Anatomical and functional changes of auditory development in cross-fostered rats.

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To test the hypothesis that manipulating maternal experience affects hearing development, we analyzed auditory changes in Wistar rats reared under standard conditions (naïve pups) to rats that were cross-fostered (CF) at postnatal day (P) 5. Micro-CT x-ray scans (MCTS) were conducted to monitor anatomical changes in the inner and middle ear of pups P11-P15. Corresponding functional changes were observed by measuring auditory-evoked brainstem responses of the same pups to clicks of varying intensities. In naïve pups, clearance of soft tissue and the presence of air in the middle ear canal (MEC) are evident at P12 and the ear canal (EC) is completely open by P15 whereas in CF, this process begins at P11 and the EC is open by P14. Growth of the MEC is larger in CF pups at P11 (5.3 ± 0.04 mm), P12 (5.6 ± 0.06 mm), P13 (5.7 + 0.04 mm) and P14 (5.9 + 0.07mm), compared to naïves at P11 (4.95 ± .1 mm), P12 (5.3 ± 0.06), P13 (5.3 ± 0.2mm), and P15 (5.6 + 0.2mm). EC volume was also greater for CF pups at P11 (4.3 ± 2.4), P12 (22.3 ± 0.9 mm), P13 (31.9 ± 2.3 mm), and P14 (38.3 ± 2.5 mm), compared to naïves at P11 (0.03 ± 0.02mm), P12 (3.6 ± 2.3 mm), P13 (15.0 ± 3.5 mm), and P15 (28.2 ± 6.4 mm). Our results show that CF accelerates hearing development in Wistar rats.

A specific deficit in central auditory processing in mouse model of developmental and autoimmune disorders

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Abstract: Language impairments associated with developmental and autoimmune disorders have long been hypothesised to arise from deficits in auditory processing, but this hypothesis remains highly controversial. The BXSB/MpJ inbred mouse strain is a powerful animal model in which to examine the proposed link between developmental and autoimmune disorders and specific, possibly central, auditory abnormalities. Male mice of this strain develop autoimmune disease early in adulthood, and nearly half the animals also have neocortical "ectopias" (nests of displaced neurons in cortical layer I) indicating abnormal thalamocortical development. Although the ectopias are not in auditory cortex, male mice with ectopias have more difficulty perceiving fast sound transitions than their non-ectopic male littermates. The origins of this auditory processing deficit are unknown. Here we show that ectopic male BXSB/MpJ mice have an extremely specific neural processing abnormality in two of the three main auditory thalamic subdivisions. *In vivo* extracellular recordings from auditory thalamic neurons revealed that neural thresholds for detection of a brief gap in noise were significantly higher in ectopic than non-ectopic animals in the ventral and dorsal subdivisions, but not the medial subdivision, of the medial geniculate body of the thalamus. Other auditory thalamic response properties tested were indistinguishable between ectopic and non-ectopic animals, as were electroencephalographic measures of peripheral and brainstem auditory sensitivity. These results indicate that ectopic male BXSB/MpJ mice have a specific deficit in neural processing of brief sound transitions. Moreover, because this deficit was evident in only two out of three auditory thalamic subdivisions, it likely originates within the brain rather than in the ear. The findings therefore suggest that developmental and autoimmune disorders can indeed be associated with abnormalities in central auditory processing, which would not be detected by standard clinical measures of hearing sensitivity.

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Decoding network mechanisms underlying complex sound discrimination using chronometry on trial-by-trial spike-field responses.

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Tonotopic organization (frequencies close to each other being represented in adjacent locations) occurs in the auditory cortices of animals and humans and is hypothesized to be important for feature extraction in complex sounds. How such frequency-specific information is combined to form a coherent auditory percept and in which brain areas such processing takes place, however, is poorly understood. Here, we present a trial-by-trial analysis of neural signals in auditory cortical areas that uncovered components of the network underlying discrimination of complex sounds.

Data collection for the present study involved training adult macaque monkeys to attend to complex auditory stimuli in a task where they were rewarded for correctly discriminating to a pink noise stimulus. Stimuli consisted of pure tones (PT) and a pitch-shifted tonal monkey vocalization (‘Coo’). Single-unit activity (“spikes”) and local field potentials (LFP, low-passed at 200 Hz from raw voltage traces recorded to sort spikes) were simultaneously recorded in primary (“core”) auditory areas and lateral belt areas (secondary auditory cortex), which receive parallel inputs from the ventral and dorsal divisions of the medial geniculate nucleus (Rauschecker et al., 1997).

Using a trial-by-trial probabilistic decoding framework that transforms spike and LFP data having different statistical properties into the space of accumulated log-likelihood ratios where they are statistically equivalent, we computed the onset latency of information arrival and discrimination latency for stimulus specific processing in core and belt areas during presentation of Coo and PT stimuli. The onset latency is the time at which neural activity from stimulus onset in a trial exceeds the ongoing pre-stimulus baseline. The discrimination latency is the time from stimulus onset at which stimulus-specific activity (Coo versus PT) diverges from baseline.

In both areas, mean onset latencies of LFPs (35 ms) preceded spikes (58 ms); however, mean discrimination latencies between spikes (111 ms) and LFPs (121 ms) showed no significant difference. Mean spike and LFP discrimination latencies in the belt areas significantly lagged behind those computed in core areas by 22 ms and 18 ms, respectively. If spikes predominantly reflect output and LFPs input to a recording area, these results indicate that information about the presence of an auditory stimulus (“object”) arrives at the core and belt areas in parallel, whereas coding of stimulus-specific features, as required, e.g., for the discrimination of Coo from PT, involves serial processing from core to belt.

High Gamma Oscillations Reveal Cortical Auditory Processing of Pitch Perturbation in Voice Feedback

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The need for communication has led to the development of vocal production in animals and humans. Conveying vocal messages is strongly dependent upon fine control of the acoustical parameters (e.g. amplitude, frequency etc.) of sounds generated by the vocal apparatus. The auditory system is known to play a key role in online monitoring and control of vocal output. As the neural processes underlying such controlling mechanisms are unknown, it has been proposed that the brain detects and corrects for vocal errors by comparing the auditory feedback from self-vocalizations with an internal representation of the intended vocal output, which is possibly provided by the vocal motor system through mechanisms such as efference copies. In the present study, the neural correlates of audio-vocal integration for voice pitch control are investigated by recording ECoG potentials from a high-resolution electrode grid over the lateral surface of the temporal lobe in response to ±100 cents pitch-shifts in voice auditory feedback from 9 patients (4 left and 5 right hemisphere implantation) who underwent surgical treatment of medically intractable epilepsy. Results revealed that the pitch-shift stimuli elicited AEP and High-Gamma power responses in a limited region over the superior temporal gyrus (STG) in the vicinity of the transverse temporal sulcus (TTS) in both anterior and posterior directions. These responses were stronger during active vocalization compared with the condition in which subjects passively listened to the playback of the same pitch-shifts in their own self-produced vocalizations. This effect is consistent with previous results of single unit recordings in non-human primates and suggests that the activity of the vocal motor system may enhance neural sensitivity to more effectively detect and correct for unexpected changes in voice auditory feedback during vocalization. The vocalization-induced modulation of auditory feedback processing (i.e. enhanced sensitivity) may be an important characteristic of the audio-vocal system to facilitate feedback-based motor control during vocal production and speaking.

Time-dependent consolidation of associative representational plasticity in the primary auditory cortex predicts the behavioral selection of specific sound information to solve an auditory problem.

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Time-dependent processes of memory consolidation strengthen memory and improve behavioral performance. Interestingly, learning-dependent plasticity in primary auditory cortex (A1) satisfies cardinal criteria of neural memory traces: receptive field shifts are associative, rapidly develop, consolidate over hours-to-days and endure (Galvan & Weinberger, 2002; Weinberger, 2007). Moreover, greater induction of plasticity in A1 confers increased strength of memory, *e.g.,* retards extinction (Bieszczad, & Weinberger, 2010; 2012). Such plasticity in A1 is therefore a likely substrate of time-dependent consolidation effects of memory on auditory behavior. Here we determined the effect of tuning consolidation in A1 on the performance of a frequency-discrimination task. Rats implanted with an array of recording micro-wires were trained with two spectrally-distant signal-frequencies (5 vs. 12 kHz) using instrumental reward. The animals exhibited consolidation*, i.e*., better performance immediately after a period of no training. Frequency response areas (FRAs: matrix of neural discharges across acoustic spectrum and level) were obtained daily several hours before training and, critically, after consolidation periods of up to 72 hrs (i.e., without continued training) to determine whether plasticity in A1predicted consolidation-induced increases in discrimination performance. Indeed, FRAs determined after consolidation exhibited responses in A1 that had enhanced the representation of the CS+ relative to the CS- frequency. Remarkably, the extent of the CS specific consolidation effect in A1 predicted the magnitude of behavioral improvement. Overall, the identification of behavioral effects of specific consolidation plasticity in A1 provides an expanded portrayal of cortical representational functions for memory and thus reveals new dimensions of cognitive processes in primary sensory cortex.
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Norm-based coding of voice in human auditory cortex

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Human listeners possess a remarkable ability to distinguish and individuate different voices, exploiting minute inter-individual variations around a generic acoustical structure. The human temporal lobe is known to contain ?temporal voice areas? (TVA) which preferentially respond to vocal sounds as well as areas involved in processing speaker identity cues, yet how different voices are coded within these areas is unclear. Here we show that voices are represented in human auditory cortex as a function of their distance to a gender-specific voice prototype.

Using fMRI in normal adult listeners, we measured activity in the TVA during auditory stimulation with a large number of voices from different speakers. Each voice stimulus was represented as a point in a 3-dimensional ?voice space? (dimensions: f0; formant dispersion; harmonic-to-noise ratio) and its ?distance-to-mean? defined as the Euclidean distance to a gender-specific voice prototype (the morphing-generated average of all same-gender voice).

Across three experiments, we find that activity in a localised region of right mid-STS shows a strong correlation with distance-to-mean. The result was observed both for simple syllables (Exp 1, 3) and for more complex words (Exp 2), and is not simply a consequence of either short-term (trial-to-trial) or medium-term (block-level) neuronal adaptation during scanning.

This result provides important new insight in the neuronal representation of individual exemplars of auditory categories and highlight similarities with coding strategies involved in face processing.

Finding histological correlates of behaviourally-identified tinnitus

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Tinnitus is the perception of sound in the absence of external stimuli, often triggered by exposure to loud noises or ototoxic drugs. Behavioural models of tinnitus have proved essential in furthering our understanding of neural changes that accompany the condition, though they can often be time consuming, so it is desirable to find a reliable alternative marker of tinnitus. We first developed a novel objective test of gap-detection in guinea pigs, hypothesising that if they had tinnitus they would be unable to detect gaps at particular frequencies. We then determined if histological correlates of tinnitus could be found, using expression of the enzyme nitric oxide synthase (NOS) as a marker for damage in the dorsal cochlear nucleus (DCN) and correlating this with our behavioural data.

Following baseline gap-detection testing sessions, guinea pigs were subjected to either unilateral noise exposure or salicylate treatment. Animals exposed to noise were tested for a further 8 weeks before histological staining was performed. Auditory brainstem response thresholds were also recorded in these animals, in order to account for hearing loss when categorising tinnitus. Animals treated with salicylate were tested at 2h and 5h post-injection, and following a 72h recovery period.

Significant behavioural changes were observed as a consequence of administering either tinnitus inducer. 33% of the noise-exposed animals were categorised as having tinnitus. All animals treated with salicylate displayed significant reductions in gap-detection. Significant asymmetries in NOS staining were observed in the noise-exposed tinnitus animals, but not for control or deafened-only animals.

Our novel gap-detection test appears to be a suitable measure for identifying behavioural evidence of tinnitus in both methods of induction. Further to this, long-term asymmetries in NOS expression in the DCN appear to be a reliable marker for noise-induced tinnitus.

Encoding of simple and complex sounds by local field potentials in primate auditory cortex

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Individual neurons in the auditory cortex (A1) frequently exhibit preferred responses to specific pure-tone frequencies (Merzenich & Brugge, 1973). Cells with similar preferred frequencies are generally found in close proximity to one another such that tonotopic organization can be observed at the cortical level. These responses have traditionally been investigated by recording action potentials of single cells. However, recent experiments demonstrate that tuning may be observed within local populations of neurons, as characterized by multi-unit spiking activity (MUA) and local field potentials (LFPs; Kayser et al., 2007; Noreña & Eggermont 2000). These studies have revealed a number of differences in tuning characteristics between LFP and spiking activity, including the degree of tuning, response latency, and tuning sharpness. Although most studies of A1 have been concerned with pure-tone stimuli, this region is also responsive to complex sounds including conspecific vocalizations (Nagarajan et al., 2002; Recanzone, 2008; Syka et al., 2005). Herein, we present an analysis of LFP responses in A1 to a variety of complex sounds. LFPs were recorded at 189 sites in A1 of two awake rhesus macaques. MUA was simultaneously recorded for direct comparison. Auditory stimuli were selected from a diverse collection of sounds including recordings of monkey vocalizations. A set of 72 complex stimuli was created with twelve exemplars from each of the following six categories: conspecific monkey vocalizations, human vocalizations, animal vocalizations, natural environmental sounds, synthetic sounds, and music clips. A wide range of pure tones were first used to determine the preferred frequency of the LFP and MUA recordings. Although evoked responses were greatest for pure tones, significant evoked responses were also observed in the LFP for a wide range of complex stimuli. Indeed, across the population of sites, a greater number of complex sounds elicited a significant response in LFP activity than in the MUA recordings: 98/189 of the LFP recordings, but only 65/189 MUA recordings were responsive to 100% of the stimuli used in this study. In addition, differences in preferred sounds for each measure of neural activity were commonly observed. For example, peak LFP activity was significantly correlated with the peak MUA response at less than half (78/189) of the sites. These findings suggest that complex sounds are well represented by LFPs in A1, and that LFP and MUA measures comprise substantially distinct information. Additional comparisons are made between responsivity to complex sounds in other cortical areas and within A1 across different LFP frequency bands.
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Key words: A1, awake, monkey, multi-unit, neuronal recordings, passive, primary, rhesus macaque, vocalizations

The budgerigar as a model for human detection of tones in noise

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Abstract: Difficulty hearing in the presence of background noise is the most significant problem for people with hearing loss. Identification of an animal model that performs similarly to humans on auditory tasks in the presence of noise will allow both behavioral and physiological investigations of masked detection. Detailed studies of detection of signals in noise have been carried out in humans using reproducible (“frozen”) noises, in which an ensemble of independent gaussian noise waveforms are used as maskers, and variations in hit (i.e., correct detection) and false-alarm rates for different waveforms are analyzed. This approach allows the identification of specific acoustic cues that are involved in detection by making detailed comparisons of predicted performance to actual performance, from waveform to waveform. Behavioral studies in non-human animals have rarely used this approach, focusing instead on average thresholds in random noise. A reproducible-noise study in rabbit showed that results were uncorrelated to human, suggesting that the rabbit uses different, and less effective, acoustic cues to detect signals in noise [Gai et al., 2007, JARO, 8:522-38]. On average, rabbit thresholds were 12 dB higher than human. In this study, thresholds in budgerigar were estimated using a one-interval, two-alternative choice task with a two-down, one-up tracking algorithm. Trials near threshold of multiple long tracks (e.g., 250 trials/track; 100 trials/stimulus, collected over several sessions) were sorted according to stimulus waveform. Hit and false-alarm rates were computed for each of the 25 reproducible masker waveforms in the ensemble. Detection thresholds in budgerigar were only 2-5 dB higher than in human. In contrast to the results for rabbit, reproducible-noise results in budgerigar were significantly correlated to those of human listeners, for both hits and false alarms, and especially for narrowband (100-Hz bandwidth) maskers. These results suggest that the budgerigar and human may use similar cues and information processing strategies for detection in noise. Models have been developed to predict diotic detection of human listeners based on specific cues in the acoustic signals, such as energy, envelope slope and fine-structure cues. These models make predictions that are significantly correlated to the budgerigar results. The models further indicate that, similar to humans, the most important cues for detection are energy and envelope slope. [Supported by NIDCD-R01001641 and NIDCD-R01010813]

Theme and Topic D.02.c. Auditory processing: Temporal, frequency, and spectral processing ; D.02.h. Auditory processing: Perception,cognition, and action

Keyword (Complete): HEARING ; NOISE ; BEHAVIOR

Mechanism of Cortical Encoding of Ultra-Sonic Vocalizations

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Abstract text:

The mammalian brain is specialized for processing of speech and other con-specific vocalizations. However, the neuronal mechanisms underlying this specialization in the central auditory system are poorly understood. To learn how the auditory cortex encodes information about rat con-specific vocalizations, we presented a library of natural and transformed USVs to awake male rats, while recording neural activity in A1 using chronically implants multi-electrode probes. The vocalizations were also presented in transformed form: temporally reversed, dilated or compressed. For responses of each neuron to each stimulus group, we fitted a simple, yet novel predictive model: a generalized linear-non-linear model (GLNM) that takes the frequency modulation and single-tone amplitude as the only two input parameters.

Many neurons reliably and selectively responded to original USVs. GLNM accurately predicted their firing rate. Neurons with high model prediction accuracy were typically tuned to tones in the ultra-sonic vocalization frequency range. However, accurate model performance is also reported for neurons that were tuned to lower frequencies, pointing to both classical and extra-classical receptive field contributions to their responses. A1 neurons exhibited specialization for USVs, as evidenced by the finding that the model prediction accuracy was lower for transformed, rather than original vocalizations. The mean firing rate was not affected by the transformations of the stimulus. Our study suggests that A1 uses a specialized neuronal circuit for processing USVs, tuned to temporal statistics of the natural vocalizations.

Frontal eye field may be “read out” differently for auditory vs. visual saccades

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Saccades to purely auditory targets are similar to those evoked by visual stimuli, which suggests that they may by generated by a common underlying neural mechanism. The Frontal Eye Field (FEF) has been implicated in the control of visual and visual-memory guided saccades, and is known to have auditory activity (Russo and Bruce, J Neurophys. 1994). However, we have previously shown that the FEF’s auditory activity is encoded in a hybrid reference frame (mix of head- and eye-centered information) that may be unsuited to controlling accurate auditory saccades (Caruso, Pages, Groh, SFN 2011).
Here, we used microstimulation to probe whether and when FEF activity contributes to the computation of saccade vector on auditory trials, and whether this “read out” is different from visual trials. On each trial, a visual or an auditory target was presented to the monkey. During the reaction time to generate the saccade, a supra-threshold electrical stimulation train was delivered to the FEF. The timing of this train was varied between zero and the average saccade latency to an auditory or visual target.
On visual trials, the saccade evoked by stimulation was affected by the location of the visual target consistent with a weighted averaging of the saccades between the target and the movement evoked by stimulation alone. The visual saccade vector was progressively weighted more in comparison to the electrically-elicited saccade as the latency of the stimulation-evoked “combined” saccade approached the latency of purely visual saccades (measured on the same task but with no electrical stimulation). In contrast, on auditory trials, saccades evoked by stimulation showed little to no contribution of programming of the impending auditory saccade. These findings suggest that FEF may contribute differently to auditory saccades than to visual saccades, even though such saccades are similar to visual saccades in metrics and kinematics.

An adaptive stimulus search method for rapid characterization of multidimensional receptive fields in auditory cortex of awake animals.*

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Primary auditory cortex (A1) neurons are tuned to a wide variety of acoustic features, from pure tone frequency to the patterning of complex vocalizations. Studies of sound coding are hampered by the inability to densely sample a comprehensive stimulus space within the timeframe of a typical recording session. As a result, tuning estimates are often derived from a predefined stimulus library, which may encompass only a fraction of a neuron's receptive field. Further, these libraries tend to vary in only one or two stimulus dimensions, leaving other relevant parameters at fixed, predetermined values. Here we describe a closed-loop adaptive search method that probabilistically alters stimulus presentation based on real time changes in neural firing rate in order to focus on high-response regions of an *n*-dimensional stimulus space. The adaptive search method was tested with recordings from chronically implanted tungsten microwires or multichannel silicon probes in A1 of awake mice. We tested two search algorithms (a genetic algorithm and a local clustering algorithm) in a five-dimensional stimulus space where carrier frequency, spectral bandwidth, level, amplitude modulation frequency, and spatial location all covaried, yielding a library of roughly 200,000 potential stimuli. Both algorithms began with 50 randomly selected stimuli and were able to converge on effective regions of stimulus space within six iterations (roughly 10 minutes). There was a high degree of concordance between independent runs of the procedure. The results of the adaptive search method were compared with well-tested approaches to representing stimulus-response relationships, such as frequency response areas, spectrotemporal receptive fields, and responses to conspecific vocalizations. This approach reduces the number of stimuli needed to densely probe an auditory receptive field while remaining sensitive to potential sparsity or nonlinearity in the neural response.

Bridging the gap: magnetoencephalography in guinea pig reveals rapid auditory cortical adaptation to stimulus statistics

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Sensory neural adaptation to stimulus statistics is observed in both humans and animals, but differences in measurement techniques often impede direct comparisons. Here we use small-animal magnetoencephalography (MEG) to show that stimulus-specific adaptation of auditory cortical responses in guinea pig resembles that observed using the same non-invasive neural measurement technique in human studies. We recorded MEG activity in guinea pigs during presentations of repeated tone pips with rare transitions between tone frequencies one octave apart. Tone-evoked MEG waveforms differed between animals, but deflections were consistently observed at 20, 50 and 150 ms latencies. Following tone frequency transitions, the amplitudes of these MEG waves showed rapid adaptation, which appeared to be largely complete after the second tone. The magnitude of adaptation was greater for the guinea pig M50 than for the other waves, and was maximal when inter-tone intervals were short but the number of tones between frequency transitions was large. This pattern of adaptation resembles that observed for the mismatch negativity which occurs in humans following changes in stimulus statistics. We also report more sophisticated forms of adaptation, similar to those observed in humans; for example, guinea pigs show MEG responses to the unexpected omission of the second tone in a tone pair. In the long term, joint MEG and electrophysiology in the same animals will allow us to elucidate the neural basis of auditory MEG responses, bridging the gap between human brain imaging and invasive animal electrophysiology.

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Behavioral correlates of auditory-object processing in rhesus macaques

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The basis of auditory perception is the grouping and segregation of regularities in the environment to form auditory objects. Understanding the processing of auditory objects is a central question in auditory perception. However, the study of auditory-object processing is complicated because generally, different perceptions are evoked by having different stimuli, thus changes in acoustics are strongly coupled to changes in a listener's reports. Fortunately, the 'galloping tones' stimulus allows acoustics and behavioral reports to be decoupled. The galloping tones stimulus is a series of two alternating tones; systematic changes in the frequency separation, intertone-interval, listening duration and temporal overlap cause changes in a listener's behavioral report. Specific manipulations of listening duration and frequency separation elicit different perceptions from the same acoustic stimuli. This type of stimulus is referred to as a 'bistable' stimulus. Behavioral performance on this task is well-described in humans, but not in any other animal species. Here, we trained rhesus macaques to perform a one-interval, two-alternative forced-choice version of the task in which they indicated whether they heard one or two auditory objects. Manipulations of listening duration, frequency separation and temporal overlap between the tones yielded behavioral responses similar to those observed in humans, suggesting that monkeys solve the galloping tones task in a manner consistent with human listeners. These behavioral data will allow further investigation into the neural mechanisms underlying auditory-object processing.

Activity of Neuronal Ensembles during the Development of Hearing: evidence for clusters of co-active neurons in the auditory brainstem of rats.

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BACKGROUND: Before the onset of hearing, cells in the auditory brainstem exhibit spontaneous patterns of electrical activity that originate in the cochlea (Tritsch *et al.*, 2010). However, little is known about patterned activity in ensembles of auditory neurons.

HYPOTHESIS: Based on our previous single cell recordings we hypothesized that groups of co-active neurons would be observed independently in high- versus low frequency regions of a developing tonotopic map.

APPROACH: We used silicon probes to record multi-unit activity simultaneously across sixteen distinct locations in the auditory brainstem of anesthetized rat pups between birth (P0) and P17. We also performed in vivo whole-cell recordings to examine subthreshold activity in anatomically identified auditory brainstem neurons.

RESULTS: Multi-unit activity recorded in low-frequency regions showed average firing rates between 1 and 24 Hz, whereas electrodes placed in high-frequency regions showed average firing rates of less than 5 Hz. This result suggests that cells switch between spiking and silent modes, and/or comprise mixtures of spiking and silent (non-spiking) cells. Using *in vivo* whole cell recordings we confirmed that 50% of recorded auditory brainstem neurons were silent cells. We did not observe cells switching between spiking and silent modes. Lastly, we performed cross correlation analysis and identified 10-30 ms correlations between nearby electrodes (50-100 um), but not between farther electrodes (>500 um).

CONCLUSIONS: Our results suggest that spontaneously co-active cell clusters in the auditory brainstem are not independent across the tonotopic map. We are currently exploring ways to record from awake pups and to perform high-density recordings to look at synchronous firing within clusters of co-active neurons.

Changes in neural activity and nitric oxide synthase distribution in an animal model of tinnitus

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Subjective tinnitus affects 10-15% of the UK population and can lead to severe distress in some cases. Animal models of tinnitus allow correlations between changes in neural activity in the auditory system, induced by acoustic trauma, and objective behavioural measures of tinnitus.

Guinea pigs (GPs) were subjected to unilateral noise trauma and tested behaviourally for the presence of tinnitus over an 8-week period. Hearing status was assessed using auditory brainstem responses. The animals were then anaesthetised, and spontaneous firing rates (SRs) and frequency-response areas were measured for single-units in the inferior colliculus (IC). Subsequently, we examined changes in nitric oxide synthase (NOS) expression histologically in the cochlear nucleus of the same animals. For practical reasons, it was not possible to examine both in the same auditory nucleus.

SRs were elevated in the IC of noise-exposed GPs, compared with controls, although no trend was apparent with regard to characteristic frequency. Using rigorous criteria for assessing the presence of tinnitus that eliminated GPs with any substantial asymmetric hearing loss, we found a significant left-right asymmetry in NOS staining in the cochlear nucleus of animals with tinnitus, compared with control animals and animals that had a hearing loss but no behavioural evidence of tinnitus.

These data support previous work showing elevated SRs in the IC following acoustic trauma. Moreover, our data show a marked, sustained change in NOS activity (an enzyme associated with pathological signalling) in the cochlear nucleus in GPs with tinnitus. Nitric oxide may play a role in post-acoustic trauma pathology in the cochlear nucleus: a structure that according to previous reports acts as a ‘trigger zone’ in driving tinnitus-related hyperactivity in higher auditory centres.

Breaking down the Cortical Representations of Speech in LFP and MUA

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The neural coding of sound in auditory cortex has been investigated extensively using various neural measures, including multi-unit activity (MUA), local field potential (LFP), and magneto-/electroencephalography (MEG/EEG). These measures reflect neural activity at different spatial scales and are available from different experimental populations, e.g. animal models, epileptic patients, and healthy human subjects. Although these neural signals are complementary, their results are difficult to bring together, since the functional relationship between them is still poorly understood. In fact, response properties measured from these signals, such as latency and the upper frequency limit of phase locking, are often not consistent with each other.

This study characterizes and compares the cortical representation of speech in MUA, high gamma power, and low-frequency phase-locked LFP. Recordings were made using high impedance electrodes in the primary auditory cortex (A1) of awake ferrets. All neural signals were analyzed under the unified framework of the spectro-temporal receptive field (STRF). Several consistent results were found. (1) STRFs estimated from MUA decay within 50 ms, whereas those estimated from phase-locked LFP last more than 100 ms, which may explain the long latency responses found in MEG/EEG studies. (2) STRFs are very similar whether measured by high gamma power or MUA. (3) Phase locking to the fast modulations of speech (70-200 Hz) is strong for LFP measures, but very weak in the corresponding MUA measures. (4) The neural tracking of fast modulations in LFP is largely independent of the neural tracking of slow modulations (<50 Hz).

These results suggest that neural signals in auditory cortex can be attributed to two major processes. The high gamma power is closely related to MUA and spiking within the local region. The phase-locked LFP contains several separated components, probably reflecting contributions from both thalamic and cortical inputs to A1.

Auditory Feature-Selective Attention in Rhesus Macaques

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Selective attention to auditory features constitutes a critical skill for animals in noisy environments. Most research into auditory selective attention in rhesus macaques has focused on attention to features between spatial locations or between sensory modalities. Thus, how rhesus macaques attend specific acoustic features within the same acoustic stream and how their performance on such tasks compares to humans remains largely unknown. Investigating such operations in rhesus may provide insight not only into the perceptual capacities of this species, but also into their cognitive abilities. In the present study, humans (n = 3) and rhesus macaques (n = 2) were cued to selectively attend one of two features (amplitude-modulation or bandwidth of carrier) within the same auditory object (a noise carrier presented from a single speaker) and to report the presence of the cued feature in a 2-alternative forced choice task. Performance, as measured by perceptual thresholds and reaction time, suffered for both humans and macaques when both the cued and non-cued features were present, but disproportionately more for macaques.

Functional characterization of auditory processing in the songbird forebrain

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In order to communicate vocally, songbirds must detect and comprehend complex acoustic features in song. Neurons in the primary auditory nucleus of the zebra finch, field L, specialize in extracting complex auditory features such as fast temporal envelope changes, harmonic structure, and changes in pitch. We used electrophysiology and immunohistochemical techniques to determine the inhibitory network roles and connections of field L neurons that select for different acoustic features. Juxtacellular recordings were made in an in vivo anesthetized preparation during presentation of conspecific song. After sufficient responses were obtained to calculate spectrotemporal receptive fields (STRFs), injections of depolarizing current filled the recorded cell with Neurobiotin from the patch electrode. Double fluorescent labeling of the Neurobiotin and an antibody for glutamic acid decarboxylase (GAD) allowed us to trace projections in some cases, and to determine that 10 of 19 recovered auditory cells were GABA-ergic. Neurons' STRFs showed a variety of tuning, which should be useful in distinguishing recognizable features of different individuals' songs. We hypothesize that uneven distribution of tuning across morphological types and anatomical locations within field L contributes to parallel pathways dedicated to processing distinct categories of auditory features. Some underlying circuits should serve song perception during social behaviors.

Online adaptive stimulus design for studying non-linear spectral integration of neurons in auditory cortex

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Neurons in primary auditory cortex (A1) have selectivity to spectral contents of complex sounds due to the non-linear interaction of excitatory and inhibitory inputs. Such stimulus selectivity is difficult to characterize using linear estimation methods or responses to simple stimuli like tones or two tones. Searching for preferred stimuli of cortical neurons has also proven challenging because of the high dimensionality of the acoustic space of possible stimuli and limited recording time. Here we present an online adaptive stimulus design approach based on neural network models. In our study, we used feed-forward network models with five subunits to approximate the computation of cortical neurons. Those subunits represented potential excitatory and inhibitory synaptic inputs. We recorded single neuron activities in A1 of awake marmosets (*Callithrix jacchus*). Stimuli were generated adaptively to optimize the parameter estimation of the hypothesized models based on the recorded firing rates from previous stimuli. In order to test whether our online models could account for the complex neural responses to various stimuli, thirty stimuli were picked from randomly generated 1,000,000 stimuli with different spectral profiles. Neural responses to those stimuli were recorded and compared with the predicted responses from the models. Our results showed that the optimal design algorithm can use less than 300 stimuli for estimating the parameters of the neural network. The models can potentially predict firing rates of various neurons. Our preliminary data also suggest that A1 neurons could have different selectivity to spectral profiles even if their single tone responses show similar frequency preferences.
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Modeling the Mismatch Negativity (MMN) in Primary Auditory Cortex of the Awake Monkey

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The mismatch negativity (MMN) is a scalp-recorded, pre-attentive component of the auditory event-related potential that is elicited by a change in a repetitive acoustic pattern. While the MMN has been extensively utilized in human electrophysiological studies of auditory processing, the neural mechanisms and brain regions underlying its generation remain unclear. Here we investigate possible homologues of the MMN in macaque primary auditory cortex (A1) using a frequency oddball paradigm in which rare 'deviant' tones are randomly interspersed among frequent 'standard' tones. Standards and deviants had frequencies equal to the best frequency (BF) of the recorded neural population or to a frequency that evoked a response half the amplitude of the BF response. Early and later field potentials, current source density components, multiunit activity, and induced high gamma band responses were larger when elicited by deviants than by standards of the same frequency. Laminar analysis indicated that differences between deviant and standard responses were more prominent in later activity, thus suggesting cortical amplification of initial responses driven by thalamocortical inputs. However, unlike the human MMN, larger deviant responses were characterized by the enhancement of 'obligatory' responses rather than the introduction of new components. Furthermore, a control condition wherein deviants were interspersed among many tones of variable frequency replicated the larger responses to deviants under the oddball condition. Results suggest that differential responses under the oddball condition reflect stimulus-specific adaptation rather than deviance detection per se. We conclude that neural mechanisms of deviance detection likely reside in cortical areas outside of A1.

NEURODYNAMIC PREDICTIONS OF MUSICAL TONALITY PERCEPTION

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Music, like language, is universal to human culture, and different musical languages are learned through enculturation. A defining aspect of a musical language is its tonality, which includes choices of musical pitches and perceptions of their relative stability. In a melody, for example, a subset of possible pitches is used, and some pitches are perceived as more stable than others. Within a tonal system, stability relationships are generally thought to be idiosyncratic, and learned based on statistical regularities within that system. This approach does not explain invariant patterns of perceived stability that have been observed cross-culturally, however. We test the predictions of a dynamical model of central auditory physiology, in which mode-locking results from nonlinear interactions between stimulus frequencies and intrinsic oscillatory neural dynamics. Mode-locked states are stable over resonance regions known as Arnol'd tongues, which depend on frequency relationships. Here we used the stability of mode-locked states to predict perceived stability of musical frequencies within North Indian tonal contexts. We compared the model's predictions to ratings of stability for ten ragas by both Indian and Western listeners. The neurodynamic model was able to predict the behavioral ratings for listeners of both cultures, and provided a significantly better fit to the ratings than duration statistics. These findings show that oscillatory auditory dynamics predict observed invariant patterns of perceived pitch organization across cultures.

Human depth electrode recording of auditory cortex responses to different pitch classes

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We sought common mechanisms for human pitch analysis by recording evoked and induced local field potential activity along Heschl's gyrus (HG) in response to three sounds associated with pitch. Data were recorded from fourteen high-impedence contacts. Each stimulus type (regular interval noise (RIN), harmonic complex (HC), click train (CT), 1/f spectrum, 1-4kHz) was presented at a rate below the lower limit of perceived pitch (20Hz) and at a rate that evokes a strong pitch percept (250Hz). A Gaussian noise served as control. Stimuli were randomly presented as part of a complex of 0.5s noise, 0.9s of RIN or HC or CT, 0.5s noise followed by 1.7s of silence.

Evoked responses were asymmetrical in time in that the transition responses from noise to both 20-Hz and 250-Hz pitch stimuli were larger than the responses from pitch to noise. All of the pitch-associated stimuli showed an induced response in the gamma range (30 – 200 Hz for 250-Hz RIN, 30 – 200 Hz for 250-Hz HC, 30 – 200 Hz for 250-Hz CT) with a latency of approximately 70 ms. Pitch-associated gamma responses occurred across HG, but were more pronounced at lateral HG electrodes. Sustained gamma (30-200Hz) responses to the 250-Hz RIN occurred in middle to lateral HG contacts but not to 20-Hz RIN. Sustained responses to the other pitch associated stimuli were weak or non-existent.

These data are consistent with previous work in which both early and late gamma responses were seen in medial and lateral HG to RIN in the pitch range [Griffiths et al, 2010]. A common gamma response across different pitch exemplars in the pitch range is seen for the early but not the late gamma response.

TD Griffiths, S Kumar, W Sedley, KV Nourski, H Kawasaki, H Oya, RD Patterson, JF Brugge, MA
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Differential Modulation of Perceptual Acuity by Coarse and Fine Discriminative Auditory Fear Conditioning

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Learning the emotional value of a specific sensory stimulus affects how similar stimuli are perceived. Reinforcing a stimulus with a reward in a discrimination task typically improves discrimination. However, the attachment of negative emotional value to a stimulus has been shown to lead either to generalization or sharpening of perceptual acuity. These opposing effects have not been measured in the same model system, and the neuronal mechanisms underlying them are not known. We hypothesized that coarse discrimination learning leads togeneralization whereas precise discrimination learning leads to sharpening of acuity. To test this hypothesis, we used discrimination auditory fear conditioning (DAF) of various precision to train mice to associate one of two tones (CS+ and CS-) with a negative reinforcement. Under coarse DAF, frequencies of CS+ and CS- were one octave apart, whereas under fine DAF, the difference was 15%. While subjects readily learned the coarse DAF task, only 50% of them learned the precise DAF (“learners”). To measure perceptual acuity, we established frequency discrimination threshold around the CS+ frequency derived from pre-pulse inhibition (PPI) curve before and after each fear conditioning session. As we hypothesized, for both learners and non-learners, coarse DAF led to decreased acuity. In contrast, for learners, fine DAF induced sharpening of acuity. Non-learners retained the already elevated discrimination threshold. We next tested whether the auditory cortex modulates changes in perceptual discrimination during PPI. We bilaterally and reversibly inactivated the auditory cortex by injection of fluorescent muscimol during PPI. While inactivating the auditory cortex did not affect learning in both coarse and fine DAF, the effect of fear on perceptual acuity was completely abolished after both DAF sessions. Our study demonstrates that precision of fear discrimination learning and the level of its success regulate perceptual acuity. Furthermore, this regulation is mediated by the auditory cortex during the perceptual read-out.

Bayesian modeling of human performance in an auditory-categorization task

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Categorization is a natural and adaptive process that is seen in all animals. That is, despite a great deal of variability within and across stimuli, animals typically ignore some sources of variation while treating others equivalently. The categorization process is complicated by the fact that (1) animals have to generalize over a large stimulus space to tolerate multiple category exemplars, and (2) a stimulus' category membership can be "ambiguous" since it can belong to multiple categories with overlapping boundaries. The mechanisms by which animals resolve these complications are not fully understood. Using auditory stimuli, we tested how asymmetric prior probabilities for a stimulus' category membership affected a listener's decisions on the categorization of a stimulus. Next, we tested whether the listener's performance matched the behavior of different Bayesian ideal categorization models.

Stimuli were pure-tones chosen from a continuous range of frequencies (500-5550 Hz), with the lower (log) 2/3 of this range assigned to one category ("A") and the upper (log) 2/3 assigned to a second category ("B"). Thus, each category had a frequency range that was unique to each category and a range that overlapped with both categories. Category priors across their respective frequency ranges were box-shaped such that all tones within a category were equally likely. Category prior probabilities were manipulated by varying the number of trials that presented a tone originating from either category A or B. Subjects performed 3 blocks of a 2-alternative forced choice experiment, with each block of trials having a different prior probability for category A [p(A) = 0.25, 0.5, or 0.75]. After hearing a tone, subjects reported the category membership of the stimulus with a gamepad. Subjects received feedback regarding their decision.

Our results demonstrated that increasing the category prior p(A) led to an increased bias toward selecting category A. While this result was consistent with a Bayesian model, a more detailed analysis suggested that subjects were not able to learn the exact shape of the prior distributions. As a result, a Bayesian model with the assumption of Gaussian priors for categories A and B was also compared to subject performance. These findings offer insight into how the auditory system may represent prior information and solve probabilistic inference tasks.

Age-related effects of NADPH diaphorse and parvalbumin expression in the rhesus macaque superior olivary complex

D.T. Gray, J.R. Engle, A. Petrovska, M.M. Stewart, G.H. Recanzone

Positive immunoreactivity to the calcium binding protein parvalbumin (PARV), and the nitric oxide synthase molecule NADPH diaphorase (NADPHd) is well documented within the central auditory system of both rodents and primates. These cell types are thought to play a role in the regulation of auditory processing at various nuclei in the ascending auditory pathway through their roles in the control of GABAergic and glycinergic inhibitory mechanisms. Studies examining the changes in expression of these cell types with age have been conducted primarily in rodent models, but are sparse in primate models. In the brainstem, the superior olivary complex (SOC) is crucial in the computation of sound source localization in azimuth, and one hallmark of age-related hearing deficits is a reduced ability to localize sounds. In order to define the density of these cell types in the SOC as a function of age and hearing sensation, we studied seven rhesus macaques ranging from 12 to 35 years of age. Animals were anesthetized and auditory brainstem responses (ABRs) were obtained for clicks and 0.5, 1, 2, 4, 8, 12 and 16 kHz tones. Detection thresholds were defined as the intensity at which ABR waves II or IV were no longer apparent. These same animals were then euthanized within 6 months of the testing and the brainstems sectioned at 25 – 50 microns and stained for PARV and NADPHd. Reactive neurons in the three nuclei of the SOC were counted in all animals and the density of each cell type calculated. We found that PARV expression increased with age and click ABR threshold in the medial superior olive, whereas NADPHd expression increased with the same two variables in the lateral superior olive. The medial nucleus of the trapezoid body showed no significant changes in the expression of these neurochemical markers with age, but did as a function of click threshold. All three nuclei increased their expression of both these neurochemical markers as a function of middle frequency ABR thresholds (4 – 8 Hz), but not at low (0.5 – 2 kHz) or high (12 – 16 kHz) frequency ABR thresholds. Together, these results suggest a possible compensatory mechanism at the chemical level employed in the SOC to combat the loss of efficacy of auditory sensitivity in the aged primate.

Keywords: monkey, nitric oxide, calcium, geriatric,brainstem

Concurrent electrical microstimulation of vocalization producing areas in anaesthetized guinea pigs

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Guinea pigs are gregarious animals with a well-characterized repertoire of about 11 vocalizations. These often accompany particular behaviours and communicate information about identity and emotional state. Vocalizations have previously been produced by electrical stimulation of at least three areas in the guinea pig brain but the call types have not been properly analyzed and we wanted to learn more about how the different areas interact in producing a call. Animals were anaesthetised with urethane supplemented as necessary by a mixture of ketamine/xylazine. Areas were stimulated using pairs of glass-coated tungsten electrodes (1 ms, 40 – 600 µA square wave pulses at 60 Hz for 1.6 s). Five areas produced calls: the anterior cingulate cortex, medio-dorsal thalamus, hypothalamus, amygdala and the midbrain periaqueductal grey substance. Eight distinct calls were defined using SAS Lab Pro (Avisoft Bioacoustics). The structure of the calls was very similar to those from spontaneously vocalizing animals from the same colony. Five of the calls were produced during the pulse train and three were produced after the end of stimulation. The during-stimulus calls were produced from discrete loci of diameter 0.2 - 0.5mm.

The post-stimulation calls were either series of screams that gradually changed to squeals (which faded away over a period of up to 30 s) or, less frequently, a series of tooth chatters (a labile call from small, discrete loci). By contrast, scream/squeal calls were produced over widely dispersed locations in all five of the brain areas. High currents gave between 1 and 8 screams, followed by a regular series of squeals. Lower currents only produced the series of squeals. To investigate the interactions between areas we stimulated pairs of areas in various combinations and found that bilateral stimulation of scream/squeal areas always had an additive effect such that the call was stronger than when stimulating either area alone. By contrast, stimulation of two areas giving during-stimulus calls was more complex. For example, stimulation of hypothalamus and amygdala gave chutter and whine respectively, whereas concurrent stimulation of both areas gave only the hypothalamic chutter.

The long duration of the scream/squeal series and the fact that the same post-stimulation call series was produced by all the brain areas implies that each feeds into a shared system of excitatory re-entrant loops that are involved in call generation. Study of the interactions of the areas producing during-stimulus calls has provided some insight into call production pathways but further work is needed.

Slow frequency modulation entrains neural delta oscillations and determines human listening behavior

Molly J. Henry & Jonas Obleser

Environmental rhythms, such as those inherent in the speech signal, are thought to provide a pacing signal for neural oscillations in a number of frequency bands. In the current study, we investigated whether, independent from amplitude envelope changes, neural entrainment to slow frequency modulations might provide a mechanism by which a listener can become prepared to optimally process important acoustic cues. In a human EEG experiment (N=12), 10-s 3-Hz frequency modulated (FM) stimuli containing individually-thresholded gaps were presented. Critically, gaps were placed uniformly with respect to the phase angle of the 3-Hz driving oscillation. If human delta oscillations entrain to frequency modulations, then the delta excitation–inhibition cycle should accordingly affect listeners' preparedness for detection of near-threshold gaps. Indeed, ongoing delta oscillations were entrained by the 3-Hz FM signal. Moreover, all listeners showed a modulation of detection performance by stimulus phase, but there was no consistent preferred stimulus phase across listeners. Instead, differences in detection performance were predicted best by the phase angle of the ongoing delta oscillation. Thus, 3-Hz brain phase at target time was consistently related to gap detection, and moreover predicted the amplitudes of the auditory evoked responses to gaps. The results demonstrate that ongoing brain oscillations entrain to slow frequency modulations with rates in the range of prosodic variations. Moreover, behavioral and electrophysiological responses to to-be-detected events embedded in the modulated signal are determined by the phase of entrained delta oscillations at the time of gap occurrence. This suggests that slow frequency variations in the auditory signal may entrain ongoing brain oscillations of the listener, thereby allowing alignment of optimal delta phase with the predicted time of occurrence of important acoustic cues.

Detection of Tone in Noise in Rat Auditory Cortex

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Sounds in natural settings always appear over a noisy background, and the way the auditory system extracts sounds from such backgrounds is of extreme importance both theoretically and practically. The masked threshold (lowest level at which the presence of a tone can be detected in the presence of a masker) increases with noise level. Such results can be explained by energy masking in the peripheral auditory system: once the signal-to-noise ratio within the critical band centered at the target tone frequency is large enough, the tone is detected. However, when additional information is supplied to the auditory system, for example by slowly modulating the masker over a wide frequency range or adding a co-modulated sideband, masked thresholds can be reduced substantially below the values expected from pure energy masking. We have previously demonstrated correlates of the reduction in masked thresholds for tones in modulated maskers (comodulation masking release, CMR) in the neuronal responses of cat auditory cortex (Las et al. 2005).
Here we are using intracellular recordings *in vivo* in rat auditory cortex in order to study neuronal responses in the auditory cortex to tones masked by broadband noise or by slowly fluctuating broadband noise maskers. We characterized the responses of neurons in auditory cortex to pure tones, broadband maskers, amplitude-modulated broadband maskers, and narrowband maskers with and without comodulated side bands, as well as their combinations with tones of varying levels. The main effects of noise on tone responses are consistent with energetic masking. While we found release from masking when using modulated broadband noise maskers compared with unmodulated noise maskers, we did not observe in the rat the 'hypersensitive locking suppression' observed in cat intracellular recordings, possibly because the locking of the neuronal responses to the amplitude modulation pattern was weak.

Interaural Level Difference tuning in auditory cortex of the human and the rat

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Sound level disparity at the two ears caused by the shadow of the head is one of the primary cues for horizontal sound localization. Sensitivity to this interaural level difference (ILD) is initially observed from the lateral superior olive, and throughout the auditory pathway. Current views of how ILD is encoded and the contribution of each structure in the auditory pathway are limited by the techniques and species being studied. For example animal cortical responses can be mapped with high spatial and temporal precision using penetrating electrode techniques, whereas human studies typically rely on noninvasive techniques such as functional magnetic resonance imaging (fMRI). Here we present a comparison of cortical ILD sensitivity between electrophysiological, intrinsic optical, and fMRI-based estimates of neural population responses. Three types of data were compared: (1) multiunit electrophysiological recordings from layer IV of rat auditory cortex (AC); (2) intrinsic optical imaging of rat AC; and (3) stimulus-parametric fMRI of Human AC. Across both species and techniques a similar hemispheric lateralization was observed, where the largest magnitude response is found contralateral to the ear receiving a larger sound level. Ipsilateral spike rate suppression is observed throughout the rat data, as well as a subset of responses that respond maximally to locations close to the midline (ILD=0). Human fMRI ILD response functions exhibited ipsilateral suppression that extended to the midline but not to extreme (30 dB) ipsilateral ILDs. Overall these results are consistent with models of cortical ILD encoding by opponent neural populations, and observed differences between rat and human may be explained with a model of thalamo-cortical and cortico-cortical systems as well as the influence of ipsilateral inhibitory responses.

Anaesthetic condition alters response time-course, long-range coordination of firing, and spike isolation quality in mouse auditory cortex

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Most central auditory research in anaesthetised animals involves the use of either ketamine or urethane anaesthesia. Here we sought to determine how these two common anaesthetic agents shape neuronal responses in the medial geniculate body (MGB) and primary auditory cortex (ACx) of mice. We recorded thalamic and cortical responses to pure tones in mice anaesthetized either with ketamine/medetomidine (K/M) or with urethane, and compared the time-course of neuronal activity in the two groups. We also used arrays of tetrodes to record simultaneously from different positions in ACx, and quantified the coordination of activity across and within cortical layers under the two anaesthetics.

The time-course of multi-unit responses in the MGB varied only moderately between the two types of anaesthesia. In ACx, however, multi-unit response time-course was substantially and qualitatively affected by the choice of anaesthetic agent. While under K/M anaesthesia responses were restricted to the onset of pure tone stimuli, neuronal activity recorded under urethane was usually dominated by sustained responses, which often outlasted the stimulus.

The coordination of neuronal activity was also greater in K/M than urethane preparations. Simultaneous recordings from different tetrodes in K/M-anaesthetised ACx showed significantly more coherence in the broadband signal, and greater correlation in threshold crossings, both across and within cortical layers.

Finally, we noted a substantial difference in single-unit isolation quality in ACx under the two anaesthetic regimens. Over 90% of tetrode recordings collected under urethane anaesthesia yielded at least one single unit, but fewer than 20% of recordings under K/M. This failure of isolation appeared to result from the greater coordination of activity under K/M anaesthesia; many threshold crossings under K/M did not represent spikes from single cells in the vicinity of the recording electrode, but rather arose from the combined activity of many cells in a larger patch of auditory cortex. The rate of such confounding events was much higher in the K/M preparations, where coordinated activity was more common.

The integration of vowel formants in rat auditory cortex

Christian Honey, Joseph Nour, Jan W.H. Schnupp

In human vowels the position of the first two resonance bands (formants) determines the vowel category (/a/, /e/, /i/ etc). It has been shown that many non-human species, including rats, can learn to discriminate vowels. But to date little is known about how neurons in the auditory cortex integrate the formants contained in vowel-like stimuli.

We played artificial vowels and random spectral stimuli to anesthetized rats while recording responses from auditory cortex. Using a bootstrap model of neural responses to estimate the resolution at which auditory cortex discriminates between different 2-formant vowels, and found that auditory cortex can resolve formant frequency information at roughly 0.08 octaves. These values are comparable to behavioral discrimination thresholds in rats.

We also used linear and non-linear models based on single formant vowels and random spectral stimuli to predict responses to 2-formant vowels. We found that multi-unit responses in auditory cortex could not be easily modeled as the sum of individual single formant stimuli, nor as the linear combination of resonance bands as derived from a regression model on the basis of random spectral stimuli. They thus exhibit significant non-linear interactions between formants.

The detection and cortical encoding of amplitude modulation in freely moving gerbils

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While a core question in auditory sensory neuroscience is the relationship between perception and single neuron coding properties it is often evaluated in separate groups of subjects. Furthermore, the auditory stimulus is typically stabilized with respect to the head during data acquisition, either by use of earphones or by immobilizing the head. While there are significant reasons for these approaches, principally related to acoustic calibration at the ear canal, the essential principles of stimulus coding have seldom been directly measured in freely moving animals as they perform a psychophysical task. Using a telemetric device we recorded responses from multiple and single units in auditory cortex as freely moving gerbils performed an amplitude modulation (AM) detection task. An appetitive GO/NOGO behavioral paradigm was used where the NOGO signal was unmodulated broadband noise, and the GO signal was a sinusoidally AM broadband noise. Behavioral sensitivity to modulation depth was measured and compared to neural sensitivity using firing rate as well as a measure of synchrony. In addition, we evaluated whether neural encoding was associated only with the acoustic dimension (AM depth), or whether it was also correlated with an animal's sensitivity and criterion.

Functional organization of spectrotemporal processing in higher-order auditory areas of human temporal lobe.

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Functional organization within the nervous system often reveals key insights into the information being represented and the processing taking place. In the human auditory system, tonotopic organization is a prominent organizing principle up through the primary auditory cortex, but less is known about the functional organization of higher auditory areas. It is of considerable interest to determine what organizing principles, if any, are present in higher-order auditory areas in humans. To probe this question, we recorded auditory responses to natural speech in the temporal lobe of awake humans using electrocorticography (ECoG). Although restricted to rare clinical settings, ECoG provides high spatiotemporal resolution of neural activity, which is ideal for investigating questions of functional organization in the auditory system. Using the high gamma component of ECoG recordings in three patients who passively listened to speech, we computed spectrotemporal receptive fields (STRFs) using maximally informative dimension (MID) analysis. Parameters derived from each STRF, including best spectral modulation, best temporal modulation, best frequency, latency, and bandwidth were mapped onto cortex to characterize the functional organization of spectrotemporal processing. One prominent outcome of this analysis shows functional organization based on spectral and temporal modulation tuning. First, there is a spectral-temporal trade-off in which regions tuned to high spectral modulations prefer low temporal modulations (high-spec / low-temp) while regions tuned to high temporal modulations prefer low spectral modulations (high-temp / low-spec). Second, there are smooth transitions from high-spec / low-temp regions to high-temp / low-spec regions thus forming an organized distribution of modulation tuning across temporal lobe auditory cortex. These results indicate that modulation tuning is a significant organizing feature within temporal lobe auditory regions and implies that the extraction of spectrotemporal modulation information is an important step in speech processing.

Tectothalamic inhibitory neurons in the inferior colliculus receive converged axosomatic excitatory inputs from multiple sources

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Large GABAergic (LG) neurons in the inferior colliculus (IC) are encircled by dense excitatory terminals positive for vesicular glutamate transporter 2 (VGLUT2), and project to the medial geniculate body. Four auditory brainstem nuclei including IC itself were identified as possible sources by examining mRNA expression of VGLUT1 and VGLUT2 in IC-projecting cells. In this study, Sindbis/pal-GFP virus was injected in these nuclei to elucidate whether neurons in the nuclei make axosomatic contacts on LG neurons or not. Labeled neurons in all four nuclei made axosomatic contacts on LG neurons. Furthermore, a single axon made one to six contacts on a LG neuron. In 3 cases, a single IC excitatory neuron was successfully labeled, and analyzed for spatial relationship between the labeled axon and LG neurons. A single IC excitatory neuron made axosomatic contacts on 10-30 LG neurons in the ipsilateral IC. Finally, double injection of Sindbis/pal-GFP and Sindbis/pal-mRFP viruses in 2 nuclei revealed convergence of inputs from
2 nuclei on a single LG neuron. The results imply both divergence and convergence of auditory information on the cell bodies of LG neurons.

Intracortical, horizontal connections contribute to cortical receptive fields and coordinate gamma oscillations across cortical space

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Many theories in systems neuroscience are based on the concept of coordination of neuronal activity across cortical space via intracortical, horizontal connections. Evaluating hypotheses involving horizontal connections, however, is challenging. This is partly due to the problem that no mesoscopic methods exist that enable observation of the activity of horizontal connections. Prior experiments manipulated horizontal connections and can hence not readily be translated to awake, behaving animals. We propose an additional approach to study the effect of intracortical horizontal connections on cortical receptive fields based on the quantitative analysis of laminar current source density patterns. To test this, we recently employed pharmacological silencing of all intracortical processing. The results could thus not distinguish between effects due to intra-columnar processing and those due to inter-columnar processing. Here, we therefore sought to limit our manipulation to intracortical, horizontal connections by surgical cutting of cortex along an isofrequency contour in the auditory cortex. Oscillations measurable on a mesoscopic level necessitate the coordination of activity across space. In consequence, intracortical connections could play a pivotal role in coordinating cortical oscillations. Of special interest in this regard are gamma oscillations which are often linked to various cognitive functions. Thus, using our approach we addressed whether horizontal connections display oscillations in the gamma frequency range following acoustic stimulation and how intercolumnar gamma oscillations relate to intracolumnar gamma activity.
We recorded local field potentials with custom-made shaft electrodes in response to presentation of pure tones from primary auditory field AI in anesthetized Mongolian gerbils. Our data indicate that intracortical, horizontal connections contribute to the width of cortical receptive fields. They also illustrate that cortical sites receive their initial input after stimulation with non optimal stimuli through intracortical sources. We found that columnar and intercolumnar driven gamma activity differs in terms of their stimulus preference with intercolumnar gamma not displaying a stimulus preference. The results also lead to the hypothesis that the coordination of gamma oscillations occurs on a local and a global level with local coordination leading to higher frequency coherence.
Taken together the present data demonstrate that intracortical, horizontal connections play an important role in generating cortical receptive fields and coordinate cortical oscillations across cortex.

How does the brain process cochlear implant stimulation? Insights from single neuron recordings in auditory cortex

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Understanding how the central auditory system processes sound from a cochlear implant (CI) could be instrumental in guiding new CI technology advances. To study the brain mechanisms involved in acoustic and electric hearing, we have developed a unique non-human primate CI model, the common marmoset (*Callithrix jacchus)*. A multi-channel electrode was chronically implanted in one cochlea; the other remained acoustically intact. This enabled us to record and compare on a neuron-by-neuron basis responses to acoustic, CI or CI/acoustic binaural combination stimuli in the awake condition. After recording extensively in auditory cortex of three implanted animals, we made an interesting and surprising observation: while most neurons respond to acoustic stimuli, many do not respond to CI stimulation, regardless whether it is delivered from contralateral or ipsilateral ear. This study focuses on the response properties of neurons that do or do not respond to CI stimulation, in an effort to better understand why so many neurons are nonresponsive to CI stimulation.

We found that CI-nonresponsive neurons have narrower tuning curves compared to CI-responsive units. Of those CI-nonresponsive neurons, a subset was tested with binaural CI/acoustic stimuli and some of these neurons showed CI-evoked suppression. The CI-suppressed neurons had even narrower tuning than neurons with no CI/acoustic interaction. This might be explained by broad cochlear excitation areas caused by electric stimulation via a CI device, which is ineffective at activating the many cortical neurons with narrow tuning and sideband inhibition. To further assess neurons' responsiveness to narrow and broadband stimuli, bandpass noises, centered at the BF, ranging between 0-2 octaves were presented. While most neurons preferred narrow band stimuli, CI-nonresponsive neurons responded more poorly to broadband stimuli than CI-responsive neurons. This observation further confirms the notion that the lack of responsiveness to CI of many auditory cortex neurons results from broadband nature of electrical stimulation on the cochlea.

Furthermore, we found that there was a greater extent of non-monotonicity in BF-tone evoked rate-level function in CI-suppressed neurons compared to CI-driven neurons or CI-nonresponsive neurons that showed no CI/acoustic interaction. Together, these results show that auditory cortex neurons that are narrowly tuned in frequency or sound level are poorly activated or even suppressed by CI stimulation. Such neurons may be important in fine frequency and level discrimination, and these results might help explain poor CI user performance in such perceptual tasks.

Behavioral paradigm to measure the lower limit of pitch for complex harmonic sounds in macaques

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Pitch is an auditory percept related to the repetition rate of periodic sounds. To study the neural correlates associated to pitch perception using non-human primate models, behavioral measurements of pitch perception in these animals are critical. In humans, the range for pitch perception is approximately 30-5000 Hz but this range is currently unknown in monkeys. In this study, we developed a behavioral paradigm to measure the lower limit of pitch for complex harmonic sounds in macaques based on changes in the rate discrimination threshold across the pitch threshold (Krumbholz et al., 2000).
We trained three rhesus monkeys using a "go/no-go" procedure (similar to Sinnott et al., 1985) to release a touch bar sensor at each detection of a change in rate. A trial was initiated by contacting the touch bar and upon contact, a holding period (1-3 sec) began. During this period, the standard harmonic complex sound was played diotically and was followed by a stimulus change interval during which a comparison sound with a different rate was presented. The monkeys responded with bar release to detected changes. Stimuli were harmonic complexes with either cosine or alternating phases and with fundamental frequencies, F0, in the range 16 to 128 Hz.
The 3 animals successfully learned this auditory detection task and showed a lower rate discrimination threshold for higher rates. This work will allow the behavioral definition of a pitch threshold against which BOLD responses to pitch-associated stimuli at different rates can be compared : a predicted property of a neural correlate of pitch is an existence region only above lower limit.

Oxytocin-based Neuromodulation Of Mammalian Social Behavior

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Social interactions are essential for normative development mental health. The neuromodulator oxytocin is believed to be important for social behavior, specifically maternal behavior. Here we investigate a form of rodent social behavior that depends on both social cues and modification of neural substrates: pup retrieval. To initiate retrieval behavior, mouse pups produce ultrasonic vocalizations (USVs) when separated from the nest. Dams and other experienced caregivers use these acoustic signals to locate and retrieve isolated pups. Importantly, virgin female mice can also learn a variety of maternal behaviors, including pup retrieval, and we hypothesize that oxytocin plays a major role in this form of learned social behavior. Preliminary data has shown that virgins can learn to retrieve pups. Furthermore, learning is accelerated after either systemic or cortical application of oxytocin. These data suggest that oxytocin-based neuromodulation, paired with acoustic stimuli, can modify auditory cortex to enable or improve learned social behavior.

Neuronal representation of temporal regularity associated with pitch perception in macaque auditory cortex

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Pitch is an auditory percept that requires neural representations of both stimulus regularity and perceived pitch. Recent human studies using direct recordings of local field potentials (LFPs) in the auditory cortex along Heschl's gyrus show that time-locked responses correlate with the temporal regularity of the stimulus, whereas sustained gamma oscillations correlate with perceived pitch (Griffiths et al., 2010; Sedley et al., 2012). The present study in a primate model system examined temporal regularity associated with pitch at both the single-unit level and at the level of cell assemblies (LFPs). Single-unit activity (52 neurons) and LFPs (38 sites) were recorded simultaneously from the core and the lateral belt (LB) of macaque auditory cortex identified using fMRI. Stimuli contained a transition between noise and either a noise with a regular repetitive structure in time, known as a regular interval noise (RIN), or a harmonic complex at seven different rates (i.e., 8, 16, 32, 64, 128, 256, and 512 Hz). Comparing neuronal responses above and below the lower limit of pitch (approximately 30 Hz in humans) allows differentiation of responses related to pitch as opposed to stimulus regularity. LFPs were analysed for evoked potentials and time-frequency analysis. Evoked responses time-locked to the stimulus regularity were observed both below and above the lower limit of pitch, whereas induced, non-time locked, high-gamma (> 70 Hz) responses associated with the transition from noise to RIN were observed particularly for rates above the lower limit of pitch. Neuronal tuning specific to the different rates of the RIN and harmonic complex stimuli was compared at the level of single-units and LFP. The tuning of single units was sharper compared to LFP, yet both types of neuronal responses exhibited tuning above the lower limit of pitch, associated with pitch perception. There were some stimulus specific differences: (i) the magnitude of responses was stronger to the RIN than to the harmonic complexes, and (ii) responses to the RIN were sustained compared to the transient nature of response to the harmonic complexes.

The results seem to be topographically distributed in that the stimulus-regularity related responses were observed mainly in field AI of primary auditory cortex, whereas the induced high-gamma responses related to the pitch percept were observed lateral to this in the belt. These neuronal results complement those from the recordings of LFPs in humans and provide insights into how single neuronal responses might support pitch perception.

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Neuroimaging and neurophysiology of Artificial Grammar learning in the primate brain: Relationship between fMRI-BOLD and neuronal activity

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Artificial Grammars (AG) can be designed to emulate aspects of human language syntax. In an effort to develop an animal model that can be studied at the neuronal level, we have been obtaining evidence that macaque monkeys can learn an auditory AG and have used functional MRI (fMRI) to study the brain regions engaged in AG learning (AGL; Wilson et al., *SFN*, 2011). While both monkey and human fMRI results seem to highlight the role of the prefrontal cortex in AGL, we wondered whether neurons in auditory cortex might be involved (where the fMRI activity response seems to be below threshold). We recorded single-unit activity and local-field potentials (LFPs) in the auditory cortex of a Rhesus macaque that also participated in the fMRI study (85 recording sites). During each recording session, the monkey was first habituated to exemplary sequences that followed the AG structure. Then, we recorded neuronal responses to ("correct") sequences that followed the AG structure and to those that violated an aspect of its structure ("violation"). Auditory responses were identified in 99 single-units and 37 LFP sites. We evaluated neuronal responses to the grammaticality of the AG structure by comparing responses to identical elements in the sequences, but under either 'correct' or 'violation' contexts. The proportion of neuronal responses sensitive to violations of the AG structure increased when there were multiple violations in the testing sequence (26% of single units; 27% of LFP sites) than when there was a more subtle single violation in the sequences (6% of single units; 6% of LFP sites). The latency of this effect was ~400 ms in the single-units and ~550 ms in the LFP. The peak latencies of neuronal responses were significantly longer to the violation than correct sequences (respectively, mean: 477 ms vs. 336 ms, $P < 0.02$), even when the response latencies to each element showed no difference (mean, 236 ms, $P > 0.05$). In conclusion, we provide evidence that auditory cortex neurons are sensitive to AG structure. Revealing the relationship between the fMRI signal and neuronal activity in nonhuman primates is likely to be important for understanding the neuronal mechanisms of certain language-related processes in humans.

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Stability of consonant pitch intervals in a nonlinear oscillator network model

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Consonance and dissonance are important aspects of musical experience, but the mechanisms underlying their perception are poorly understood. Current psychoacoustic explanations based on linear resonance attribute tonal dissonance to interferences between simultaneous spectral components, but these accounts cannot explain the pattern of consonance and dissonance found between non-simultaneous tones in a melodic sequence. Empirical studies show that pitch intervals based on simple frequency ratios (“consonant” intervals) are more stable and coherent in memory than those based on complex ratios (“dissonant” intervals), hence affording better discrimination and change detection. Neural populations at various stages of the auditory pathways are known to exhibit the properties of nonlinear oscillation such as active amplification and mode-locking. We present an explanation of the stability of consonant intervals in memory by nonlinear resonances in the auditory system. We use a multilayered frequency gradient network of nonlinear oscillators to simulate existing experimental data on the memory stability of both harmonic (simultaneous) and melodic (sequential) intervals with simple and complex frequency ratios. Individual oscillators in the network are a canonical model of neural oscillation which is an extension of the normal-form Hopf oscillator by retaining high-order nonlinear terms that enable higher-order resonances and hysteresis among other features. Oscillators in the lower layers resonate to various combinations of their natural frequencies and stimulus frequencies and those in the top layer serve as memory units. Numerical simulations show that the amplitude and persistence of activities in the memory layer are higher for consonant intervals than dissonant intervals. It is also shown that Hebbian learning between and within layers can reinforce the memory stability of consonant intervals. This replication of perceptual data by a neurodynamic model supports the hypothesis that the principles of oscillatory neurodynamics underlie the perception of pitch and harmony.

Decoding memories of 'noise-like' stimuli from patterns of brain activity

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In a previous behavioural study, Agus et al (2010) showed that when subjects are exposed to meaningless noise patterns, a robust memory of these patterns can be formed. In this study using fMRI we addressed the brain bases of these memories. The stimuli, 'tone clouds', were stochastic patterns of multiple brief tones at random frequencies (0.1 to 10 kHz)

During training, subjects were presented with 1.5-s stimuli comprising either three identical and contiguous 0.5-s tone clouds (Repeated Tone Cloud, RTC) or three different and contiguous 0.5-s tone clouds (Non-repeated Tone Cloud, NTC). Both RTC and NTC stimuli were generated anew for each trial. Unknown to the subjects, however, three RTCs which were identical from trial to trial (Reference Tone Cloud, RefTC), were presented randomly mixed among trials of RTC and NTC. The task of the subject was to detect if the given stimulus had repetitions by pressing one of the two buttons. Given the repeated exposure to the identical spectrotemporal structure of the stimuli, subjects were expected to form (implicit) memories of RefTCs. This was confirmed during behavioural testing.

To interrogate the brain bases for this memory effect, we carried out multi-voxel pattern analysis (MVPA) to define regions in which the three different RefTCs produced different local patterns of fMRI BOLD activity. We manually delineated six regions of interest (Heschl's gyrus, planum temporale, superior temporal sulcus, entorhinal/perirhinal cortex, parahippocampal gyrus and hippocampus) in each subject. We found that it was possible to predict or 'decode' significantly above chance which of the three RefTCs was being heard from patterns of BOLD activity across voxels in the planum temporale and hippocampus, but not in any of the other regions. This shows that information about the distinct RefTCs was represented in these two brain areas. In a control analysis the classifier was unable to separate patterns of activity in any brain area corresponding to the RTC stimuli.

The existence of specific patterns of activity in planum temporale is consistent with its proposed role as a computational hub in which sound 'templates' are created that are used for higher order processing. To the best of our knowledge, this is the first study to demonstrate memory for low level spectrotemporal features of auditory stimuli in the hippocampus. Our findings are consistent with the emerging view that the hippocampus plays a wider role in cognition than traditionally thought.

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Fast auditory responses in dorsal premotor cortex of the rhesus monkey

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In monkeys previously trained on an auditory-motor sound-producing task ("monkey piano"), listening to such self-produced sounds activates, among other regions, the dorsal premotor cortex (dPMC) (fMRI study, Artchakov et al, SfN 2012). Using microelectrode recordings, we looked for auditory responses in one of the activation loci in the dorsal bank of the arcuate sulcus spur in monkeys performing a go/no-go auditory discrimination task. White noise was the behavioral target, and a set of artificial (pure tones, band-pass noise bursts) and natural (monkey calls, environmental sounds) stimuli were tested, and neural responses compared to those in auditory cortical areas (ACx: A1 and caudal belt). Selectivity to spatial location of the test sounds was also studied. We observed numerous fast and phasic auditory responses with strong preference for white noise. During the first 100 ms ("on" response), selectivity for artificial sounds in dPMC was comparable to ACx, but selectivity for natural sounds was higher in dPMC. This effect was not seen in the "sustained" response (beyond 100 ms) where selectivity in dPMC tended to be lower than in ACx. In contrast to ACx, dPMC responses did not show consistent firing patterns locked to stimulus feature, as shown by very poor linear discriminator performance and lack of correlation of firing rate with stimulus spectrotemporal structure. Azimuth selectivity was similar in dPMC and ACx, while elevation selectivity was better in dPMC. Neural response latencies in dPMC were remarkably fast: 16 ms on average, comparable to A1 and area CL of the caudal belt, but slower than in area CM of the caudal belt. Direct connections between ACx and dPMC that could support these fast responses have been demonstrated anatomically (Ward et al, J Neurophysiol, 1946; Romanski et al, Nat Neurosci, 1999; Morecraft et al Brain Res Bull, 2012). The results provide support for a recent dorsal-stream model, which predicts the stream's contribution to linking sounds with actions, and involvement of premotor cortex in the processing of sound sequences (Rauschecker, Hear Res, 2011).

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Spectral and temporal acoustic features map subfields in human auditory cortex

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Functional studies in both human and nonhuman primates have clearly demonstrated that both visual and auditory cortex are populated by multiple subfields. However, functional characterization of those fields has been largely the domain of animal electrophysiology, thus limiting the extent to which human research can be informed by nonhuman primate work (and vice versa). In this study, we used high-resolution functional magnetic resonance imaging (fMRI) to characterize human auditory cortical subfields using a variety of low-level acoustic features. Sensitivity to spectral features was assessed using trains of pure tones, band-passed noise, white noise, and harmonic stimuli with amplitude envelope evenly modulated at 4 Hz. Sensitivity to temporal features was assessed using amplitude-modulated (AM) white noise (WN) at several rates, ranging from 1.3 to 52.1 Hz. On average, the gradient of cochleotopic organization extended from posteromedial to anterolateral along superior temporal cortex, with the main reversal of this organization corresponding to the border between the putative "core" or primary subfields A1 and R. These two subfields were centrally located along the orthogonal direction and responded equally well to all spectral and temporal envelopes, but exhibited higher frequency selectivity (narrower frequency tuning) than the rest of auditory cortex. Similar characteristics were observed in a third area that may correspond to RT, an additional core area previous identified in nonhuman primates. Surrounding subfields, on the other hand, were more selective to spectral and temporal envelope type, and likely correspond to belt and/or parabelt regions. More specifically, lateral "belt/parabelt" regions were more selective for stimuli with spectral envelopes associated with perceptual pitch (i.e., pure tones, harmonic series, and narrow-band noise). Posterior regions preferred noise stimuli and low AM rates, and exhibited low frequency-selectivity. Preference for high AM rates was located in mid-medial and anterolateral subfields. These data support the idea that auditory cortical subfields can be functionally dissociated based on their selectivity to low-level spectral and temporal acoustic features. Further characterization of these and other cochleotopic regions using attributes of the spectral envelope may allow further parcellation of core and belt, and further exploration of distinct regions in terms of their functional organization (e.g., combination sensitivity).

Auditory receptive field estimation with bandpass noise

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Receptive fields (RFs) of auditory neurons are used as the basis to formulate models of neural sound processing. Because many neurons in auditory cortex are unresponsive to pure tones, especially in the lateral belt of primates, bandpass noise is frequently used to estimate their characteristic frequencies (CFs) and bandwidths. In light of recent research indicating that receptive field definition can affect the conclusions drawn from neurophysiological data (Reynolds, J.H., Heeger, D.J. 2009), we examined computational models of auditory neurons to evaluate the possibility of mis-estimating the response properties of an auditory neuron when using bandpass noise as the probe stimulus. We did so by constructing computational models of simplified auditory neurons and subjecting these model neurons to simulated sounds that have the same characteristics as real sounds typically used estimate auditory receptive fields. The results of these simulations indicate that using bandpass noise for estimating CF results in a systematic bias when applied to auditory neurons having asymmetric RF structure. Because many subsequent neuronal measurements (e.g., threshold, bandwidth) depend upon accurate CF estimates, biases in this first step can result in skewed population data. In particular, reliable estimates of bandwidth tuning require a highly accurate CF estimate in order to be credible. We found that mis-estimates of CF can lead to inaccurate conclusions of bandwidth tuning in model auditory neurons. Furthermore, we tested these modeled results in marmoset auditory cortex by characterizing real neurons using pure tones, wideband noise, bandpass noise and random spectrum stimuli (RSS). These physiological data, in agreement with the computational results, indicate that neurons with asymmetrical receptive fields are easily mis-characterized when probed with bandpass noise having a bandwidth near the same value as the neuron under study. The use of bandpass noise in estimating characteristic frequency therefore should be performed with care to avoid these potential biases.

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Functional topography of thalamocortical and intracortical inputs to layers 4 and 6b

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In the sensory forebrain, thalamocortical axons transfer information from the thalamus to layers 4 and 6b of sensory cortical areas. Yet, receptive field properties in layer 6 are generally more complex than those in layer 4. Thus, it remains an open question whether such differences reflect distinct inheritance patterns from the thalamus or if instead they are derived from local cortical circuits. To distinguish between these possibilities, we utilized *in vitro* slice preparations containing the intact thalamocortical pathways in the auditory and somatosensory systems. Responses from neurons in layers 4 and 6b that resided in the same column were recorded using whole-cell patch clamp. Laser-scanning photostimulation via uncaging of glutamate in the thalamus and cortex was then used to map the functional topography of both thalamocortical and intracortical inputs. We found that the thalamocortical inputs to layers 4 and 6b originated from the same thalamic domain, but the intracortical projections to the same neurons differed dramatically, with those to layer 6b originating from broader areal and laminar regions than those to layer 4. Our results suggest that the intracortical projections to layer 6b likely contribute more to their complex receptive fields, while the thalamocortical inputs to layer 6b instead may be concomitantly attenuated. As such, the functional circuitry of the thalamocortical network is comprised of concurrent and convergent networks that lead to computationally divergent outcomes emerging from the intracortical network.

A nonlinear dynamical systems approach to pitch perception

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Poster preferred

Many diverse sounds generate the percept of pitch, despite widely varying spectral and temporal properties. Neither the attributes of sound nor the neural mechanisms underlying these phenomena are completely understood. Simple spectrotemporal transformations tend not to capture our rich and varied perceptions, whereas more complex computational and probabilistic theories run up against biological plausibility. Physiological findings including cochlear amplification, nonlinear distortion products, and mode-locking of action potentials suggest that nonlinear responses may play a fundamental role in auditory signal processing. Here, we explore the signal processing properties of nonlinear oscillation, and ask whether these properties could resolve certain apparent anomalies in pitch perception. We use tonotopic networks of neural oscillators designed to mimic the anatomy and physiology of the human auditory pathway. Among other things, these networks simulate mode-locking to both the fine structure and amplitude modulation of complex stimuli, a recently observed characteristic of auditory brainstem responses. In a series of experiments, we stimulated the model with three types of pitched stimuli: missing fundamental complexes, sinusoidally amplitude-modulated and iterated rippled noises, and various click-train stimuli. We measured the amplitude responses of individual oscillators as well as the frequency spectra of mean field network activity. We observed that the dominant resonances of the nonlinear network matched the frequencies of pitch judgments by humans. Thus, the responses of the network bear important similarities to pitch judgments in diverse situations that have otherwise proven difficult to capture in a single model. Implications for a theory of nonlinear signal processing by the auditory system are discussed.

Human psychophysics of an auditory frequency-contour discrimination task

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Perceptual decision-making is a deliberative process that converts incoming sensory information into a categorical judgment. The specializations by the auditory system to process temporal information are likely to affect the temporal dynamics of auditory decision-making. We hypothesized that a change in the inter-tone burst interval (IBI) of a tone-sequence stimulus, which affects its temporal regularity and hence its perceptual qualities, also affects the speed and accuracy of a categorical judgment about the stimulus.

To test this, we designed a task that required subjects to report whether a sequence of tone bursts was increasing or decreasing in frequency. Subjects were asked to make their judgments as quickly and accurately as possible (response-time; RT) or to make the judgments after listening to a stimulus for a particular duration, varied on each trial (variable-duration; VD). We varied two properties of the stimulus on each trial: 1) the coherence of the burst-by-burst changes in frequency, which affected difficulty, and 2) the inter-burst interval (IBI), which was reported by subjects to affect whether the tone sequence was heard as a single continuous sound (short IBIs) or as a series of discrete tones separated by a gap (longer IBIs).

We fit RT data with a drift-diffusion model and found that longer IBIs decreased the boundary height of the model, a strategic adjustment of the speed-accuracy trade-off governed by the decision process. There was also an increase in the rate of information accumulation for the shortest IBI condition, even when accounting for the differences in the tone presentation rate across IBI conditions. This result suggests that when a stimulus is perceived as continuous, there is more effective information integration than when a stimulus is perceived as discrete tones. Next, we used a reverse-correlation analysis to examine the time course of the relationship between trial-by-trial fluctuations in the stimulus and in choice. We found that stimulus fluctuations were predictive of choice for the first ~15–20 tones, consistent with an accumulation-to-bound process that ended slightly before the measured RT. Finally, we analyzed the VD data to further assess the time course of sensory accumulation. We found an increase in accuracy as the listening-duration increased for medium and high coherences, but little to no increase in accuracy for low coherences, suggesting that the quality of the sensory evidence may affect the accumulation process. Together, these results imply a complex decision process roughly consistent with an accumulation-to-bound, but may include specializations in temporal processing in the auditory system.

Tuning to interaural time difference in human auditory cortex

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An important binaural cue used to localize and segregate sound sources is the interaural time difference (ITD) resulting from earlier arrival of sound at the nearer of the two ears. Throughout the auditory neuraxis, ITD-tuned neurons are observed to respond best to earlier stimulation of the contralateral than ipsilateral ear, consistent with sound sources in the contralateral hemifield. In human auditory cortex (hAC), ITD tuning has been assessed by measuring such contralateral bias in overall population responses or their surrogates (e.g., BOLD fMRI). Studies sampling a limited set of ITD values have provided mixed evidence for [Krumbholz et al., Cereb Cortex 15:317-24, 2005] and against [Woldorff et al., HBM 7:49-66, 1999] contralateral bias in hAC; the degree and pattern of ITD tuning thus remain unclear. In the present study, we used BOLD fMRI to quantify hAC tuning to ITD across a wide range of values (0, ±200, ±500, ±800, ±1500ms) imposed on narrowband click trains (4000 Hz carrier freq, 1.8 kHz half-max bandwidth, 500 Hz click rate) presented at 80 dB SPL. Using a continuous, event-related paradigm (TR=2s, 42 slices, 2.75 x 2.75 x 3mm resolution, 3T), responses to 1s click train sequences (jittered 1 - 5s interstimulus intervals) were collected. Counterbalanced ordering of ITD values followed a continuous carryover design [Aguirre, NeuroImage 35:1480-94, 2007] to maximize sensitivity to direct effects of ITD and any potential stimulus history 'carryover' effects. Participants responded with a right-handed button press to infrequent pitch changes unrelated to the experimental question and visually fixated on a center cross to minimize eye movements.

In a companion study examining the response to parametrically varied interaural level difference (ILD) [McLaughlin & Stecker, SFN 2011], we found both direct effects of ILD modulation and stimulus history effects in posterior AC regions. In contrast, results of the current investigation show neither contralateral bias nor any other clear ITD tuning, nor any apparent carryover effects of stimulus history. We hypothesize that this ostensible lack of tuning to ITD may be due to weak stimulus salience and/or the limits of traditional fMRI analyses in assessing effects that are either subtle, focally limited, or spatially distributed. Follow-up studies thus employed a range of stimuli (including lower-rate click trains and noise bursts) and analyses (including multi-voxel pattern and population receptive field analyses) to test for effects. Results will be discussed in the context of current hAC models of auditory spatial processing. Work supported by NIH R03-DC009482-02S1 and NIH R01-DC011548-01A1.

CORE AUDITORY CORTEX OF THE CAT REVEALED USING HIGH-FIELD FMRI

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The hierarchical organization within auditory cortex remains a topic of debate. In a hierarchy, lower order areas process more basic components before information is sent to higher processing stages. A basic component of sound is the pure tone. Therefore, the lowest ranking areas in an auditory hierarchy should process tonal stimuli and would most likely be organized according to frequency. Tonotopy, the organization according to tonal frequencies, has been demonstrated in animals using invasive electrophysiological techniques. Previous electrophysiological investigations have demonstrated tonotopy in primary auditory cortex (A1), the anterior auditory field (AAF), the posterior auditory field (PAF) and the ventral posterior auditory field (VPAF). Functional magnetic resonance imaging (fMRI) has been used to demonstrate tonotopy in auditory cortex of humans and monkeys. To our knowledge, no previous study has combined the non-invasive fMRI method with tonotopic investigations of cat auditory cortex. We used a 7T MRI scanner to identify primary, or core, auditory cortex of the cat. Six tones, 1 kHz, 5 kHz, 10 kHz, 16 kHz, 20 kHz and 30 kHz, were presented along with a broad band noise (BBN) in a block design interleaved with baseline blocks in which no stimulus was presented. Following preprocessing, data pertaining to each tone were analyzed for size and location of activation in order to assess tonotopy in A1, AAF, PAF and VPAF. Tonotopy was successfully identified in A1, progressing from low to high frequencies perpendicular to a posterior-anterior axis, agreeing with previous studies. Similarly, a reflected tonotopic organization was identified anterior to A1, corresponding to AAF. A similar tonotopy could not be identified in PAF or VPAF although significant activations were present during 1 kHz tone stimulation. The BBN produced acoustically evoked activations along the posterior ectosylvian sulcus (*pes*) and across A1. However, the strongest activations by a BBN were along the *pes* corresponding to PAF and VPAF. This suggests that PAF and VPAF may be dedicated to processing more complex acoustic stimuli. The tonotopic organization of A1 and AAF, along with the selectivity of PAF and VPAF for BBN stimulation, indicates that the auditory “core” in the cat consists of A1 and AAF.

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Context affects the responses of marmoset frontal cortex neurons during natural vocal communication

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Primates evolved sophisticated behaviors in order to effectively navigate their respective social and ecological landscapes. While these behaviors clearly had a significant impact on the evolution of neural mechanisms in primate neocortex, relatively little remains known about how the brain functions during natural behaviors. Our aim here was to examine neural activity while common marmoset monkeys (Callithrix jacchus) engaged in natural vocal communication. Examining the responses of neurons during any natural behavior requires that these recordings take place in freely moving animals. As such, it was necessary to better characterize the differences in neural activity between subjects in this context as well as more traditional restrained contexts. We recorded the activity of individual frontal cortex neurons in the following contexts. (1) Natural Communication. Here we engaged subjects in their natural, species-typical vocal behavior known as antiphonal calling: This behavior involves the reciprocal exchange of vocalizations between conspecifics. We employed novel interactive playback software that effectively simulates the dynamics of antiphonal calling in order to engage subjects in this natural communication behavior. (2) Passive Listening: Restrained. Here we presented a sequence of vocalizations while animals were restrained in a primate chair. (3) Passive Listening: Freely Moving. Here we presented subjects with the same sequence of vocalizations as in the 'Restrained' condition, but in this condition subjects were freely moving. The same set of vocalizations was used in all three of these behavioral contexts and only individual neurons recorded in all three contexts were used in the analysis. Furthermore, in order to better characterize the nature of neural activity in restrained and freely moving animals we recorded 5minutes of spontaneous neural activity before and after each of the Passive Listening conditions. Analyses here focused on two aspects of neural activity. The first set of tests sought to address the issue of establishing baseline activity in freely-moving marmosets. Since stimuli are not presented at regular intervals during bouts of natural communication and the animals' movements are under their own volition, we tested the relationship between these factors and several dimensions of neural activity. Results showed that the mean spike rate during baseline periods did not increase from the Restrained to the Freely-Moving condition. Rather, nearly half the population showed a decrease when subjects during the latter condition. Preliminary evidence also indicated that variability in spike timing also differed between the conditions. The second set of analyses tested the responses of neurons to vocalization stimuli in each of the three test contexts. Overall, the majority neurons were only responsive to vocalization stimuli in one of the three contexts. In other words, a neuron responsive during the Passive Listening: Restrained context was unlikely to be responsive to the same vocalization stimuli in the two other behavioral contexts. Additional analyses were performed to test the source of this difference. Preliminary tests indicate several factors may contribute to the observed differences between the conditions, such as changes in neural variability due to mobility, differences in the repetitive nature of stimulus presentation and active communication.

Adaptation to Temporal Correlation in the Primary Auditory Cortex

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According to the efficient coding hypothesis, sensory systems adapt to stimulus statistics so that the dynamic range of the response matches the dynamic range of the stimulus. We hypothesize that the temporal correlation (TC) of complex sounds may form a statistical measure that triggers adaptation in the auditory nervous system. We tested the effect of changing TC of a synthetic sound on response properties of neurons in the mammalian primary auditory cortex (A1). Using chronically implanted multi-tetrode microdrives, we recorded responses of units in A1 of awake rats to acoustic broadband stimuli with varying TC. For each neuron, we quantified the change in firing rate, spectro-temporal receptive field (STRF) and non-linear response function of a linear-non-linear model. The average temporal length of the STRF increased with increased TC. Furthermore, neurons exhibited heterogeneous responses to increasing TC; either increased gain or baseline firing rate. Together, these changes suggest multiple mechanisms for TC-dependent adaptation in A1. We next examined the time course of firing rate adaptation to the stimulus TC. For each unit, we compared the prediction accuracy of a linear-non-linear model fitted to either low or high TC stimulus. In response to a stimulus with alternating TC over time, the responses of neurons to low TC periods were better predicted by the model when fitted to low TC stimulus. However, for 200ms following high to low TC transitions, we found that the model fitted to high TC stimulus predicted the firing rate better than the model fitted to low TC. This finding shows that both the firing rate and the receptive field time course adapts over several hundred milliseconds upon transition from high to low TC. Our results demonstrate a novel form of adaptation in which A1 neurons modulate their response properties to match the temporal dynamics complex sounds.

Spatial and nonspatial processing in the primary auditory cortex of awake behaving macaque monkeys

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The mammalian auditory cortex simultaneously encodes the spectral, temporal and spatial characteristics of auditory stimuli. These acoustic details are first processed by the primary auditory cortex and are then sequentially relayed through other non-primary auditory cortical regions (e.g., the rostral superior temporal gyrus, the prefrontal cortex and parietal cortex), which form a hierarchical network of spatial (caudal) and nonspatial (rostral) auditory processing pathways (Hackett, Hear. Res. 271:133, 2011). The current study examines how the response properties of single auditory cortical neurons are influenced by an auditory discrimination task that is dependent on either the spatial or non-spatial aspects of an acoustic stimulus. We recorded the responses of single neurons in the auditory cortex of a young adult macaque monkey to 100 percent amplitude modulated noise (500 ms duration) presented from one of five locations. The monkey was trained to initiate a trial by depressing a lever. Two S1 stimuli (30 Hz AM rate) were presented (250 ms ISI) and then a third stimulus (S2) was presented that was either different from or the same as the S1 stimuli. If the monkey released the lever to the different S2, or kept the lever depressed when it was the same, it was rewarded with a drop of juice. In blocks of trials the change in the S2 stimulus could be either to a different AM rate from the same location or from a different location but the same AM rate. Alternating blocks were presented to each neuron and the monkey was cued to the type of change by having the first several trials be a clear change in either AM rate or location. Preliminary findings revealed that neurons of the primary auditory cortex are sensitive to a variety of stimulus- and task- relevant events. The vast majority of neurons showed auditory-evoked activity during the presentation of these stimuli. Additionally, some units showed either an enhancement or a reduction in activity between the first and second S1. We also noted neurons that had a higher evoked activity when the monkey performed the AM discrimination task compared to when it performed the spatial task even thought the physical characteristics of the stimuli were identical. Other neurons showed the reverse relationship. These findings suggest that cognitive and behavioral factors, evoked by attention to different acoustic properties of a sound, can influence the activity of auditory cortical neurons early in the hierarchical processing streams. The respective, highly processed information may then be useful for other auditory regions during higher-order auditory processing, such as decision making, learning and memory.

The Cortical Pitch Complex: Responses to Resolved Harmonics, Unresolved Harmonics, and Distortion Products

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Pitch is a defining perceptual property of many real-world sounds, including music and speech. Classically, theories of pitch perception have distinguished between temporal and spectral cues. These cues are rendered distinct by the frequency resolution of the ear, such that some harmonics produce “resolved” peaks of excitation in the cochlea, while others are “unresolved”, providing a pitch cue only via their temporal fluctuations. Perceptually, unresolved harmonics produce a weak pitch compared to resolved harmonics, which has been taken as evidence for the importance of spectral cues in pitch perception. Despite longstanding interest, the neural structures that process pitch, and their relationship to these cues, has remained controversial, and many human neuroimaging studies have focused on responses to temporal pitch cues conveyed by stimuli with unresolved harmonics. Here, using fMRI, we report: 1) All 23 subjects tested exhibited a “pitch complex” (PC) anterior to primary auditory cortex that responded substantially more to harmonic tones than noise, replicating previous findings. 2) The PC’s response was mainly driven by spectrally resolved harmonics, although a weak but consistent response was observed in the same regions for unresolved harmonics relative to frequency-matched noise. 3) Notably, this selective response for resolved harmonics was only observed with concurrent noise designed to mask low-frequency components introduced by nonlinearities in the ear (‘distortion products’). In the absence of masking noise, we observed strong responses to tones irrespective of resolvability, suggesting that distortion products (DPs) have a surprisingly large effect on the cortical response, effectively acting as resolved frequency components and potentially explaining previously observed responses to pitch in the absence of spectral cues. 4) Consistent the role of DPs, we also observed enhanced responses to unresolved harmonics compared with frequency-matched noise in regions that were selective for low-frequencies but that were otherwise insensitive to pitch. This response enhancement was eliminated by adding harmonics in Schroeder phase, which has been shown to minimize DP amplitudes, and was not observed in regions selective for high-frequencies where DPs are typically weak or absent. Taken together, these results demonstrate the existence of a set of pitch-sensitive brain regions that mainly respond to resolved frequency components, and suggest that DPs have a relatively large impact on cortical responses as measured by fMRI.

Organization of human auditory cortex: Response latencies on Heschl's gyrus and posterior lateral superior temporal gyrus.

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The functional organization of human auditory cortex is incompletely understood. Non-human primate models serve as a principal framework upon which the auditory cortex is hierarchically delineated into core, belt and parabelt fields. Most studies agree that the posteromedial portion of Heschl's gyrus (HG) represents core auditory cortex. Anterolateral HG has been variously interpreted as either core or belt auditory cortex. Interpretation of posterolateral superior temporal gyrus (PLST) is even more problematic, though some studies characterize this region as representing part of the parabelt. Standard connectivity patterns derived from non-human primate models envision that core cortex directly projects to belt, but not to parabelt, whereas belt regions are a major source of direct input for auditory parabelt. In this scheme, response latencies can be hypothesized to progress in serial fashion from posteromedial to anterolateral HG to PLST. In this study, we examined this hypothesis by comparing response latencies to multiple stimuli, measured across the three anatomical regions using simultaneous intracranial recordings.

Experimental subjects were neurosurgical patients undergoing chronic invasive monitoring for medically refractory epilepsy. All research protocols were approved by the NIH and The University of Iowa Institutional Review Board. Stimuli ranged from simple to complex sounds, such as trains of acoustic clicks and human speech. Electrophysiological data were recorded simultaneously from HG and perisylvian cortex using multicontact depth electrodes and subdural grid electrodes, respectively. Response latencies were determined by examining averaged evoked potentials and event-related band power in the high gamma frequency range.

Preliminary results demonstrate that the earliest responses in auditory cortex occur in posteromedial HG. However, responses elicited from sites in anterolateral HG were neither earlier in latency from sites on PLST, nor more robust. These findings are not supportive of a model envisioning flow of information along HG to PLST. In contrast, data suggest that a portion of PLST may represent a relatively early stage in the auditory cortical hierarchy. Parallel analyses examining the relative extent of activation elicited by pure tones, bandpass noise and speech are ongoing to evaluate whether these response patterns can assist in parcelation of auditory cortical regions (see companion presentation by Steinschneider et al.).

Macaque sensitivity to compound amplitude modulation: Effects of component frequency and phase.

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Most of the variation in the temporal envelope of natural sounds occurs at relatively low frequencies (Voss and Clark 1975; Singh and Theunissen 2003). Slow amplitude modulations (AM) are particularly prominent in human and animal vocalizations, and it is evident that this envelope variation carries important communicative information. For example, comprehension of human speech is possible with as few as three modulated noise bands (Shannon et.al. 1995). How the brain extracts this information is currently of much interest in both psychophysical and physiological acoustics. Several adaptation and masking studies support the notion that temporal envelope analysis is effectively based on a "modulation filterbank", a bank of independent bandpass filters each sensitive to a narrow range of AM frequencies (e.g., Kay and Matthews 1972; Bacon and Grantham 1989; Ewart and Dau 2000). To test this model, and examine its possible physiological bases, we have begun training rhesus macaques to detect envelope modulation in compound AM (cAM) stimuli, consisting of broadband noise carriers where the modulation function is the sum of two sinusoids. The frequencies of these sinusoids are either quite close (e.g., 5 and 6.25 Hz), designed to lie within a modulation filter, or farther apart and so not within the same filter (5 and 15 Hz). Additionally, the phases of the two sinusoids are either aligned at 0 deg or 180 deg apart. This phase manipulation produces two signals with identical modulation spectra, but different waveforms and envelopes. If cAM sensitivity is based upon a modulation filterbank we would expect summation effects for detection of the signal components lying within a filter, but little or no summation for those not within. We would also expect phase difference to have no effect on summation. To date, we have obtained preliminary results from one macaque. Comparison of thresholds for detection of the pure sine component AM, to those for detection of compound AM, suggests that summation is greater in the case of 5 + 6.25 Hz cAM, but that it also occurs to some degree for the 5 + 15 Hz cAM. It appears that phase also has an effect, with greater summation for cAM with non-aligned phase. Thus, our results at this point are not strongly supportive of a modulation filterbank model in macaques comprising narrow independent filters, though they may be more congruent with a model in which the filters share a common noise source.

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Time Course Variability of Sound Evoked Synaptic Inputs in Inferior Colliculus (IC) of Mouse.

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The time courses of the sensory neurons are important in coding the temporal character of the sensory inputs. The IC neurons are known to have large diversity in their time courses of the spike responses to sound. The IC receives and integrates the temporal information from more than one source in the brainstem. However, the synaptic basis for this integration in IC is unclear. Here, we used *in vivo* whole-cell voltage clamp recordings to study the synaptic responses of IC neurons to tones or white noises.

We recorded the excitatory and inhibitory synaptic currents (EPSC and IPSC) by holding the neurons at the reversal potentials of the opposite inputs for each, which were examined pharmacologically *in vivo*. From 34 neurons, we recorded EPSCs and from 24 neurons we recorded IPSCs. Interestingly, the EPSCs showed high variability in their peak time (10 – 200 ms to the 200 ms stimuli). Some inputs showed rapid transient time course and others showed slow rising, which were similar to the transient and build-up spike responses, respectively. On the other hand, IPSC showed less variability in their peak time (10 – 100 ms).

To study the origin of the diversity, we examined whether the diversity in the time course of EPSCs resulted from the series resistance error. We plotted the parameters of size and time course of sound evoked EPSCs against the series resistance, and there was no correlation between them. However, in the spontaneous EPSCs (sEPSCs), there was clear correlation between the parameters of EPSCs and series resistance. The series resistance become higher, the sEPSCs become smaller and slower. To estimate the error range that series resistance cause in evoked responses, we utilized a linear modeling that convolve the sEPSC and presynaptic spiking patterns. The modeling showed that the error was the largest when the EPSCs were transient and the smallest when the EPSCs were slow rising. The modeling also showed that the series resistance distortion did not change the temporal shape radically and the error was at most 10 ms in peak time.

For some neurons, we recorded both extracellular and intracellular responses. Recordings of both extracellular and intracellular responses from the same neuron suggest that the synaptic input patterns predict the spike responses.

These results showed that the diversity in EPSC time course underlie the diversity in spike responses. Further, the diversity in the EPSCs was likely to be shaped principally by the spike patterns of the presynaptic brainstem neurons. The difference in the diversity of EPSCs and IPSCs could reflect their different pathways in the brainstem.

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PSYCHOPHYSICAL ESTIMATES OF AUDITORY FREQUENCY SELECTIVITY IN THE COMMON MARMOSET (CALLITHRIX JACCHUS)

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The common marmoset, a small-bodied, New World primate species with a large vocal repertoire, has emerged as a promising non-human primate model in auditory neuroscience. A full appreciation of the physiological response to sound in these animals will require a basic understanding of their hearing sensitivities. Previous psychoacoustic work has shown that marmosets have a hearing range extending from 125 Hz to 36 kHz with an area of heightened sensitivity between 7 and 10 kHz - the frequency range of many of their most common vocalizations. We have tested auditory frequency tuning of marmosets using a psychophysical task in which tone thresholds were measured as a function of notched noise masker bandwidth. The resultant threshold data can be used to estimate the equivalent rectangular bandwidth (ERB) of the auditory filters using procedures originally developed for human subjects. We tested four different frequencies spanning much of the hearing range of this species (500 Hz, 1 kHz, 7 kHz, and 16 kHz). Results show that marmosets have ERBs that are generally comparable to those measured in humans and other mammalian species. However, compared to humans, they have wider ERB's at 500 Hz and narrower ERB's at 7 kHz. This difference may reflect tradeoffs between a basilar membrane that is half of the length measured in humans, a hearing range extending 20 kHz higher than in humans, and the need to process high-frequency species-specific communication signals.
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Single-unit responses to amplitude modulated tones and noise in the auditory cortex of aged macaque monkeys

Keywords: auditory, cortex, temporal processing, primate, aging, single-unit electrophysiology

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A major complaint by individuals with age-related hearing loss is a difficulty in understanding speech. Often, this deficit occurs even when audiometric thresholds are normal. This and other evidence suggests that this is likely due to processing deficits in the central auditory pathway. Amplitude modulations carry much of the relevant information in a speech signal, therefore, understanding how auditory cortical neurons process amplitude modulated (AM) stimuli and how that processing changes with normal aging is essential to understanding age-related central auditory temporal processing deficits. In order to investigate this question we recorded from single neurons in core (A1 and R) and caudal belt (CM, CL) fields of auditory cortex in two alert macaque monkeys (mean 25 years old) while presenting them with 500 ms duration 100 percent sinusoidally AM broadband noise and AM tones with the carrier at the best frequency of the neuron. Modulation frequencies varied from 2 to 128 Hz. For each stimulus modulation frequency, modulation tuning functions were constructed based on the firing rate as well as the vector strength. Best modulation frequencies (BMF) were taken as the peak of both the firing rate based modulation functions (rBMF) and temporally (vector strength) based modulation functions (tBMF). Rate and temporal tuning functions were fit with Gaussian and/or sigmoid functions in order to calculate bandwidths (full width at half height and/or high or low pass from the inflection point) for each cell. Results were compared to a similar study of AM encoding in primary auditory cortex in younger monkeys (Yin, P., et al., *J. Neurophysiol.* 105:582, 2011). Our results in older monkeys were consistent with those from younger animals using both rate and temporal metrics with respect to the percentage of AM-sensitive cells and the bandwidth of sensitivity. In contrast, across the population of neurons recorded in young monkeys, rBMFs and tBMFs were more common at low AM frequencies (<10 Hz). In older monkeys, however, while tBMFs were similarly distributed at lower frequencies, rBMFs were skewed towards higher AM rates (>60Hz). Joint distribution analysis revealed that this shift towards higher rBMFs occurred in cells across the range of tBMFs. Thus, in older monkeys a large proportion of auditory cortical neurons that were sensitive to AM stimuli encoded low AM frequencies by synchronizing to the stimulus, but showed a monotonically increasing firing with increasing AM rates. These results suggest that natural aging results in a change in how auditory cortical neurons encode the rate of amplitude modulated signals at low and high modulation rates.

The causal role of the inferior colliculus in perception: effects of electrical stimulation on frequency discrimination in primates.

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A central challenge for neuroscience is to determine the relationship between neural and perceptual function. Neural recording and imaging methods provide correlative information about how neurons respond to various stimuli, but cannot establish a causal connection between neural function and perception. Electrical microstimulation can bridge this gap. Microstimulation has expanded our understanding of how the visual system generates perception (e.g. Salzman, Britten, and Newsome), but to date most stimulation studies in the auditory system have used non-perceptual assays (with the notable exception of studies involving the periphery: i.e. cochlear implant users).

The representation of sound frequency is a major area of interest in auditory perception. Sound frequency influences neural activity in two ways: (1) neurons are tuned for specific sound frequencies due to varying resonance along the basilar membrane, forming a place code for sound frequency; and (2) neurons synchronize their firing to the cycles of the sound wave, producing a temporal code for sound frequency. Despite decades of research establishing these two fundamental elements of the neural representation of sound frequency in the auditory pathway, there is comparatively little evidence that ties either property in specific brain regions to a causal role in the perception of pitch.

Monkeys were trained to perform an auditory forced-choice task in which they indicated whether the frequency of a probe tone was higher or lower than a reference tone. We then microstimulated sites in the inferior colliculus (IC) in combination with the probe tone. Stimulation (40-80 microamps, 200Hz) biased performance in 23 of 56 experiments (41%). The shift in performance relative to a given reference frequency was correlated with the best frequency of the site.

This finding suggests that IC neurons contribute to frequency perception in a fashion related to their best frequency. This is a promising finding from the standpoint of harnessing the auditory representation of the IC for auditory prostheses (e.g. Lim, Lenarz, et al.). Future work will be needed to illuminate the potential additional role of temporal coding for frequency in this structure.

Auditory spatial perception aligns with long-term changes in eye position: A novel robust adaptation phenomenon.

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Vision and audition represent the environment in head/body-centric spatial calibration that underlies perceptual 'space-constancy.' A common head reference requires an additional input to track ever-changing eye position in the head, given head-fixed ears. We have characterized a novel adaptation phenomenon in which auditory (but not visual) spatial perception shifts slowly toward changes in eye position (mean magnitude 40% of Δeye; 1' time-constant). Experiments determined that this phenomenon is: 1) linearly related to the magnitude of oculomotor shift, 2) independent of any visual reference (occurs in darkness), 2) common to all auditory spatial channels (azimuth and elevation), 3) accompanied by a shift in perceived straight-ahead (PSA), 4) unaffected by neck orientation, and [most recently] 5) depends upon the change in eye position and its duration at the time of target presentation, and not influenced by subsequent eye movements. Findings suggest a simple set-point control strategy by which auditory spatial alignment shifts directly with an oculomotor (and retinal) position signal (e.g. low-pass efference copy). We propose that this robust adaptive mechanism reflects an important developmental imperative for cohesive alignment across sensory and motor systems necessary for effective spatial behavior. By exploiting the more precise visuo-motor system, auditory space (and PSA) efficiently aligns with vision by adapting passively to a long-term oculomotor reference. This phenomenon highlights the importance of controlling for eye position in the investigation of auditory spatial perception and behavior, that of other relevant sensory/perceptual systems, and underlying neural mechanisms.

Age-Related Changes in Auditory Processing of Speech-like Stimuli Assessed at the Population and Cellular Levels

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Loss of temporal processing in elderly human listeners due to deficits in the central auditory pathway may result in loss of speech perception with age. This study aims to further understand the representation of speech-like stimuli in aging using non-invasive electrophysiological measurements in a rat model system complemented by single unit recordings from the inferior colliculus (IC). Frequency following responses (FFRs) were obtained for speech and speech-like stimuli which change in their voice onset time (VOT 0-60 ms, on the /ba/-/pa/ continuum) presented to aged (20-22 months old) and young (3-5 months old) Fischer-344 rats. FFRs were also obtained in response to the envelope and fine structure of these speech sounds modulating a noise or 8 kHz tone carrier, matched for individual hearing thresholds. The FFRs obtained were differentially filtered to isolate the responses to the envelope and to the fine structure. FFRs revealed a greater age-related decrease in cross-correlation with the stimulus fine structure compared to the envelope. This decrease was more pronounced in the sustained portion of the stimulus. Cellular correlates of these changes were obtained from single unit recordings from the IC of young and aged animals. Changes in the accuracy of representing VOT based on first-spike latency, as well as changes in representing the speech-like waveforms based on rate and phase-locking suggest similar changes as observed in the FFRs to be present at the level of the single neuron in the IC. Potential implications for age-related loss in processing fine structure, based on existing hypotheses of decrease in inhibition are discussed.

Visual influences on neurons in voice-sensitive cortex

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The brains of human and nonhuman primates are thought to contain brain regions that have specialized for processing voice and faces. Although voice- and face-sensitive regions have been primarily studied in their respective sensory modalities, recent human functional magnetic resonance imaging (fMRI) studies have suggested that cross-modal interactions occur in these regions. Here, we investigated whether, and how, neuronal activity in a voice region is modulated by visual (face) stimulation.
Using fMRI-guided electrophysiology, we targeted neurons in a voice-sensitive region in the right supra-temporal plane of two rhesus macaques. We used dynamic faces and voices of different human and monkey individuals for stimulation, including congruent and incongruent audiovisual pairs.
We observed robust non-additive visual influences of facial information on the auditory responses of neurons in this voice-sensitive region. In accordance with previous studies, the direction of the audiovisual interactions seemed primarily determined by the phase of visually-evoked theta oscillations at auditory stimulus onset. Yet, we found that, in addition, speaker-related stimulus features such as caller familiarity and identity and call type, studied within a multifactorial experimental design, differentially modulated the crossmodal effects. In particular, familiar voices consistently elicited larger audiovisual influences than unfamiliar voices, despite auditory responses being similar. Finally, we found neurons to be differentially sensitive to stimulus congruency: the specificity of audiovisual influences was disrupted when violating the congruency of a conspecific voice/face pairing by substituting the monkey face with a human face.
In conclusion, our results describe the nature of the visual influences on neuronal responses in a voice-sensitive region in the primate brain. This study links to human fMRI studies on multisensory influences in voice/face regions, provides insights on the neuronal cross-modal effects in these regions and hypothesizes that neurons at face-sensitive regions might show comparable multisensory influences from the auditory domain.

Inactivation of ventral prefrontal cortex impairs audiovisual working memory.

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The ventral frontal lobe is well known for its role in language processing and social communication. Previous work from this lab has demonstrated that individual neurons within ventrolateral prefrontal cortex (VLPFC) process and integrate face and vocal information (Romanski et al., 2005; Sugihara et al., 2006). We have also recently shown that VLPFC neurons are active during audiovisual working memory (Hwang and Romanski, 2010). The effect of VLPFC lesions on tasks which assess learning or memory has been equivocal, with some studies demonstrating an impairment on visual learning and memory, auditory discrimination, rule learning, and decision making, while other studies have failed to demonstrate any deficits during working memory tasks. In the current study we asked whether VLPFC was essential in an audiovisual non-match-to-sample (NMTS) task designed to assess auditory and visual working memory. During the task, monkeys attended the audiovisual sample and were required to press a button when a non-matching stimulus, i.e. one whose auditory or visual track differed from the sample audiovisual movie, occurred. Our subjects, rhesus macaques, detected the non-match with a button press in order to receive a juice reward. We inactivated VLPFC while subjects performed the task by cooling the cortical surface of VLPFC below 20° C. During each testing session, 100 baseline trials were completed (WARM trials) and then the cortex was cooled below 20° C, and another 100 trials were completed (COLD trials). We assessed performance accuracy and reaction time in the auditory and visual non-match trials of the audiovisual NMTS task during WARM and COLD trials. Performance accuracy was significantly decreased during COLD trials compared to performance during WARM trials. Interestingly, performance accuracy was significantly worse on auditory mismatch trials compared to visual mismatch trials during the COLD trials. Reaction time was not significantly different between warm and cold trials. This data confirms that VLPFC plays a role in audiovisual processing and that VLPFC may be essential in auditory working memory.

Task-dependent spatial responses in auditory cortex of common marmosets

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Auditory cortex is essential for behaviors involving sound localization in mammals. Although spatial processing in auditory cortex has been extensively studied in passive subjects, there are few studies of spatial processing under behaving conditions. In this study, we investigated how representation of space by auditory cortex neurons is modulated as specific regions of space become behaviorally relevant. We recorded single-unit responses in auditory cortex of marmosets (Callithrix Jacchus), an arboreal New World monkey, while they performed a spatial discrimination task with either a contralateral or ipsilateral stimulus bias. We asked whether any observed changes in response properties would depend on either the spatial parameters of the task, or the spatial tuning properties of the neurons themselves. We found a population of neurons for which firing rates to target locations recorded during task engagement were increased when compared to those recorded during passive listening. There was also a smaller increase in firing rates to target locations in hit trials compared to miss trials. A subset of neurons showing increased firing rates to targets also had increased firing rates to background (non-target) locations. Neurons which showed increased firing in response to one target location tended to have increased firing rates to other target locations as well, and neurons with increased firing rates in the one behavior condition (e.g. contralateral stimulus bias) tended to also have increased firing rates in the opposite condition. Furthermore, neurons with increased firing rates included those preferring both contralateral and ipsilateral locations in the passive condition. Taken together, these results suggest responses of a subset of neurons in auditory cortex are modulated by spatial task.

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Neuronal correlates of selective auditory attention in rat prefrontal and primary auditory cortices

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How does the brain solve the cocktail party problem? Humans and other animals can focus on behaviorally-relevant sounds and ignore distracters. We have developed a rat model of selective auditory attention: the ability to respond to target sounds despite potentially conflicting information from simultaneous distracter sounds. To our knowledge, this is the first rodent model in which the animal selectively attends one of two simultaneously presented sounds, and can alternate the target of attention within a single session. Next, we have recorded extracellular single-unit activity in primary auditory cortex (A1) and the prelimbic area (PL) of prefrontal cortex of rats performing this task. A subpopulation of A1 neurons modulate their responses to the stimuli in a way that accentuates the representation of the target stimulus, compared with the simultaneous distracter stimulus. Furthermore, recordings from PL show that this prefrontal region is also modulated by attention: rather than firing equally for all attentional conditions, many cells significantly preferred to fire when the animal was attending just one of the task stimuli. In contrast to the results from A1, this modulation (1) affected a larger fraction of the recorded cells, (2) was greater in magnitude, and (3) preceded the stimulus onset. We suggest that these prefrontal neurons may actually drive task-relevant plasticity in A1, giving rise to the observed attentional effects in the sensory response. To test this theory, we next plan to measure functional connectivity between these regions during behavior. Moreover, now that the behavioral paradigm has been established in rats, future work will capitalize on the many genetic tools available in rodents to complement and extend what is known about attention from studies in human and non-human primates.

Local field potential activity in primate A1 during auditory delayed matching-to-sample and operant conditioning task performance

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The primary auditory cortex in non-human primates is located in the superior temporal gyrus and contributes to auditory perception and learning-induced plasticity (Kanold, 2012; Dexter, 2007; Bjordahl, 1998; Weinberger, 1998; Weinberger 1995). To further investigate auditory processing, local field potential (LFP) recordings were obtained from A1 in two awake, behaving rhesus macaques using an auditory delayed matching-to-sample (DMS) task. A wide variety of auditory stimuli were used: animal, human, and conspecific monkey vocalizations, environmental sounds, music clips, synthetic sounds, pure tones, and white noise. Each individual trial utilizes two auditory cues separated by a 5 second delay to measure retention. If the two cues are the same (match trial), the animal presses a button and receives a food reward, if different (non-match trial), no response is required and no reward is delivered. Interspersed with the DMS trials, are operant conditioning trials using both positive and negative conditional stimuli (CS+; CS-) consisting of different patterned white noise bursts. The CS+ is always paired with the opportunity for reward if the conditioned button-press response is made, and the CS- never predicts the possibility of reward. Preliminary analyses of broadband LFP recordings from a subset of locations in A1 show differential activity on correct DMS match and nonmatch trials. Evidence from the nonmatch trials during Cue 2, when compared to Cue 1 activity, show a significant early negative component at 30 ms after cue onset suggesting a very fast recognition of the nonmatching nature of the stimulus. Significant changes for the match trials were seen as early as 40 ms and were prominent at 270-510, and 600-1000 ms when compared to both Cue 1, and to Cue 2 on nonmatch trials across two positive peaks occurring for the cue and cue offset. Differential task activity in the frequency bandwidths theta (4-8Hz) and gamma (25-100Hz) was also evident, with the gamma activity encoding certain aspects of the sound stimulus and displaying oscillatory activity, which may be important for attention (Fell, 2003). The theta activity encoded more of the period related to response preparation, which was not noticeable in the gamma activity. In the evoked activity profiles to the well-learned CS+ and CS- cues, differences were observed when comparing the two stimuli to each other and to the other DMS cues during the task, showing faster onset latencies with smaller cue and offset responses. These results expand upon the idea that A1 demonstrates neuronal plasticity and may be capable of storing and/or differentially tagging some sounds as important.

Robust automatic speech recognition using sequential spike code

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Human speech recognition is highly robust to additive noise, but artificial speech recognition systems often fail in noisy conditions. We present a computational model for robust speech recognition that identifies sequences of auditory features using a sparse spike code. A simulation of the auditory periphery provides input to a population of feature-detecting neurons, which selectively respond to spectro-temporal patterns of 50ms duration. The receptive fields of the neurons are learned using a support vector machine. The neuron population's activity forms a spike code that contains stereotypical spike sequences corresponding to transitions between phonetic elements in speech. We identify words by quantifying the similarity of their spike sequences with those in a set of templates. Testing the method with a digit recognition task, we find that it gives superior results to a hidden Markov model, despite the absence of detailed noise modeling.

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The prevalence of mode-locked spike trains in the responses of cochlear nucleus neurons to periodic stimuli

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We report the prevalence of mode-locked spike patterns to the envelope of periodic stimuli in all neuron types in the cochlear nucleus (CN) of the cat. The CN is the site of termination of afferent auditory nerve (AN) fibres and its neurons can be divided into 4 major types, depending on their position in the CN, cell morphology and pure tone responses. Classical analyses of auditory neural responses to periodic stimuli have characterised the propensity of neurons to fire at a particular phase of a periodic stimulus – phase-locking. We previously demonstrated that stellate cells in CN display temporal firing patterns of a higher order, poorly described by pure phase-locking. Firing patterns were characterised by orderly sets of intervals which were related to the stimulus period, but more than one spike was fired per cycle and this pattern was repeated. These patterns were consistent with the concept of mode-locking, a general property of non-linear oscillators.

Here we sought to determine whether higher order spiking patterns were present in all CN unit types by re-analysing previously published datasets containing responses to sinusoidally amplitude-modulated (SAM) tones in around 600 CN neurons. To quantify the relative distribution of mode-locked spiking patterns across different response types, we developed statistical tests to determine when spike patterns were more complex than could be explained due to the modification of stimulus phase by the influence of action-potential refractoriness, such as in the AN.

Consistent with our earlier work, chopper neurons, which exhibit highly regular spiking in response to constant stimulation and are found in ventral CN, demonstrated the largest prevalence of mode-locking behaviour (40%). Onset neurons, which fire reliably at stimulus onset but with little or no sustained response, exhibited less mode-locking (10%). Primary-like neurons, which have similar sustained response profiles to AN fibres, displayed little mode-locking (5%), although a higher percentage of primary-like with notch neurons (15%) were classed as mode-locking. Interestingly, pause build-up neurons, found mainly in dorsal CN, exhibited a high prevalence of mode-locking (35%).

Thus, all cell types in CN can exhibit some complex spiking behaviour, but this is most common in chopper units in ventral CN and pause build-up neurons in dorsal CN. In these cell types, mode-locking appears to provide a good description of spike-timing. Spike-timing coding of SAM tones in other cell types is generally well described as being dependent on stimulus phase, which is then modified by refractoriness at higher spike rates.

Frequency-specific connectivity in the macaque auditory cortex

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Core auditory cortex in macaques consists of multiple tonotopic fields along the supratemporal plane (STP). From caudal to rostral, mirror reversals of the tonotopic gradient within the core demarcate the primary, rostral, and rostrotemporal fields (AI, R, and RT), capped by the rostrotemporal polar field (RTp) beyond the core. These mirror reversals create multiple distinct representations of a given frequency across the STP. Simultaneous recordings using micro-electrocorticography (micro-ECoG) revealed resting-state functional connectivity between regions of similar frequency preference (Fukushima et al., Neuron. 2012. 74:899), but the corresponding anatomical connectivity is unknown. We set out to determine to what extent the similarity in frequency preference among cortical sites could be attributed to parallel thalamic inputs, and/or frequency-specific cortico-cortical connections. In two monkeys, tonotopic maps of auditory cortex were delineated in the awake state by micro-ECoG arrays spanning the length of the STP. After recordings were concluded, neuroanatomical tracers were injected through the arrays, specifically targeting the pairs of high- and low-frequency regions that mark the borders of the core auditory cortical fields. In case 1, bi-directional dextran tracers were injected in two low-frequency sites: at the border between AI and R, and between RT and RTp. In a second case, retrograde fluorescent tracers were placed at these two low-frequency sites, as well as two high-frequency sites: caudal AI, and the border between R and RT. The origin of thalamo-cortical projections was identified by retrograde labeling in the medial geniculate nucleus (MGN). Projections to the two low-frequency sites were found to arise from adjacent or intermingled populations of neurons in the most ventral portion of the MGN ventral subdivision (MGv). In contrast, projections to high-frequency auditory cortex arose from more dorsal locations within the MGv, with little or no overlap between the regions projecting to rostral and caudal core fields. Density of cortico-cortical connections was greater between distant sites of similar frequency preference than between adjacent sites with different frequency preference. For example, the injection into the caudal low-frequency region (AI/R border) resulted in dense retrograde and anterograde label near the rostral low-frequency region (RT/RTp border), whereas label in high-frequency regions of R and RT was comparatively sparse. In summary, frequency-matched sites on the STP receive parallel input from separate populations of thalamic neurons, as well as frequency-specific serial projections from within the STP.

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To assess relevant stimulus features for sensory systems, researchers frequently perform reverse correlation techniques. In auditory cortex, simple reverse correlation procedures produce the SpectroTemporal Receptive Field (STRF). However, the STRF model assumes linear neural encoding, which is often insufficient to explain neural activity. More complex models of receptive fields characterize multiple relevant stimulus dimensions and spiking non-linearities. To fit this type of model, we utilize the Maximally Informative Dimensions (MID) procedure. The MID procedure maximizes the mutual information between the spiking response of the neuron and the projection onto multiple stimulus dimensions, termed MIDs. Multiple significant MIDs can be found in higher auditory stations of cats, but only rarely found in lower auditory stations. To determine if multiple MIDs are present only in higher, predatory mammals, such as cats, we also carried out a MID characterization of A1 in mice and rats. Similar to the A1 of cats, rodents also have strong secondary stimulus dimensions. Furthermore, these secondary stimulus dimensions are typically activated by either the presence or absence of a specific feature, and therefore demonstrate symmetric spiking non-linearities. Due to this symmetric non-linearity, these stimulus dimensions cannot be found with linear reverse correlation techniques. Comparisons of shapes, features, and complexity of MIDs between mice, rats, and cats are also explored.

Evaluating the necessity of norepinephrine for experience-dependent plasticity during auditory cortical development

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During circumscribed “sensitive periods” in postnatal development, passive sensory experience can play a profound role in shaping neural responses in sensory cortex. For instance, the proportion of units in the adult auditory cortex that respond to a particular frequency can be increased by exposure to that frequency during the sensitive period. Although recent work has begun to reveal how auditory responses mature during the sensitive period, the mechanisms responsible for permitting plasticity during this time are not known. Work in the visual system suggests that the neuromodulator norepinephrine (NE) may play a role, as early research indicated that it is required for ocular dominance plasticity in visual cortex. However, this finding has been contested. Here, we investigated whether norepinephrine is required for sensitive period plasticity in the auditory cortex using the dopamine beta-hydroxlyase knockout mouse (Dbh -/-), which is norepinephrine-deficient from birth. Mapping multi-unit electrophysiological recordings across auditory cortex, we compared auditory responses in adult Dbh -/- mice and their heterozygotic counterparts (Dbh +/-), which have normal levels of NE. Despite the lifelong absence of this neuromodulator, best frequencies, tuning bandwidths, firing rates, and gross tonotopic organization were comparable between animal groups. These results suggest that, in contrast to early work in the visual system, NE during the cortical sensitive period is not required to develop normal receptive fields and cortical topography. However, the possibility remains that compensatory mechanisms intervene during development in Dbh -/- mice to right cortical maturation. Thus, we present the results of a follow-up study wherein we attempted to drive plasticity directly by exposing litters of Dbh -/- and Dbh +/- mice to a biased acoustic environment during the murine auditory cortical sensitive period. Upon reaching adulthood, these animals underwent electrophysiological mapping of their auditory cortices, and preliminary results suggest differential effects of exposure on Dbh +/- and Dbh -/- mice. If confirmed in future work, this would imply that NE makes a significant contribution to auditory cortical maturation.

Information Transfer in the Ventral Auditory Processing Stream

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Neocortical sensory processing is thought to occur simultaneously in multiple cortical streams as the brain transforms sensory information into more cognitive representations. Neuroanatomical and lesion studies have identified two processing streams in audition: spatial elements of a stimulus are processed in a "dorsal" stream extending along the parietal lobe, and stimulus identity or quality is processed in a "ventral" stream extending rostrally along the temporal lobe. While there is compelling neurophysiological evidence for a "dorsal" stream in audition, physiological studies of a "ventral" stream are limited.

This study utilized conditional mutual information to examine the temporal dynamics of information processing along the superior temporal gyrus. We examined information transfer of action potential (AP) and local field potential (LFP) responses to species-specific vocalizations between primary auditory cortex (AI) and rostral parabelt auditory cortex (PBr) in a macaque. Additionally we examined information content of LFP responses to English phonemes in the STG of three human patients.

In the macaque, we show that the first 200 milliseconds of responses in PBr contain more information about vocalization stimuli when the first 200 milliseconds of responses in AI are known. In contrast, responses in AI contain more information about species-specific vocalizations when responses in PBr are known for longer duration responses. In the human patients, we show that there is increased information for phonemes patients reported hearing than for phonemes the patients heard.

These results elucidate the temporal progression and directionality of information processing along the ventral auditory processing stream, and provide insight into the neural representation of language perception.

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A statistical dynamic model for buildup of stream segregation with an ambiguous ABA auditory stimulus.

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When presented with ABA tone sequences with an intermediate frequency difference between the tones, subjects report alternating between two distinct percepts of the sound (Pressnitzer & Hupe, 2006). In some epochs, the tones sound coherently grouped in a galloping rhythm, whereas in the other epochs, the tones sound like two unrelated monotonic beep trains at different frequencies and rhythms. The progression from the first of these perceptual states to the second is thought to recruit intrinsic mechanisms that the auditory system relies on for stream segregation, i.e., the ability to distinguish different sound sources in a mixture (van Noorden, 1975). We developed a statistical model to describe the buildup of the segregated percept from coherent epochs. The buildup function is the probability as a function of time that a subject will perceive an unchanging stimulus as two distinct sound sources, given that the percept started as coherent. Rather than treating buildup as a process of accumulation over time of sensory evidence or of some intrinsic neuronal process, such as adaptation, our model explains the evolving probability of segregation over time as a simple consequence of alternations between random durations drawn independently from distributions for the two percepts. In our model, segregation dynamics can be predicted by these distributions of percept durations alone. We collected data from human subjects as well as from neural competition model simulations. The behavioral experiments used long (>4 min) presentations of ABA tone triplets with different frequency differences between the tones. We constructed buildup functions by estimating the probability over time that a fixed stimulus was perceived as two streams based on an event-triggered average aligned to each switch into the coherent percept. Preliminary experimental data is consistent with the predictions of our statistical model-- by fitting a gamma distribution to the percept durations for each percept, we can simulate buildup functions that matched those found experimentally. Moreover, we found that scrambling the order of the experimentally observed percept durations does not significantly change our computed buildup function. Simulations using noisy competition models give similar results, even though there are some correlations between durations from percept to percept. Finally, we have solved analytically our statistical model for the buildup dynamics. Our buildup functions, which treat percept durations as statistically independent, provide good approximations for the buildup functions obtained from both behavioral data and simulations from competition models.

Organization of human auditory cortex: Response patterns elicited by simple and complex sounds on Heschl's gyrus and posterior lateral superior temporal gyrus.

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One proposed functional neuroimaging method to identify core, belt and parabelt regions within the auditory cortex examines differences in the relative strengths of activation elicited by pure tones, bandpass noise and speech sounds (Chevillet et al., J Neurosci 2011, 31:9345-52). It is unclear, however, whether this method is applicable when examining electrophysiological responses recorded directly from auditory cortex. In this study, we compared responses elicited by these three classes of sounds, recorded simultaneously from posteromedial and anterolateral segments of Heschl's gyrus (HG) and posterolateral superior temporal gyrus (PLST).

Subjects were neurosurgical patients undergoing chronic invasive monitoring for medically refractory epilepsy. All research protocols were approved by the NIH and The University of Iowa IRB, and subjects who consented to the research could rescind consent at any time without detriment to their medical evaluation. Event-related band power in the high gamma frequency range was examined. This measure has been shown to correlate better than the averaged evoked potentials with activation determined by functional neuroimaging studies (Mukamel et al., Science 2005, 309:951-4; Niessing et al., Science 2005, 309:948-51). Locations of recording sites were confirmed by co-registration of pre- and post-implantation structural imaging and aided by intraoperative photographs.

Pure tones elicit large-amplitude responses within a restricted portion of PLST. Therefore, the presence of robust responses to pure tones may not be sufficient to define the core auditory cortex, as used previously (Chevillet el al., 2011). Similarly, bandpass noise and speech elicit robust responses on PLST, though speech sounds appear to activate more extensive areas of PLST relative to simpler stimuli. This latter response attribute may be an important marker in field delineation. We are continuing our examination by comparing relative strengths of responses to different classes of sounds and evaluating whether they can serve as a basis for demarcating core, belt and parabelt in the human auditory cortex.

Population coding of sound level in primary auditory cortex

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Two distinct types of neuron responses to sound level exist in primary auditory cortex. Monotonic neurons' firing rates increase with sound level and possibly saturate, whereas non-monotonic neurons exhibit their highest firing rates at an intermediate sound level. One hypothesis regarding the role of these two types of neurons in sound level encoding is that non-monotonic neurons are particularly useful for encoding sounds invariantly across sound level, while monotonic neurons are most useful for encoding the actual level of a sound with high fidelity. We examined the capacity of these two types of neurons to contribute to level-invariant and level-fidelity encoding by analyzing neural responses of 544 marmoset primary auditory cortex neurons to pure tones of different sound levels. From the entire population of neurons, subpopulations were created having a variety of sizes and proportions of non-monotonic neurons. The separability of the group responses to tones of different sound levels was then assessed for each subpopulation by applying *k*-means classification. For all population sizes, subpopulations with higher non-monotonic proportions consistently produced somewhat higher mutual information indices and classification purity for *k*-means classification results, indicating that non-monotonic neurons might contain more information for differentiating sound levels than monotonic neurons. To determine the performance of the two types of neurons in an actual coding task, an optimal rate-based linear estimator was constructed for each subpopulation to generate either a constant discriminability (level-fidelity task) or a constant representation across sound level (level-invariant task). Then coding performance was quantified in terms of decoding error. Interestingly, in the level-fidelity task, non-monotonic neurons provided no advantage for decoding. Instead, a non-monotonic neuron proportion greater than about 50% became detrimental to population performance. In the level-invariant task, decoding performance improved with non-monotonic neuron proportions up to 60-70% and then began to deteriorate for higher non-monotonic neuron proportions. Together, the results from the two decoding tasks indicate that a combination of the two types of neurons would give the most accurate decoding. In conclusion, our study shows that non-monotonic neurons might contain more information about sound level identity than monotonic neurons. However, in the case of linear rate decoding, the two types of neurons must work together to produce optimal coding performance.

Neuromagnetic signatures of segregation in complex acoustic scenes

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The natural auditory environment consists of multiple dynamically varying sound sources. In order to make sense of this complex mixture of sounds, we need to segregate individual sources, such as the sound of the violin in an orchestra. The brain has evolved specialized mechanisms for performing such auditory scene analysis, but the underlying mechanisms remain to be fully explained.

We improved upon earlier experimental paradigms based on deterministic patterns of pure tones and modelled the acoustic scenes using a stochastic figure-ground stimulus (SFG, Teki et al., 2011). The stimulus comprises a series of chords (25ms long) containing random frequencies that vary from one chord to another in a range from 200 Hz to 2.5 kHz. To study segregation, we introduced a figure by randomly selecting a certain number of frequencies (where that number defines 'coherence') and repeating them over a certain number of chords (where that number defines 'duration'). This manipulation allows us to parametrically control the salience of the figure, which is indistinguishable from the background at any given point of time. The figure can only be extracted by binding across both time and frequency, and we found that behaviourally, listeners are very sensitive to the emergence of these complex figures. We have previously established a role for the intraparietal sulcus (IPS) in stimulus-driven segregation of these figures (Teki et al., 2011) and ongoing work further suggests a role for temporal coherence (Shamma et al., 2011) in segregation in such complex acoustic scenes (Teki et al., 2012).

We used Magnetoencephalography (MEG) to investigate mechanisms underlying the emergence of figures with different salience (coherence of 2, 4 or 8; 0.6 long) presented after the statistically similar background segments (0.6 s). Listeners were engaged in an incidental visual task and were naive to the existence of the changes in the SFG stimulus. In another condition, we presented the same stimuli but interspersed with alternating white noise segments, as we previously found that this manipulation does not affect detection performance (Teki et al., 2012).

Analysis of time-locked activity in auditory cortex shows an initial onset response to the emergence of the figure, followed by a sustained response which follows the figure while it is present in the stimulus. Source analysis is on-going. The figure onset responses occur about 100ms in the coherence=8 condition, and 150 ms for coherences 4 and 2. These latencies correspond to a duration of 4 (or 6) chords and parallel behavioural performance (obtained separately). Latencies from the 'noise' condition reveal the same threshold, suggesting that the segregation mechanism was not affected by the introduction of noise bursts between successive chords. Time-frequency analysis is ongoing using a beamformer approach (Sedley et al., 2011) to identify early and late oscillatory activity in sources within auditory and parietal cortex.

Tectothalamic inhibitory neurons in the inferior colliculus receive converged axosomatic excitatory inputs from multiple sources

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Large GABAergic (LG) neurons in the inferior colliculus (IC) are encircled by dense excitatory terminals positive for vesicular glutamate transporter 2 (VGLUT2), and project to the medial geniculate body. Four auditory brainstem nuclei including IC itself were identified as possible sources by examining mRNA expression of VGLUT1 and VGLUT2 in IC-projecting cells. In this study, Sindbis/pal-GFP virus was injected in these nuclei to elucidate whether neurons in the nuclei make axosomatic contacts on LG neurons or not. Labeled neurons in all four nuclei made axosomatic contacts on LG neurons. Furthermore, a single axon made one to six contacts on a LG neuron. In 3 cases, a single IC excitatory neuron was successfully labeled, and analyzed for spatial relationship between the labeled axon and LG neurons. A single IC excitatory neuron made axosomatic contacts on 10-30 LG neurons in the ipsilateral IC. Finally, double injection of Sindbis/pal-GFP and Sindbis/pal-mRFP viruses in 2 nuclei revealed convergence of inputs from 2 nuclei on a single LG neuron. The results imply both divergence and convergence of auditory information on the cell bodies of LG neurons

Responses of marmoset frontal cortex neurons during a natural vocal behavior: antiphonal calling

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Little is currently known about the role that primate frontal cortex plays in natural vocal communication. Here we recorded single neuron activity in marmoset frontal cortex while subjects engaged in a natural vocal behavior known as antiphonal calling. This behavior involves the reciprocal exchange of vocal signals between conspecifics. Specifically, the behavior involves both sensory (hearing vocalizations) and motor (producing vocalizations) components. As such, antiphonal calling provides a unique opportunity to investigate the interaction between these systems within a single natural communication behavior. To characterize the neural basis of this vocal behavior we combined two methods. First, we elicit this behavior under experimental conditions by implementing a novel interactive playback method. Second, we implement a technique for recording neural responses from freely moving marmosets. In the current study we recorded the responses of neurons in the ventral prefrontal and premotor cortex, as well as the dorsal premotor cortex. Overall we observed that neurons in prefrontal cortex were responsive to both the sensory and motor components of the behavior. Responses to vocalization stimuli appeared to be dependent on the communication context. Neurons responsive to vocalizations during antiphonal calling were less likely to elicit a response when a vocalization was presented but did not elicit a vocal response. Furthermore, several sensory-motor interactions were evident in prefrontal cortex neurons during antiphonal calling. In contrast to prefrontal cortex, dorsal premotor cortex exhibited little sensory activity, but showed strong responses just prior to the onset of vocal production. Overall, these data suggest that frontal cortex does play an important role in primate vocal communication and contributes to both vocalization processing and the motor control of vocal production.

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Population receptive field analysis of human primary auditory cortex.

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Purpose: We describe here a method that provides robust maps of human auditory cortex using a standard 3T scanner and an adaptation of the population receptive field (pRF) analysis method that was developed by Dumoulin and Wandell (2008).
Methods: Pure tone stimuli were presented to subjects in forward or reverse progressions of 14 frequencies (88-8000 Hz) at an equal perceived volume (65-85 dB) using methods based on Da Costa et al. 2011. Our pRF analysis assumes that each voxel has a sensitivity function that is a one-dimensional Gaussian as a function of log-frequency. The center (x) of each Gaussian corresponds to the center or best frequency (Hz), while the standard deviation (σ) provides a measure of population bandwidth. Best-fitting parameters for each voxel were obtained by fitting the acquired time series to a model time course. Independently generated topographic maps for best frequency and bandwidth were created for each scan.
Results: Robust pRF maps of the PAC revealed clear subdivisions (hA1, hR) that were functionally delineated by clear mirror-symmetric frequency gradients (Formisano et al. 2003, Striem-Amit et al. 2011, Humphries et al. 2010) which followed the morphology of Heschl's gyrus (Da Costa et al. 2011). Estimates of population tuning bandwidth were also obtained. Maps of the pRFs were highly replicable with high cross-correlations across individual scans. Comparison of data across scans using pulse sequences at two different frequencies of auditory noise demonstrated that the disruption of frequency estimates was restricted to voxels tuned to the frequency of the scanner noise.

Auditory attention during a natural cocktail party in common marmosets

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Sound arrives at the ears in a mixture from many sound sources. Humans have the extraordinary ability to follow single conversations in environments full of interfering noise. The perception of different sounds occurs effortlessly, yet how the auditory system interacts with higher-level cortical areas to decompose the composite sound wave and recompose those components into the percept of the speaker is not well understood. In order to investigate this phenomenon, known as the cocktail party problem (Cherry, 1953), we are developing an acoustically complex and naturalistic auditory scene in which we exploit a natural communicative behavior of the common marmoset. When occluded from conspecifics, marmosets engage in antiphonal calling. This vocal behavior is the reciprocal exchange of long-distance contact calls, known as phee calls. Our experiment consists of a multi-speaker set up in which two speakers (each simulating individual marmosets) are occluded from the subject and are broadcasting phee calls at different latencies and probabilities in response to subject calls. Subjects must use the cues available to determine which speaker is willing to engage in vocal interactions and which is not. In essence, the subject must attend to one speaker while simultaneously ignoring calls from the other speaker. Preliminary data suggest that the latency with which a marmoset makes a response and the response probability are important cues in communication. We found that the shorter the speaker’s response latency and the higher the response probability, the more likely a subject is to engage in communication. However, at low response probabilities the latency of a speaker response is less important and the likelihood that the subject will elicit antiphonal calls dramatically decreases. We have also shown that marmosets differentially respond to one speaker over another, thus attending to that speaker while ignoring the other, based on the latencies and probabilities that each speaker encapsulates. Examining the cocktail party effect in marmosets will allow us to focus future work on investigating neural activity in higher-level cortical areas involved in attention, planning, perception, and the decision-making involved in antiphonal calling in a noisy setting.

Multielectrode recordings within and across structures in the inferior colliculus and optic tectum

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The barn owl auditory localization pathway is a prime candidate for connectome reconstruction. The value of this project will be enhanced by functional characterization of diverse circuit elements in vivo. We are using a seven channel multielectrode array to record simultaneously from neurons distributed within and across stations of the serial processing hierarchy, from the lateral shell of the central nucleus of the inferior colliculus (ICCls), to the external nucleus (ICx), to the optic tectum (OT). Neurons within the ICx compute sound source location by integrating complex inputs, and are arranged systematically to form a map of auditory space. From single electrode surveys it is known that neighboring neurons exhibit similar spatial tuning, but the precise variance between neighbors, and the cataloging of distinct response profiles, is best assessed by sampling local clusters using a tightly spaced concentric array. This is paired with recording from spatially matched sites in either the ICCls or OT, to assess functional connectivity using cross-correlation analysis. Recording sites will be marked using electrolytic lesions and fluorescent tracing. In total, these data will be essential for accurately modeling activity flow through the reconstructed network.

Resting-state functional connectivity reveals auditory-limbic network in tinnitus

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The auditory disorder tinnitus is characterized by the perception of sound in the absence of an external source. Despite the prevalence of this disorder, its pathophysiology remains poorly understood. A large body of evidence has revealed changes in the auditory system of patients with tinnitus, including damage to one or more sites along the auditory pathway, both peripheral and central; however, auditory damage alone seems insufficient to cause chronic tinnitus. Given this constraint, and the growing body of evidence implicating limbic involvement, we propose that limbic dysfunction may play a critical role in causing, as well as perpetuating, the tinnitus percept. For our current study, we chose to elucidate this dysfunction using functional connectivity magnetic resonance imaging (fcMRI). Since behavioral data have indicated that tinnitus is most noticeable in the absence of tasks or distractors, we chose to analyze connectivity from resting-state fcMRI data, i.e., data acquired when subjects were not performing any tasks. Specifically, we used Independent Component Analysis (ICA), a data-driven, non *a priori* statistical technique, to identify roughly 25 functionally connected resting-state networks (RSNs). Auditory, visual, "default-mode," and other neurophysiologically plausible networks were consistently detected in all subjects, along with non-neurophysiological networks, e.g., respiration and heart rate, which were removed from further analysis. Of particular interest was a network that appeared in ICAs of tinnitus patients, but not of controls matched for age and hearing loss. This network demonstrated a unique inverse relationship between medial Heschl's gyrus (mHG) and the Nucleus Accumbens (NAc), suggesting a direct or indirect connection between the two regions. Apart from revealing a novel auditory-limbic network, these results are consistent with previous reports of NAc involvement in tinnitus (Leaver et al. 2011), and suggest a far-reaching tinnitus network incorporating non-auditory regions (e.g., Schlee et al. 2008). The present study offers the additional advantage of superior spatial resolution afforded by fcMRI while elucidating this network more precisely. Overall, our data suggest a much larger role for the limbic system in tinnitus pathophysiology than previously thought, thus opening new avenues for potential treatments of the disorder. Furthermore, additional study of limbic connectivity may shed light on the system's involvement in other sensory pathways, which could potentially provide a bridge between tinnitus and certain forms of chronic pain.

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Pulse induction in pseudorandom sequences measured with pulse attribution and tapping rate

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The question of pulse perception involves asking, for any given rhythmic sequence, whether the sequence has a pulse, and if so what is its frequency. Experimentally, these issues are usually addressed separately, by asking participants to provide judgments of isochrony for jittered sequences (pulse attribution) or by asking participants to tap at a perceived pulse rate for rhythmic patterns (pulse finding). In this experiment, the stimuli were isochronous sequences modified with varying levels of Kolakoski jitter. Levels of jitter ranged from small to large and were roved randomly. In separate blocks, participants were asked to provide pulse attribution judgments and to tap at the pulse rate. For small levels of jitter, pulse attribution ratings were high and participants tapped periodically at the mean sequence rate. For intermediate levels of jitter, pulse attribution ratings dropped and tapping variance increased. At certain high levels of jitter, pulse attribution ratings increased and participants entrained at a new tapping rate. Thus, by smoothly varying a single parameter, the percept changed from that of jittered isochrony to that of rhythmic patterning. Moreover, spectral energy peaks predicted mean tapping rate and stronger peaks corresponded to higher pulse attribution ratings, consistent with a neural resonance model of pulse perception. These results may lead to a better understanding of pulse perception in irregular or randomized sequences.1

A hypothetical role for echolocation in shaping left hemispheric specialization for processing social calls in mustached bats

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Evidence suggests that the degree of left hemispheric specialization in the auditory cortex (AC) for processing social calls, such as human speech sounds, is dictated by acoustic structure and not semantics. Specifically, the relatively greater precision with which the left AC processes time-critical (temporal) information enables it to detect the rapid frequency modulations (FMs) that comprise social calls, which are analogous to formant-transitions in speech. The right AC, on the other hand, has greater precision at processing frequency-related (spectral) information that enables it to track prosodic variation and pitch. Elements of this Asymmetric Sampling of Time have been identified not only in human AC but also in the Doppler-shifted constant frequency processing (DSCF) subregion of mustached bat AC. Here, we use published observations and theorems to suggest how an idealized version of the classic left hemispheric specialization for speech processing, characteristic of human AC, evolved in the DSCF area. We review how DSCF neurons use the tonal component of the returning, Doppler-shifted, second harmonic of the echolocation signal in this species (echo-CF_2) to calculate the relative velocities of targets, including prey. Precise velocity calculations based on the echo-CF_2 are thus ethologically advantageous to the mustached bat but can only be achieved by refined frequency discrimination. The Nyquist Sampling Theorem dictates that refining frequency discrimination comes at the expense of temporal precision, and refined temporal precision is necessary for detecting and processing rapid FMs in social calls of this species. Thus environmental pressures and physical limitations forced right hemispheric DSCF neurons to develop greater spectral precision, enabling them to precisely track target velocity and other frequency variations but restricting their ability to detect and process short, rapid FMs. Left hemispheric DSCF neurons, on the other hand, developed greater temporal precision and can thus process the short, rapid FMs used in social calls but perform frequency discrimination relatively poorly. We acknowledge and address discrepancies related to sex differences. If orientation sounds shape left hemispheric specialization of social calls, it would be further evidence that this asymmetry is driven by acoustic structure and not semantic content. Left hemispheric specialization for social calls and rapid FMs in mustached bats, far from being a simple scientific anomaly, could help unravel fundamental phonological mysteries related to hemispheric differences in speech processing.

Frequency selectivity throughout the auditory system

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Frequency selectivity is a fundamental and extensively studied property of the auditory system, yet it is not clearly known whether it is established at the periphery or whether central mechanisms make a contribution. This is due, in part, to the fact that two distinct approaches are taken, psychophysics and physiology, the results of which are difficult to reconcile. Psychophysical estimates are made using masking paradigms, whilst many physiological measurements in the past were made using pure-tone responses. Also, psychophysics measures detection thresholds, which are not necessarily comparable to the mean spike rates used in physiology. Finally, psychophysical techniques have been refined over time. Modern methods show that perceptual auditory filters exhibit non-linear characteristics presumably reflecting cochlear filtering. For example, cochlear suppression results in wider auditory filters for simultaneous maskers.

In an attempt to bridge the gap between the two approaches, and shed some light on the question of frequency selectivity throughout the auditory system, we measured auditory filter widths in single neurons in the Inferior Colliculus (IC) and the Auditory Cortex (AC) of guinea-pigs using a notched-noise masking paradigm typically used in psychophysics. Signal Detection theory was used to convert the firing rate of the cells into neurometric functions, similar to psychometric functions. Roex functions were then fit to obtain neural auditory filter shapes and Equivalent Rectangular Bandwidths (ERBs) from masked thresholds. In addition filter estimates were made by fitting a roex function to the pure-tone response area, allowing a direct comparison with the notched-noise masking approach.

Units that produced clean ‘neurometric functions’ yielded auditory filter widths which were relatively homogenous and increased with characteristic frequency (CF). Bandwidths derived from notched-noise stimuli from both IC and AC units agreed well with one another, with peripheral measurements (Auditory Nerve and Cochlear Nucleus) using pure-tones, and psychophysical measurements in guinea-pigs. However, filter widths calculated using pure-tones were on average roughly twice as large as those using notched-noise masking. This suggests that frequency selectivity measured using masking in central auditory neurons reflects peripheral filtering and matches perceptual estimates of bandwidths, despite variations in neuronal pure-tone tuning characteristics.

Closed-loop audiomotor training improves neural and behavioral discrimination of weak signals in noise in mice and men

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Perceiving weak sounds in noisy backgrounds represents a fundamental challenge for normal and hearing-impaired listeners alike. In this study, we addressed whether the discrimination of faint signals in noise could be improved at both neural and behavioral levels through intensive daily training on a new type of signal-in-noise discrimination task. We began by training mice to use continuous auditory feedback to locate randomly positioned virtual targets in a training arena. In keeping with the children's game "hot and cold", the level of a tone presented in a broadband noise masker was continuously updated in real time according to the distance separating the mouse from the virtual target location. Targets were set to the least favorable signal-to-noise ratio (SNR), requiring that mice use closed-loop auditory feedback to navigate a SNR gradient until they had identified the spatial position associated a barely perceptible tone in noise. Over 16 weeks, mice learned to perform the task more accurately and efficiently as evidenced by significant increases in their success rate and a 20% reduction in the time required to find the target. Tonal receptive fields derived from acute extracellular recordings in the primary auditory cortex of trained mice revealed superior noise resistance and enhanced representation of the intensity and frequency of the target stimulus relative to control mice that passively experienced each day of training. Additionally, increments in signal level were associated with larger changes in neural firing rate in trained mice, perhaps representing a neural mechanism to maximally discriminate small changes in intensity level. Ongoing experiments have engaged normally hearing human listeners in an analogous training task, wherein avatars search for low SNR targets in a virtual training arena. This approach permits a comparative analysis of audiomotor learning strategies and allows us to test whether signal-in-noise training with simple parametric stimuli generalizes to "real world" hearing challenges such as speech comprehension in noisy backgrounds.

Time course of contrast gain control in ferret auditory cortex

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Recent work in our laboratory (Rabinowitz et al, Neuron 2011) has found that neurons in the ferret's auditory cortex adjust their gain (sensitivity) according to the recent contrast of auditory stimulation. When sound contrast is low, neuronal gain is high, so that small changes in sound level can be detected. When sound contrast is high, neuronal gain is reduced, so that neuronal responses are less likely to saturate. This mechanism has several desirable properties. For example, it allows a wide range of sound contrasts to be accurately encoded by a single neuronal population, and makes the population response relatively invariant to changes in sound contrast.

Here, we investigate the time period over which neurons measure the contrast of recent sounds. There are two interesting possibilities. First, one might expect neurons to change their gain in a statistically optimal way. If this were the case, one would expect gain changes to occur more rapidly if the stimuli themselves are rapidly varying. For slowly-varying sounds, a longer period of time is required to measure the sound contrast, and so gain changes would be expected to occur more slowly. The alternative hypothesis is that the time period over which gain is measured might be fixed, suggesting that gain control will fail for slowly-varying sounds.

To distinguish these possibilities, we presented sequences of discrete random chords (DRCs) to anaesthetised ferrets while extracellularly recording the responses of cortical neurons. Each chord is a superposition of pure tones, where the level of each tone is chosen from a uniform distribution. We varied the speed of the DRCs so that new chords were presented at time intervals ranging from 6.25ms to 100ms. The contrast of the DRCs also changed at regular intervals (0.5s to 2s). We estimated spectrotemporal receptive fields for the neurons, and used these to measure the time taken for neurons to adjust their gain after a change in contrast.

Initial data suggest that ferret cortical neurons do not alter their contrast integration time when the speed of the stimulus changes; integration times are fixed at around 100ms. This suggests that cortical neurons do not change their gain in a statistically optimal way. Instead, gain control may be matched to the average contrast statistics of natural sounds.

Laminar differences in functional organization of the mouse primary auditory cortex

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A distinguishing feature of the mammalian brain is the six-layered neocortex organized into radial columns. In primary sensory areas of the neocortex, sensory information enters in the thalamorecipient layer and is further processed in supragranular layers. While topographic maps of stimulus features are well-documented in the neocortex, the local intrinsic cortical circuitry might transform the topographic representations between cortical laminae. However, the existence and details regarding the nature of this transformation are unknown. Here, we used in vivo two-photon Ca^{2+} imaging to sequentially probe the organization of the mouse primary auditory cortex in supragranular and thalamorecipient layers. We show that while the spatial organization of neural response properties (tuning) within the supragranular layer can be heterogeneous, the organization in the thalamorecipient layer is more homogeneous. Moreover, stimulus-driven correlated activity (signal correlations) between neurons is higher in the thalamorecipient layer whereas trial-to-trial covariance (noise correlations) is higher in supragranular neurons than in the thalamorecipient layer. These findings reveal a transformation of sensory representations that occurs across a single cortical layer. The laminar differences in processing within the auditory cortex could generate sequentially more complex analysis of the acoustic scene incorporating a broad range of spectro-temporal sound features.

MODIFIED AREAL CARTOGRAPHY IN THE CAT AUDITORY CORTEX FOLLOWING EARLY AND LATE ONSET DEAFNESS

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Cross-modal plasticity following deafness is an adaptive response that enables deaf auditory cortex to provide enhanced abilities to remaining sensory systems. This cortical reorganization has been shown in the cat auditory cortex following early onset deafness in electrophysiological and psychophysical studies. However, little information is available concerning structural compensations underlying these functional adaptations. Therefore, the purpose of this study was to examine if areal cartography in auditory cortex is modified following early onset deafness (n=5). As a control, we also examined mature hearing cats (n=5) and cats with late onset deafness (n=5). Cats were ototoxically deafened postnatally before hearing onset or in adulthood (>6M). Cerebral cytoarchitecture was revealed immunohistochemically using SMI-32, a monoclonal antibody that stains neurofilaments and is used to distinguish auditory and visual areas in cats, monkeys and humans. Areas of auditory cortex were delineated in coronal sections and their volumes were measured. The data showed: 1) Staining profiles observed in hearing cats were conserved in both early deaf and late deaf cats. 2) In both early deaf and late deaf cats there was a reduction in primary auditory cortex (A1) volume. 3) In early deaf cats, the secondary auditory cortex and ventral auditory field volumes were greater than hearing controls. Overall, borders between dorsal auditory areas (anterior auditory field, dorsal zone) and adjacent visual areas were shifted ventrally in early deaf cats. This may reflect a reduction in A1 volume and/or expanded visual cortex. These results establish that following deafness, cortical plasticity results in significantly different areal cartography from that of hearing animals.