see Scott and McGettigan, 2013). Thus, it is possible that these factors are also driving the difference in hemispheric lateralization for FM sweeps observed in the present study. Future investigations of lateralization using a variety of rates and frequency ranges, particularly those more closely matched to what is commonly found in vocalizations, would enable a more precise understanding of the contributory mechanisms.

The unilateral, right-hemisphere activity elicited by 1 kHz NBN is not easily interpreted. This stimulus is the same as other NBN stimuli, except that it is centered at 1 kHz. The frequency difference could conceivably result in a variance in lateralization since, unlike the other NBN stimuli, it is within normal vocalization frequency range. However, it cannot account for the unilateral nature of the activation.

## A. BBN Activations





**Fig. 10.** Broad band noise (BBN) activations. A) Contrast for the BBN stimulus across all animals. Statistically strongest peak for each cluster is indicated by blue crosshairs for either the left (L) or right (R) hemisphere. B) Average percent signal change for blocks of the BBN stimulus. Anterior and posterior arrow heads indicate the anterior ectosylvian sulcus (*aes*) and posterior ectosylvian sulcus (*pes*), respectively. Shading indicates significant difference (p < 0.05) from baseline.

#### Tonotopy using narrowband noise

Using pure tones, Hall and Lomber (2015) demonstrated tonotopy within core auditory cortex of the cat, namely areas A1 and AAF, and a weaker tonotopic progression along the *pes* in areas PAF and VPAF. However, it was noted that more complex stimuli were particularly effective at eliciting activation along the *pes*. In the present study, NBN stimuli selectively activated regions along the *pes* enabling tonotopy to be better visualized within PAF and VPAF (Fig. 5). In contrast, tonotopy was not visualized in core areas using NBN stimuli. In combination, these findings echo those from rhesus monkey and human studies that found core areas to be more frequency selective and belt areas more responsive to complex, or behaviorally relevant, acoustic stimuli (Kusmierek and Rauschecker, 2009; Petkov et al., 2006, 2009; Schönwiesner et al., 2014; Woods et al., 2010). Thus, the current study

further supports the claim that areas A1 and AAF form a core auditory cortex similar to that observed in non-human primates. In addition, the tonotopic organization and preference for complex stimuli observed in PAF and VPAF warrant comparison with auditory belt areas in the monkey (Kusmierek and Rauschecker, 2009; Petkov et al., 2006).

#### Vocalization representation in auditory cortex

Cats have a wide variety of vocalizations, used for communication between animals (Boudreau and Tsuchitani, 1973). Similar to human speech, cat vocalizations have components such as sweeps and harmonic stacks (Figs. 3C, D; Gehr et al., 2000). Distinct vocalization differences from individual cats also allow for discrimination between animals. The importance of vocalization in identification and communication



**Fig. 11.** Average percent signal change. A) Average percent signal change across all voxels in an individual area for each of the NBN stimuli. B) Average percent signal change across all voxels in an individual area for remaining stimuli. Error bars are 95% confidence intervals. Horizontal bars indicate where a significant difference (p < 0.05) exists between two stimuli within an individual area.

between individual cats suggests that there would be a subdivision of auditory cortex dedicated to the processing of these stimuli.

In the current study, vocalizations elicited a BOLD response that included much of the bilateral auditory cortices. In both hemispheres, active voxels were found on the middle ectosylvian gyrus including A1, A2, IN, and T, and along the pes including PAF, VPAF, and VAF. However, a contrast designed to identify areas that respond preferentially to vocalizations rather than more generally to stimuli with harmonicallyrelated frequency components demonstrated a focus of activity in area T. Petkov et al. (2008) found similar results using conspecific vocalization stimuli with monkeys, noting activity within auditory cortex corresponding to both core and belt areas as well as activity outside of auditory cortex, in the posterior-parietal cortex of conscious behaving subjects. The pattern of excitation in non-human primates extends to anterior auditory cortex (Petkov et al., 2008). Interestingly, the temporal pole in the cat extends ventrally, while in primates it extends anteriorly; thus the vocal representation in ventral auditory fields of the cat and anterior auditory cortex of the monkey may be well-aligned. Additionally, a region of the insular cortex of rhesus monkeys is also selectively activated by vocalizations (Remedios et al., 2009), providing a neural homologue to similar speech-responsive areas in the human (e.g. Wong et al., 2004). Auditory responsivity of insular areas in cat cortex has not been well studied (but see Hicks et al., 1988), and warrants closer examination in future studies of vocalization-specific responses.



**Fig. 12.** Vocalization timecourses in IN and T. Average percent signal change of active voxels within IN (green) or T (blue) for blocks of vocalization stimuli. Shading in corresponding colors indicates significant difference (p < 0.05) from baseline.





**Fig. 13.** Vocalization and harmonics contrast. Contrast of the vocalization stimuli against the harmonic stimuli. Coronal and axial sections reflect those indicated in the line drawing.

It has been suggested that conclusions regarding the existence of a single vocalization-specific area of auditory cortex should be made with caution as evidence suggests multiple areas working in concert (Bizley and Walker, 2009; Gaucher et al., 2013; Petkov et al., 2008). For example, Petkov et al. (2008) demonstrated that areas outside of auditory cortex become active in response to vocalizations in the macaque brain, indicating more integrative processing. Thus, it is possible that areas within auditory cortex that respond preferentially to vocalizations are, in fact, processing features of more complex acoustic stimuli rather than being specifically tuned to vocal stimuli per se. Consequently, it should be noted that area T, which is selectively activated by vocalization stimuli in the current study, may be processing features present in vocal stimuli rather than the vocalization as a whole.

While fMRI has the ability to examine the entirety of auditory cortex, area IN, located just anterior to T, was difficult to activate using the present methods. While we were able to demonstrate cortical activity across the remainder of auditory cortex using these stimuli, it may be that a particular feature for which IN is tuned was not included. It is also possible that the effects of anesthesia in the current study may be

precluding significant activity in IN. It may be that future investigations using an un-anesthetized preparation may be more successful in recording activity in areas like IN that will be more comparable to that observed in the macaque (Petkov et al., 2008).

#### Hierarchical organization

Electrophysiological and anatomical evidence has indicated that A1 and AAF in cat auditory cortex function at the same level (Figs. 1B, C), similar to core auditory cortex of the monkey (Carrasco and Lomber, 2009a, 2011; Hackett, 2011, 2015; Lee and Winer, 2011; Petkov et al., 2006, 2009). This has also been confirmed recently using fMRI, where activity in response to pure tones was isolated largely within these two areas (Hall et al., 2014; Hall and Lomber, 2015) while BBN-elicited activity was concentrated along the *pes* (Hall et al., 2014; Hall and Lomber, 2015).

Recent anatomical investigations have placed PAF just above core areas of the auditory processing hierarchy (Lee and Winer, 2011) with principal inputs originating from A1, VAF, and VPAF (Lee and Winer, 2008). Results from behavioral investigations using reversible deactivation have indicated that A1 and PAF are functionally tuned for auditory localization (Lomber and Malhotra, 2008; Malhotra et al., 2004; Malhotra and Lomber, 2007). Stimuli in the current study were not manipulated to include changes in localization (diotic presentation results in the perception of sound originating at the midline) and resulted in robust peaks of activation along the "what" pathway proposed by Lee and Winer (2008) as well as in PAF. Anatomical evidence for a connection from AAF to PAF has been noted (Lee and Winer, 2008): thus it appears that PAF may be in receipt of information critical both to stimulus identification and localization. Indeed, a recent investigation presenting conspecific vocalizations to un-anesthetized cats suggested that it would be premature to exclude PAF from pathways involved in auditory identification (Ma et al., 2013). Taken together, the results of Ma et al. and the current study suggest that the position of PAF within the proposed hierarchy is worth investigating further.

The processing of conspecific vocalizations, specifically for identification, has been compared to facial recognition in the visual cortex (Gauthier et al., 2000; Petkov et al., 2008). Cortical areas involved in face perception are at the highest level of the hierarchy within the "what" stream. In the present investigation, T was selectively responsive to conspecific vocalizations. This agrees with the proposed flow of information within auditory cortex of the cat (Carrasco and Lomber, 2011; Hackett, 2011) and confirms the hierarchy proposed by the anatomy (Lee and Winer, 2011).

#### Conclusion

The current study uses non-invasive imaging techniques to examine the functional hierarchy of processing in a well-studied model of auditory perception. Using a variety of simple and complex stimuli, we were able to image activity in areas of cortex that respond poorly to the simple pure tone stimuli employed in a large proportion of the existing literature. Through the presentation of narrowband noises centered on different frequencies, we demonstrate tonotopic activity in cortical areas along the posterior ectosylvian sulcus. Moreover, we provide functional evidence of specialized processing of vocalization in temporal cortex. Collectively, these data provide the first comprehensive view of the functional hierarchy of auditory processing in the cat, bolstering a body of work that has, to date, been limited to anatomical evidence.

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