APAN 2016 POSTER ABSTRACTS

1 Utilizing multisensory integration to improve auditory alarm design in the intensive care unit

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Sound exposure in the hospital can have deleterious effects on patients and practitioners. Clinicians perform worse on tasks involving patient monitoring in noisy and highly attentionally demanding environments. Research on the signal-to-noise ratio of alarms can decrease the overall sound exposure by decreasing the alarm fraction contribution of total sound.

Alarms in the ICU sound frequently and 85-99% of cases do not require clinical intervention. As alarm frequency increases, clinicians develop 'alarm fatigue' resulting in desensitization, missed alarms, and delayed responses. This is dangerous for the patient when an alarm-provoking event requires clinical intervention but is inadvertently missed. Alarm fatigue can also cause clinicians to: set alarm parameters outside effective ranges to decrease alarm occurrence, decrease alarm volumes to an inaudible level; silence frequently insignificant alarms; and be unable to distinguish alarm urgency. Since false alarm and clinically insignificant alarm rates reach 80-99%, practitioners distrust alarms, lose confidence in their significance, and manifest alarm fatigue. Yet, failure to respond to the infrequent clinically significant alarm may lead to poor patient outcomes. Fatigue from alarm amplitude and nonspecific alarms from uniform uninformative alarms is the post-monitor problem that can be addressed by understanding the acoustic features of alarms and the aural perception of clinicians.

Our experimental paradigm determines near-threshold auditory perception of alarms, and then uses clinical scenarios to determine the stimulus-response relationships for changes in auditory alarm intensity, spanning negative to positive signal-to-noise ratios (SNRs), when performing an audiovisual secondary task designed to tax attentional and decisional resources. The result is a stimulus-response curve in dB above ambient noise.

Results show near-threshold auditory perception of alarms is around -27 decibels (dB) from background noise at 60 dB. Additionally, with visual offset of a patient monitor, there is preserved performance measured by response time and accuracy to a clinical task at -11 dB as compared with +4dB with worsening at more negative SNRs. Thus, clinician performance is maintained with alarms that are softer than background noise. These results can inform future work on alarm fatigue to address the music perception and cognition components of novel psychoacoustic alarm presentations in concordance with existing standards (IEC 60601-1-8).

2 Role of Auditory Thalamus in the Cortical Frequency-specific Plasticity

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Auditory learning induces frequency-specific plasticity in the auditory cortex. However, the role of the intracortical circuitry in the development of the cortical plasticity remains unclear until the potential contribution of the corticothalamic and thalamocortical loop is excluded. Here, we examine the frequency-specific plasticity in the auditory cortex (AC) by intracortical electrical stimulation (ESAC) with and without inactivation of the auditory thalamus. We found that ESAI induced cortical frequency-specific plasticity in the control condition when the auditory thalamus was not inactivated. Similar pattern of cortical plasticity was induced by ESAC when the auditory thalamus was inactivated during the ESAC. The best frequencies (BFs) of the recorded cortical neurons shifted towards the BFs of the electrically stimulated ones. In addition, the BF shifts were linearly correlated to the BF differences between the recorded and stimulated cortical neurons. More importantly, the ratio of the linear function with thalamic inactivation was nearly the same as the ratio of the linear function in the control condition. Our data suggest that the induction of frequency-specific plasticity in auditory cortex does not rely on the corticothalamic and thalamocortical loop, thus the intracortical circuitry appears to independently underlie the cortical frequency-specific plasticity.

3 Noise-robustness of cortical responses to natural sounds increases from primary to non-primary auditory cortex

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In everyday listening, the sounds from sources we seek to understand are often embedded in background noise. This noise alters the pattern of spikes in the auditory nerve, often to a profound degree. In order to recognize sources of interest, the brain must to some extent become robust to the effects of these background noises. To study the neural basis of listening in real-world background noise, we measured fMRI responses in auditory cortex in eight human listeners to a broad set of thirty natural sounds, presented in quiet as well as embedded in thirty different everyday background noises (e.g., a bustling coffee shop, crickets chirping, heavy rain hitting pavement). We quantified the extent to which neural responses were robust to background noise by correlating each voxel's response to the natural sounds in isolation with its response to those same natural sounds mixed with background noise. We then squared this correlation coefficient to get a measure of variance explained, and normalized it by the reliability of the voxel's response, measured across split halves of the data. This measure quantifies the extent to which a voxel's pattern of response across natural sounds is the same when the natural sound is presented in quiet and when it is embedded in noise. Responses in anatomically-defined primary areas (TE 1.1 and 1.0) were substantially affected by background noise (r**2 ~ 0.40). However, voxel noise-robustness increased with distance from these primary areas: nearby non-primary areas were slightly more robust, while more distal areas were hardly affected by the background noises (r**2 ~ 0.85). Mean responses in primary and non-primary regions were both only slightly lower in the presence of background noise, indicating that this effect was not due to the background noises differentially suppressing responses in primary areas. Our results illustrate the neural basis of a core aspect of real-world listening, and offer evidence of a potential hierarchy in human auditory cortex.

4 NMDA receptor-dependent temporal processing plasticity in the developing auditory cortex requires GABA(B) receptor-mediated inhibition

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Faithful tracking of rapidly successive acoustic signals in the primary auditory cortex (A1) is vital to processing of temporal information and perception of natural sounds such as human speech and animal vocalizations. However, how cortical stimulus-tracking capacity developmentally emerges remains poorly understood. Using in vivo whole-cell recordings, we found that inhibition in the developing rat A1 was initially prolonged and strong, leading to cortical responses with considerably poor temporal resolution. Unexpectedly, brief exposure to repeated acoustic stimulationsounds repeated at high ethological rate produced significant and long-lasting shortening of inhibition duration, resulting in strongly improved periodicity of cortical responses. Selective interruption of the signaling pathway Blockade of postsynaptic GABAB rather than GABAA receptors shortened inhibition duration, prevented exposure-induced plasticity and improved cortical stimulus-tracking ability. Furthermore, the blockade of NMDA receptors abolished exposure effect. These results identified GABAB receptor as a key player in NMDA receptor-dependent mediating, at least the initiation of, experience-dependent, non-map plasticity of temporal processing in the developing cortex.

5 Weighting perception of ambiguous motion stimuli: The curious case of audition trumping vision

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The ability to combine and integrate information from the different senses into a single coherent percept is an inherent ability of our nervous system. Moreover, this ability is crucial when available sensory information is degraded and/or ambiguous, and can confer powerful behavioral and perceptual benefits. While a large body of work has focused on static multisensory stimuli, less is known about the principles underlying the integration of dynamic (i.e. ethologically valid) stimuli. To address this question at both the behavioral and neuronal levels, we employed dynamic motion stimuli (i.e. random dot kinematograms and auditory motion embedded in noise) in a two alternative forced choice task in which subjects had to judge the direction of motion. We manipulated both stimulus efficacy (i.e. motion coherence) and congruency between auditory and visual motion (i.e. leftward or rightward) stimuli on a trial-by-trial basis. Subjects performed the task while high-density EEG data were concurrently acquired. Preliminary findings revealed behavioral benefits under congruent multisensory presentation conditions as compared to either unisensory condition alone. These behavioral benefits were further increased as a function of motion coherence. Intriguingly, under incongruent pairing conditions, we found that subjects more heavily weighted auditory information. Moreover, auditory weights were further increased for pairings with high (60%), as opposed to low (6%) visual motion coherence. These findings seem to be inconsistent with prior findings, that suggest that subjects attribute higher perceptual weights to visual information in spatial tasks (i.e. Modality Appropriateness Hypothesis). Analyses of the scalp evoked responses focus on revealing the neuronal correlates in terms of response strength (Global Field Power) and neuronal generators (Topographic Dissimilarity) underlying the attribution of perceptual weights, and ultimately sensory-motor transformation. Moreover, we seek to identify the neuronal loci that are differentially recruited as a function of stimulus efficiency and behavioral choice. Some of the most informative analyses focus on trials in which the stimuli are identical but it which the behavioral responses differ, thus providing insight into the network differences attributable to sensory statistics or perceptual choice. We expect to observe increased neuronal responses (e.g. GFP) in congruent trials underlying behavioral benefits. However, incongruent pairings, would result in the recruitment of differential neuronal networks, as a function of the perceptual weights attributed to either unisensory cue.

6 Reward cues direct auditory attention and modulate fMRI activations in monkey auditory cortex

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Training nonhuman animals on active auditory tasks is notoriously difficult and time consuming, typically requiring hundreds of daily training sessions. Advancing and developing animal models for human auditory cognition critically depends on innovating the approaches for training nonhuman animals and assessing how auditory-attention related effects influence cortical networks. In this study, we tested whether a novel paradigm based on reward incentive cues, which was originally used to show that monkeys learn a visual categorization task in tens of trials (Minamimoto et al. 2010, Neuron), could be adapted to speed up auditory task training and to direct monkeys' auditory attention. First, we trained monkeys to respond to a 400-ms “coo” target sound to receive a juice reward. Then at trial onset, we introduced either high (HiRe) or low (LoRe) reward incentive cues indicating that a correct response would be associated with, respectively, a big and immediate juice reward or a small and delayed reward. We hypothesized that monkeys' performance in the simple auditory target detection task would be systematically better during HiRe than LoRe trials after they learned to discriminate the cues from each other. We compared monkeys' auditory target detection performance when the HiRe and LoRe cues were either two different sounds or visual patterns. Further, in the condition with visual cues, a 2 s tone was played to redirect monkey's attention to the auditory modality after the presentation of the visual cue but before the onset of the “coo” target sound. We found that after only a few training sessions with 100–300 trials, monkey performance showed a significant difference between HiRe and LoRe trials with both auditory and visual cues. However, this difference was systematically bigger, more reliable and faster to achieve when visual incentive cues were used. Thus during fMRI we used the auditory target detection task with visual cues. We hypothesized that the monkeys would attend to the sounds more during HiRe than LoRe trials and, as a result, fMRI activations in auditory cortex would be higher during the HiRe trials. Our results showed that the reward incentive cues significantly biased monkeys' auditory task performance during fMRI. Moreover, activations in auditory cortex were significantly stronger during the HiRe than LoRe trials. Thus, this novel behavioral paradigm successfully revealed activation modulations in the monkey brain associated with focused listening. Remarkably, these results were obtained after less than 15 days of task-specific behavioral training.

7 True deviance sensitivity in awake freely moving rats

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Stimulus-specific adaptation (SSA) is the decrease in responses to a common stimulus that does not generalize, or only partially generalizes, to other stimuli. SSA is usually measured using oddball sequences, in which a common (standard) tone and a rare (deviant) tone are randomly intermixed. The larger responses to a tone when deviant, however, do not necessarily represent true deviance sensitivity. They can be explained by the tone not being adapted when deviant due to its rarity. Another possible explanation is that the tone when deviant violates the expectation to hear a standard tone, thus the larger response to it is deviance detection. A common test for deviance sensitivity uses a 'deviant among many standards' control sequence, where many different tones serve as the 'standard', thus eliminating the deviance of the deviant. When the response to the same tone when deviant (against a single standard) is larger than the responses to the same tone in the control sequence, it can be concluded that true deviance sensitivity occurs. In anesthetized rats, responses to deviants and to the same tones in the control condition are comparable in size.

We recorded local field potentials and multiunit activity from auditory cortex of awake, freely-moving rats, implanted with 32-channel drivable microelectrode arrays and using telemetry. We observe highly significant SSA (deviant>standard) in the awake state. Moreover, the responses to a tone when deviant were significantly larger than the responses to the same tone in the control condition. These results establish the presence of true deviance sensitivity in primary auditory cortex in the awake state.

8 Effect of fear conditioning on stimulus specific adaptation to complex sounds in freely moving animals

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Stimulus-specific adaptation (SSA) is the reduction in responses to a common stimulus that does not generalize, or only partially generalizes, to other stimuli. Previous studies have demonstrated stimulus specific adaptation (SSA) in primary auditory cortex of many mammalian species to a variety of sound stimuli. SSA has been studied mainly in sounds with no behavioral relevance. We hypothesized that a behaviorally meaningful sound should show less adaption compared to the same sound when it doesn’t have a behavioral meaning.

To test this hypothesis, we used discriminative fear conditioning in rats, using two word-like stimuli. One stimulus (derived from the word ""Danger"": CS+) was coupled with foot shock whereas the other stimulus (derived from the word ""Safety"": CS-) was presented without a concomitant foot shock. In order to verify learning, rats were tested for the amount of freezing to the two stimuli on the day following conditioning. In addition, we used pseudo-conditioning (using the same stimuli without foot shock) and reverse conditioning (using ‘Safety’ as CS+ and ‘Danger’ as CS-).

We monitored neural responses to the auditory stimuli using a chronic implantation of multi-electrode arrays in the auditory cortex of the rats. We recorded responses telemetrically in freely moving animals before, during, and after conditioning.

To test SSA, we recorded auditory responses to oddball sequences composed of the word stimuli in the days following conditioning. Our results show that in the animals conditioned to the word stimuli, SSA of the CS+ stimulus became smaller whereas SSA of the CS- stimulus increased. These results may suggest the sounds that are important behaviorally adapt less, presumably in order to remain highly detectable by the auditory system.

9 Predictability modulates excitation in the auditory cortex of macaques

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In a previous study (Selezneva et al, 2013), neuronal responses from the macaque primary auditory cortex had sensitivity to the type of isochronous sequence being presented. We defined isochrony as the occurrence of all tones with a strict periodicity, in our study 400ms apart. Stimuli consisted of complex tones of either 50 or 200 ms (also referred to as "short" and "long" respectively). Short and long tones were presented either in regular sequences of short-short-long triplets or in irregular sequences in which they were randomly permuted (scrambled). The modulation of neuronal responses was in particular evident in a higher firing rate during the long tone in the regular isochronous sequence.

In this experiment we parametrically varied isochrony and regularity to determine whether either or both factors were important in the facilitation of neuronal responses by the rhythmical sequences. We presented 6 types of sequences with regular isochronous, regular partially isochronous and regular non-isochronous tone sequences, as well as irregular sequences where the long tones were randomly permuted among the short tones. The macaques were passively listening to these sequences and were not required to make a behavioural response.

A total of 101 multiunits with excitatory responses were analysed from two monkeys. A repeated measures ANOVA with 2 fixed factors, isochrony and regularity (i.e. whether the stimuli were arranged in short-short-long triplets or were randomly scrambled) was carried out. Both factors were significant in modulating the response of the population of neurons to the long tone. The responses to the 200ms stimuli were highest in the two regular isochronous sequences without scrambling.

We conclude that neural activity in the auditory cortex was modulated by regularities in a sound sequence. The modulation led to higher network excitation during the regular isochronous and partially isochronous sequences, the most rhythmical sequences with the highest degree of temporal predictability.

References

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10 Cortical mechanisms of perceptual learning

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Auditory perceptual learning is defined as a long-term improvement in the detection or discrimination of acoustic stimuli. One broadly held hypothesis is that core auditory cortex plays a critical role in the perceptual learning process. To test this idea directly, we manipulated auditory cortical activity while Mongolian gerbils (Meriones uniguiculatus) trained on an aversive Go-Nogo amplitude modulation (AM) detection task. We reversibly attenuated auditory cortical activity bilaterally, via a low dose of muscimol, during perceptual training. Muscimol infusions impaired behavioral improvement while still permitting animals to generate psychometric functions. This finding suggested that either muscimol infusion prevented learning from occurring, or prevented its expression. To distinguish between these possibilities, we exposed the same animals to additional training sessions during which saline was infused into auditory cortex. Training paired with saline infusions improved detection thresholds. Together, these findings indicate that reducing auditory cortical activity during training prevents perceptual learning.

To establish a quantitative relationship between auditory cortical activity and perceptual learning, we implanted chronic microelectrode arrays into left auditory cortex of a separate group of naïve animals. We wirelessly recorded single and multi-unit activity as animals trained on the AM detection task described above. Neurometric sensitivity was tracked across days and directly compared to psychometric performance. As performance improved, we observed a significant correlation between simultaneously recorded neural and behavioral thresholds within individual animals. However, when recordings were made from animals while they were disengaged from the task, we found that neural thresholds remained relatively constant across days and were not correlated with behavioral performance. Collectively, our results suggest that auditory training leads to task-dependent enhancements of cortical sensitivity that ultimately support perceptual learning.

11 Asymmetry in neural responses to “on-beat” and “off-beat” sounds in the gerbil inferior colliculus

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It is a well-appreciated ability of humans (and possibly other species) to spontaneously perceive a periodic pulse in rhythmic sounds such as music. Recent work using electroencephalography (EEG) in humans has revealed a possible neural correlate of beat perception (Nozaradan et al., 2011; 2012). Through an approach termed “frequency-tagging,” neural entrainment to the beat is identified as the selective enhancement of beat and meter-related frequencies in the amplitude spectrum of the EEG relative to the prominence of those frequencies in the envelope of the sound. This approach has led to a substantial body of work exploring sensory, motor, and cognitive aspects of beat perception, but it sheds little light on where and how beat processing first emerges in the auditory pathway. We recorded from the central nucleus of the inferior colliculus (ICc) of anaesthetized gerbils in response to a subset of the rhythmic patterns used in these previous EEG studies. When we apply frequency-tagging analysis, we find that both local field potential (LFP) responses and firing rates from multi-units from gerbil ICc would appear to entrain to beat and meter-related frequencies like in human EEG. Intrigued, we developed a time-domain analysis that demonstrates that both LFP and spiking activity show larger responses to sounds occurring on the beat relative to otherwise identical sounds that are not on the beat. A cluster analysis of our dataset of 249 single and multi-units revealed seven representative classes of neural responses that differed in response latencies, strength of onset responses, and sustained activation. These clusters also differed in how suppressed responses become as a result of sounds in recent stimulus past. We quantified this sensory adaptation by fitting an exponential function to response strength as a function of time since the previous sound occurrence, and found that the stronger responses to on-beat relative to non-beat sounds is captured by predictions based on these exponential fits. This suggests that midbrain-level adaptation may play a role in biasing the neural representation of rhythmic patterns to favor the configuration that we as humans eventually perceive as a beat. Our findings also urge caution in the interpretation of frequency-tagging analysis applied to neurophysiological data since the positive result we obtained in the gerbil ICc can be explained by sensory adaptation without particular need for selective entrainment to beat and meter.

12 Histone modification enables song-specific auditory memories in an avian model.

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Vocal communication relies on the brain's ability to process, learn and remember important sounds. Long-term memories (LTM) of salient sounds require the expression of genes that subserve stable changes in neural function, structure, and connectivity in the auditory areas of the brain. Molecular epigenetic mechanisms regulate gene expression required for this memory formation. For example, the enzyme histone deacetylase 3 (HDAC3) gates the transformation of an auditory experience into memory. Bieszczad et al. (2015) demonstrated that rats treated with a selective HDAC3-inhibitor (RGFP966) acquired a specific and unusually detailed auditory associative memory for pure tones, which occurred with highly specific neuroplasticity in primary auditory cortex (A1).

We test the hypothesis that HDAC3-inhibition enables long-term neuronal memories for ethologically-relevant communication signals with complex acoustic features (Phan & Bieszczad 2016), using an avian model. The songbird caudomedial nidopallium (NCM) is analogous to superficial layers of mammalian A1 or to a secondary auditory cortex and contributes to auditory discrimination and song memory. Neurons in NCM undergo neuroplasticity in the form of stimulus-specific adaptation (SSA). SSA occurs when presented with repeated song stimuli, evoked responses to familiar (F) stimuli adapt more slowly than to novel (N) stimuli. Comparison of adaptation rate (the slope of the decrease in response amplitude as a function of repetition number) between F and N songs provides a measure of the strength of song memories.

Normally, 200 repetitions of a conspecific song will lead to LTM measured ~20h later. We exposed adult male zebra finches (n=7) to ≤ 40 repetitions of 8 novel zebra finch songs, below the usual threshold for memory formation. Systemic injection of RGFP966 (n=3) or vehicle control (n=4) followed exposure. Neural responses in NCM were recorded 20h later to the 8 previously exposed F songs and to 8 never-before-heard N songs. In vehicle treated birds, SSA rates were not significantly different between the N and F songs, indicating no memory of the F stimuli (K-S test; $p=0.575$, $D=0.084$, $Z=0.740$). In birds injected with RGFP966, adaptation rates were shallower (less negative) for F stimuli than for N stimuli (K-S test; $p=0.016$, $D=0.206$, $Z=1.50$). This difference indicates that RGFP966 treatment enabled memories for specific song stimuli. Therefore, HDAC3-inhibition can effectively transform a sub-threshold auditory experience (minimal repetitions of song exposure) into a LTM of that experience, apparently by lowering the threshold number of exposure events required for memory to form.

13 Affective representations of auditory stimuli in human insular cortex

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Accumulating evidence has suggested the role of the insula in emotion recognition. To examine whether the insula is involved in the perception of emotion from auditory stimuli, we recorded electrocorticographic (ECoG) signals from epilepsy patients when they were presented with emotional and non-emotional sounds. Neural signals recorded from different regions of insular cortex revealed different response properties. Posterior region of insular cortex, which is anatomically connected to sensory cortex, showed robust responses to all acoustic stimuli. Similar to the Heschl's gyrus, this region exhibited strong responses that are synchronized to the fundamental frequency of periodic stimuli. No differences were found in the posterior region of insular cortex between responses to emotional and non-emotional sounds. However, the anterior region of insular cortex on the right hemisphere showed robust high gamma responses to emotional sounds, but showed weak or no responses to non-emotional sounds, which indicated emotionally selective processing. In contrast, the anterior region of the left insular cortex did not show emotionally selective responses. Latency analyses showed much shorter response latency in the posterior region than the right anterior region of the insular cortex. Collectively, these observations suggest a role of the anterior insular cortex on the right hemisphere in transforming the basic sensory representations into inner affective representations.

14 Neural noise in the human electroencephalogram predicts perceptual decisions

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Perceptual decisions close to threshold are error-prone and unstable. With less information to base a decision on, the impact of spontaneous variations in brain activity increases. This is taken to extremes when discriminative information is absent altogether: When comparing two identical stimuli, pre-stimulus differences in brain activity and varying post-stimulus neural responses to the stimuli (together referred to as “neural noise”) must be driving the ensuing decision. Evidence from both modeling and experimental work on the discrimination of identical stimuli suggests that neural noise could indeed lead to varying percepts. Here, we investigated the potency of different indicators of neural noise in the electroencephalogram (EEG) to predict the later perceptual decision.

We recorded the 24-electrode scalp EEG while human subjects (n = 16; age 19–74) discriminated two identical, consecutively presented pure tones (SOA = 900ms, 650 Hz) and reported whether the first or second tone was higher in pitch. Since evoked responses did not differ between decisions, we pursued two routes of analysis to address trial-by-trial variations of pre-stimulus noise and systematic differences in the neural post-stimulus response. First, we analyzed trial-wise Weighted Permutation Entropy (WPE) of the broadband EEG signal (1–100 Hz), an information-theoretic measure quantifying the regularity of time series data. WPE around presentation of the first tone allowed classification whether participants would later report the first versus the second tone to be higher in pitch (above-chance classification in 12 out of 16 subjects). Second, Theta band (6–9 Hz) Inter-Trial Phase Coherence (ITPC) as a measure of stimulus-evoked activity around the presentation of the first tone was higher over central electrodes when this first tone was later chosen as compared to trials of the opposite decision. Lastly, we quantified differences in phase concentration around tone onset with a phase bifurcation index. Higher phase concentration (i.e., lower neural noise) in the Delta- (1–4 Hz, before onset of the first tone) and Theta-Band (at onset of the first tone) at fronto-central sensors marked decisions for the first tone. In sum, both time-domain, information-theoretic measures and time–frequency, phase-coherence measures suggest that auditory decisions in the absence of physical stimulus evidence can serve as a proxy for the degrees to which neural noise is involved in varying percepts and to which neural noise can promote perceptual learning."

15 Scalp EEG predicts listener’s attentional focus and attentional demands under continuously varying signal-to-noise ratio

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In natural auditory scenes, the sound pressure level of the many sound sources varies over time. If a listener attends to one sound source (i.e., the signal) and ignores the other sound sources (i.e., the noise), the time-varying signal-to-noise ratio (SNR) can be extracted. In concurrent-speaker paradigms, the low-frequency oscillatory responses (~1–5 Hz) in the magneto- and electroencephalogram (M/EEG) phase-lock to the slow amplitude fluctuations (i.e., the temporal envelope) of speech. Importantly, this neural phase-locking is enhanced for attended versus ignored speech and furthermore for higher versus lower signal-to-noise ratios. In addition, the power of neural alpha oscillations (~10 Hz) correlates with the top-down demands of effortful listening and might indicate the inhibition of task-irrelevant perceptual input and neural processes. However, it is unclear in how far listening depends on the interplay of low-frequency phase and alpha power in time.

In order to extract the time courses of low-frequency phase-locking and alpha power in an approximated real-life listening scenario, four human subjects (aged 23–47) were asked to listen to one of two simultaneously presented audiobooks while the EEG was recorded. Over time, the two audiobooks followed two uncorrelated level time courses, yielding a highly variable underlying SNR time course varying between –6 and +6 dB. We employed regularized regression to predict (i.e., to forward-model) the EEG responses from the acoustic input signals. In detail, first, spectro-temporal profiles of attended and unattended speech were used to predict low-frequency phase-locking. Second, the underlying SNR time course was used to predict the power of induced alpha oscillations.

Under these continuously varying listening conditions, the attended speaker could be identified with an accuracy significantly above chance in all individuals by predicting the low-frequency phase-locking both of the attended and unattended speaker from the spectro-temporal representations. Best prediction of the listener’s attentional focus was found at fronto-central scalp channels. Furthermore, a fronto-central alpha power enhancement followed increases in the SNR with a temporal delay of several seconds.

These data pose a new approach to identifying a listener’s attentional focus from EEG data applying a combined model for the prediction of low-frequency phase and alpha power. In this respect, our results suggest that low-frequency phase and alpha power reflect the enhanced neural encoding of attended acoustic input and the ensuing deployment of attentional control to overcome listening demands, respectively."

16 Early auditory experience modifies neuronal firing properties of neurons in zebra finch auditory cortex

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Juvenile, male zebra finches learn to sing based upon auditory experience with adult conspecifics during a limited time window called the critical period. They first hear and memorize tutor songs (normally their fathers') during a sensory learning period (<~50 days). Then they match their own vocalizations to memorized tutor songs using auditory feedback. We recently reported that early tutor song experience shapes neuronal auditory responsiveness in the caudomedial nidopallium (NCM), homologous to the mammalian higher auditory cortex (Yanagihara and Yazaki-Sugiyama, 2016). Here we examined development of neuronal properties with tutor song experience during the sensory learning period (between post-hatching day [PHD] 20, 40, and 60) in male and female NCM using whole-cell patch clamp in vitro. We found three types of neuron in NCM with distinctive spontaneous firing rates; silent, low frequency (< 7 Hz), and high frequency (> 9 Hz). High-frequency neurons were found only at PHD 20 and 40. The proportion of low-frequency neurons increased from PHD 20 to PHD 40, then decreased to the PHD 20 level by PHD 60 in both males and females. Some low- and high-frequency neurons showed tonic bursts during spontaneous firing (burst type neurons) in both sexes, but the percentage of burst neurons increased at PHD 40 only in males, returning to the PHD 20 level by PHD 60. When juvenile birds were isolated from their fathers at PHD 10, which extends the sensory learning period, high-frequency neurons could be found even at PHD 60. Also the proportion of low-frequency neurons and the ratio of burst-type neurons were higher at PHD 60, compared to normal juveniles, i.e. they are more like PHD 40 in normal juveniles. These findings suggest that early song experience modifies NCM neuronal properties, especially firing properties that might be necessary for song memory formation.

17 Role of Auditory Cortex in Feedback-Dependant Vocal Control in Marmoset Monkeys

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Human speech is a sensory-motor process requiring constant self-monitoring to ensure accurate vocal production. This auditory feedback monitoring allows one to quickly adjust speech production in order to compensate for perceived changes in vocal output. Although many animal species show similar feedback-dependant vocal control, the underlying neural mechanisms remain largely unknown. Previous work has demonstrated neural sensitivity in the auditory cortex to altered feedback during vocal production. However, the functional role of this cortical activity during vocal production is not known. We investigated the contribution of the auditory cortex to feedback-dependant vocal control during self-initiated vocalizations in marmoset monkeys. Using real-time frequency-shifted feedback, we found that marmosets exhibited feedback-dependant control of their vocalization acoustics. Pairing frequency-shifted feedback with electrical microstimulation of auditory cortex, we found that stimulation induced changes in vocal production and compensation. Finally, we examined vocalization-related auditory cortex activity using chronic recordings from implanted multi-electrode arrays and found a variable relationship between site-specific microstimulation effects and neural responses. These results demonstrate that marmosets are a good model for studying feedback-dependant vocal control, and suggest a causal role of auditory cortex neural activity in the vocal production and control process.

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18 Evolution of a reference frame along a brain pathway: persistently hybrid coordinates of auditory signals in Frontal Eye Fields implicate the Superior Colliculus in computing eye-centered sound location

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Cues for determining visual and auditory locations differ. The optics of the eye provide for eye-centered visual signals. Sound location is inferred from cues that depend on the sound's position with respect to the head and ears. The computations necessary to integrate these different cues are a central problem in multisensory and sensorimotor integration.

Previous work has shown that auditory signals are transformed into eye-centered coordinates for integration with vision. This process begins at least as early as the inferior colliculus (Groh et al. 2001) and may in fact begin with eye position-dependent displacements of the eardrum (Gruters et al. SfN 2015).

The transformation is "completed" by the time the saccade-related bursts of superior colliculus (SC) neurons are generated: these bursts specify sound location in eye-centered coordinates (Lee & Groh 2012). Yet, to date, these are the only known pre-dominantly eye-centered auditory signals in the brain; all other known signals reflect hybrid head- and eye-centered information (IC, A1, LIP). The SC may compute the eye-centered signal in time or it may receive this signal from an as yet unknown source.

Since the frontal eye fields (FEF) plays a similar role to the SC in saccade generation, and projects to the SC, we sought to evaluate the reference frame of auditory signals in the FEF in comparison to the SC. Previous work by Russo and Bruce (1994) had established that the FEF's auditory signals vary with eye position, but had not fully determined the reference frame. Information about FEF's auditory code and its evolution in time can resolve whether the computation of eye-centered sound location is broadly present in saccade-programming areas or unique to the SC (and maybe its afferents).

We tested the activity of 324 FEF neurons while 2 head-restrained monkeys performed saccades to the locations of sounds from different fixation positions. We dissociated target-related and saccade-related activity in time by delaying the saccade go-cue relatively to target onset.

We found that auditory signals were prevalent in the FEF, occurring in as many as 76% of FEF neurons. At sound onset and throughout the saccade preparation, sound location was encoded in hybrid head- and eye-centered coordinates. Only during the saccade burst we observed a modest shift towards eye-centered coordinates (roughly 60% of neurons remained hybrid, while the eye-centered neurons increased from 15% during the sensory period to 30% during the motor period).

Overall, the results in the FEF contrast considerably with the results from the SC, and implicate the SC as the main player in the final computation of eye-centered auditory target location.

19 DREADD-MEDIATED SILENCING OF PROJECTIONS FROM BASOLATERAL AMYGDALA TO NUCLEUS ACCUMBENS DISRUPTS PRE-PULSE INHIBITION IN RATS

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Sensorimotor gating is a fundamental process through which the central nervous system filters motor responses to redundant or irrelevant stimuli; this process can be assessed operationally through measurement of prepulse inhibition (PPI) of the acoustic startle response (ASR). PPI is a well-conserved effect across species in which the magnitude of ASR is attenuated by presentation of a low-intensity prepulse prior to the startle-inducing stimulus. PPI deficits have been reported in a number of neuropsychiatric disorders. Investigations of circuitry underlying PPI have relied primarily on lesion and pharmacological inactivation studies, both of which lack the ability to target circuitry in a projection-specific manner. The use of chemogenetic technology allows pathway specific targeting through the use of designer receptors exclusively activated by designer drugs (DREADDs). These receptors allow for the selective inactivation of DREADD-expressing neurons by otherwise inert compounds (clozapine-n-oxide, CNO, hM4D agonist). Our lab has previously reported (Forcelli et al., 2012) that inhibition of basolateral amygdala (BLA) disrupts PPI, and that this effect is mediated by the ventral pallidum (VP). However, BLA does not project directly to VP, but rather through a relay in the nucleus accumbens (NAcc). Here, we sought to test the hypothesis that inhibition of projections from to NAcc would be sufficient to impair PPI, providing functional evidence for the proposed circuit. 12 Long Evans rats were injected unilaterally into BLA with AAV-hSyn-hM4D(Gi)-mCherry DREADD construct paired with an ipsilaterally placed cannula targeted to the NAcc. Using an SR-LAB rodent startle response system, we determined that silencing of BLA projections terminating in the NAcc disrupted sensorimotor gating as measured by a reduction in PPI. Rats were treated with either systemic CNO (10mg/kg) or with intra-NAcc injection of CNO (1nmol). The former treatment was intended to silence all BLA projections, while the latter targeted BLA terminals in NAcc. Intracerebral microinfusions of 1mM CNO resulted in a significant decrease in PPI at prepulse intensities of 3 and 6dB above background ($p<0.05$). Additionally, systemic injections at a dose of 10mg/kg CNO yielded a significant decrease in PPI at a prepulse of 3dB above background ($p<0.05$). These results demonstrate that DREADD-mediated silencing of the direct BLANAcc pathway results in a disruption of sensorimotor gating function as quantified by a loss of

prepulse inhibition to the acoustic startle, and suggest that projections from BLANAcc are sufficient to account for the PPI-disruptive effects of BLA silencing.

20 Dopaminergic modulation of vocalization-selective neurons in the inferior colliculus acts via D2-like receptors

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Background: The ability to understand speech relies on the accurate processing of these sounds by the auditory system. A variety of factors may impede accurate representation, including disorders associated with neuromodulatory systems. For example, individuals with Parkinson's disease suffer from deficits in speech perception, suggesting that dopamine may be involved in the normal encoding of behaviorally relevant sounds. The inferior colliculus (IC) receives inputs from multiple auditory and non-auditory sources and is rich in both dopaminergic terminals and D2-like receptors. Recent studies in our lab demonstrated that dopamine heterogeneously modulates responses of individual neurons to tones in the IC of mice. However, it is currently unknown which type(s) of dopamine receptors is/are involved in such alteration of neuronal responses to auditory stimuli, and whether dopamine affects neuronal responses to communication sounds. In this study, we tested the following hypotheses: dopamine acts via D2-like receptors to alter auditory-evoked neuronal responses in the IC; dopamine alters neuronal responses to conspecific vocalizations in the IC.

Methods: We recorded extracellular responses of single neurons in the IC of awake mice. We compared neuronal responses to tones and mouse vocalizations before and after iontophoretic application of dopamine and D1- or D2-like agonists or antagonists. We quantified how activating or blocking dopamine receptors changed the rate and timing of action potential spikes.

Results: We found that the effects of both dopamine and a D2-like agonist on spiking rate in IC neurons were heterogeneous as both similarly increased or decreased auditory-evoked responses to pure tones, while a D2-like antagonist reversed the effects of dopamine. Moreover, both dopamine and a D2-like agonist similarly affected repsonses of IC neurons to vocalizations in the same relative direction as responses to tones, while a D2-like antagonist reversed the effects of dopamine.

Conclusions: Our study increases the understanding of neurophysiological mechanisms underlying hearing and auditory-based communication. We found that dopaminergic neuromodulation in the IC alters responses to behaviorally relevant sounds, and that such modulation occurs via D2-like receptors. Understanding how dopamine modulates

auditory processing will ultimately provide insight into mechanisms underlying specific communication- and auditory-based neurological disorders.

21 Studying Vocal Communication of Marmoset Monkeys (Callithrix jacchus) in a Rich, Socially-interactive, Captive Environment

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Communication behaviors of non-human primates can be considered an evolutionary precursor for human social interactions and may serve as an important behavioral assay to study disorders in human social behaviors such as autism spectrum disorders. The common marmoset (Callithrix jacchus) is a highly vocal New World primate species that has emerged in recent years as a promising model system for studying neural basis of vocal communication. Marmosets live in social groups in their natural habitat and maintain a high level of social interactions between individuals in captivity through their vocalizations even. However, studies examining marmoset vocalizations so far have mostly focused on calls produced by individual animals or vocal exchanges between a pair of animals (e.g., antiphonal calling behavior). What has been missing is the characterization of vocal behaviors of marmosets in a richer social environment composed of a group of individuals. In order to fully understand vocal behaviors of marmosets, it is necessary to study call sequences generated by animals living in a social setting and quantify vocal exchanges among multiple animals. To tackle this problem, we have developed a behavior monitoring system in a large breeding colony that is capable of recording and analyzing vocalizations produced by multiple marmosets over a long period of time. By using parabolic microphones and miniature wireless microphones carried by individual marmosets, we are able to detect both loud and quiet calls in a noisy environment and identify individual callers when marmosets are either single-housed or group-housed. Our preliminary data demonstrate that marmosets preferentially communicate with a subset of other individuals through vocal exchanges. Such analyses enable experiments to study social interaction behaviors in this species and the neural substrates for vocal communication in a natural environment.

22 Regularity-dependent changes in neuronal adaptation in the awake rat auditory cortex

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Adaptation to stimulus context is an ubiquitous property of cortical neurons and is thought to enhance the efficiency of sensory encoding. In the auditory cortex, this has been further related to the behavioral importance of stimuli, with neurons responding weakly to frequently repeated tones and strongly to rare tones in oddball paradigms. Such history-dependent adaptation suggests a functional significance in the context of novelty detection or (automatic) attentional focusing on important stimuli, strongly related to the 'mismatch negativity' signatures recorded from the scalp in humans.

As the prediction of future stimuli (i.e. the degree of novelty) is strongly related to the regularity of stimulation in the preceding tone sequence, we tested this hypothesis for "predictive coding" further by systematically varying the regularity (sequential arrangement and temporal pattern) of stimuli while recording from different areas of the auditory cortex (A1, AAF, VAF, and SRAF) in awake rats. Chronically implanted movable electrodes allowed for recording of activity from multiple single neurons and of local field potentials simultaneously. A total of 217 neurons were recorded from six animals.

Neuronal characteristics and adaptation behavior was found to be significantly different between auditory fields. Neurons in primary fields (A1, AAF, VAF) were narrowly tuned to sound frequency and showed less stimulus-specific adaptation while responses in the secondary field (SRAF) were broadly tuned an exhibited strong adaptation in most cases. Regularity-dependent differences in adaptation related to stimulus history, however, were observed in the secondary field only. Neurons showed significant differences in adaptation between regular or more random sequential patterns of stimuli (standard/deviant).

Dependence on temporal regularity was tested by using either rhythm-like temporal patterns (regular repetition rate) or different inter-stimulus intervals for standard and deviant stimuli in several oddball paradigms. General adaptation was not influenced by sole changes in temporal regularity. Only local interactions between adjacent stimuli could be observed as expected by the mechanism of adaptation (i.e. stronger adaptation for reduced inter-stimulus intervals). Taken together, this indicates strong differences in adaptation behavior between cortical areas and the importance of secondary cortical areas for encoding of regularity dependence. Such encoding of higher-order interactions in stimulus sequences is necessary for the detection of unexpected acoustic event in natural environments.

23 Assessment of subcortical physiological discrimination and phase locking in infants

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The frequency-following response (FFR) is an objective measure of subcortical auditory coding. When recorded to syllables differing in frequency content, it can be used as a measure of subcortical physiological discrimination. Poor neural synchrony may impact the temporal encoding of frequency-specific spectral features and result in poor neural phase differentiation of stop consonants. Phase differentiation has been assessed in preschoolers and school-age children, but it has not yet been established in infants. This study investigated the feasibility of assessing subcortical physiological discrimination and phase locking in infants using the FFR as a first step towards developing an objective predictor of later language development.

The FFR was recorded in fifty-two normal hearing infants (ages three to twelve months) and fifteen normal hearing young adults to two speech syllables (/ba/ and /ga/) presented to the right ear. Data were analyzed to obtain measures of phase differentiation (subcortical physiological discrimination), phase locking, and frequency encoding.

Phase differences between /ba/ and /ga/ were present in the consonant region in both infants and adults. Phase locking was significantly more robust in young adults for high frequencies than in infants, but robust phase locking was present at the fundamental frequency for both infants and adults. Spectral amplitudes of the temporal envelope were higher in the young adults than infants.

These findings demonstrate the feasibility of obtaining these measures in infants as young as three months. The presence of subcortical physiological discrimination and robust phase locking to the fundamental frequency of the envelope and to the first formant of the fine structure in normally-developing infants provides a basis against which to compare responses in infants who are at risk for language disorders."

24 Effects of L-dopa on the benefit from attention to memory

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Selective attention to working memory (i.e., retrospective attention) is known to facilitate recall performance. We previously showed that retrospective attention to syllable objects in auditory working memory improves representational quality of the attended object. However, the extent to which multiple attention-related top-down brain networks and sensory (i.e., auditory) cortical regions are modulated by auditory retrospective attention is relatively unknown. Furthermore, dopamine is known to enhance working memory and cognitive flexibility. Yet, it is still unclear whether increased level of dopamine modulates neural activity that underlies retrospective attentional benefits. By using functional magnetic resonance imaging (fMRI) and pharmacological manipulation, we investigated the neural basis of auditory retrospective attention benefits in respect to dopaminergic modulation. Human participants (N=22, aged 25–35) underwent two separate scanning sessions, each with either 150 mg of L-dopa (Madopar) or placebo, while performing a syllable pitch-discrimination task. On each trial, participants encoded and maintained two sequentially presented syllables. During maintenance, a valid or neutral visual retro-cue was presented to guide participants' attention to a to-be-probed syllable in memory. Behaviourally, directing attention to the to-be-probed syllable via exogenous valid retro-cues led to faster and more precise detection of pitch change occurred at probe. However, under L-dopa the response-time benefit from valid retro-cues was reduced as L-dopa increased the speed of response even in the uninformative neutral cue trials. Neurally, during the cue and maintenance period the primary auditory cortical regions were suppressed regardless of cue conditions. Overall, retrospective attention to a specific syllable led to enhanced activations in language-related networks, such as left inferior frontal gyrus and left posterior superior temporal regions as well as top-down attentional control networks, such as fronto-parietal and cingulo-opercular networks. However, L-dopa attenuated the extent of neural modulation in attentional networks, especially in the right dorsolateral prefrontal cortex and right insula by enhancing neural activity in the neutral cue trials. Overall, our results suggest that retrospective attention to auditory working memory engages top-down networks to actively select and maintain attended objects in memory, but increased dopamine level generally reduces attentional benefits from the exogenous cue to direct attention to memory.

25 The role of nitric oxide in modulating neuronal activity in the ventral cochlear nucleus

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Tinnitus chronically affects an estimated 10-15% of adults and is characterised by the perception of sound independent of external stimuli. Nitric oxide synthase (NOS) expression has been studied in guinea pig ventral cochlear nucleus (VCN) where it is located in a sub-population of each cell type. Following unilateral acoustic over-exposure, a within-animal asymmetry of NOS expression was found exclusively in the 75% of animals that developed tinnitus (Coomber et al., 2015). The decrease in NOS expression in the contralateral VCN was observed as soon as 1 day after acoustic-over exposure, and the asymmetry in NOS expression was strongest at eight weeks after noise exposure. This provided evidence for a role of nitric oxide (NO) in tinnitus, and not simply as a biomarker for hearing loss.

Here, we describe the use of iontophoresis to apply the NOS inhibitor L-NG-Nitroarginine methyl ester (L-NAME) to units within the VCN of the anaesthetised guinea pig. Upon identification and characterisation of a single unit, hour-long, pure tone pulse-trains were presented at the characteristic frequency (200 ms tone pip, 800 ms silence, 3600 repeats). The number of spikes per one second sweep were counted, allowing analysis of the changes in auditory-driven or spontaneous activity. An 80nA ejection current was applied through an iontophoresis barrel containing 50mM L-NAME during a 20 min. period starting 15 min. after the start of the pulse-train; allowing assessment of the impact of blocking NO production on identified neuronal types.

Reducing NO production through NOS inhibition caused a significant increase in spontaneous and auditory-driven firing rate in 20% (2/10) of our VCN unit sample. This effect was found in both chopper and primary-like units. These results indicate that NO has a role within the VCN of reducing neuronal excitability. This effect of NO on excitability may be reversed in tinnitus animals, producing an increase in transmission with potential to contribute to the ‘increased central gain’ thought to be present in tinnitus animals.

The next stage will involve application of L-NAME to VCN neurons in guinea pigs following noise exposure and behavioural confirmation of tinnitus, therefore allowing us to determine the functional role of NO in tinnitus."

26 Behavioral discrimination of channel specific microstimulation for central auditory neuroprostheses

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Neuroprostheses offer the potential to restore a modicum of sensation back to individuals in need. One major way in which sensation is restored consists of placing electrodes to enable spatial segregation along the one or two-dimensional axes representing the sensory epithelium and fundamental stimulus dimension, namely, frequency along the cochlea for hearing or skin region for somatosensation. Part of the reason for the ongoing success of the cochlear implant is its ability to adequately stimulate specific regions along the tonotopic axis of the cochlea, allowing for adjacent channels to stimulate groups of neurons in different frequency bands, though with partial overlap. Moving more centrally from the cochlea, the tonotopic axis remains, but the way in which electrical stimulation permits behavioral discrimination is poorly understood. For example, Auditory Brainstem Implants have shown reduced efficacy for behavioral perception as compared to cochlear implants, are far more difficult to implant, and occasionally stimulate undesirable nearby structures (Brackmann et al. 1993). Primary auditory cortex (A1) may be a more desirable stimulation target due to the ease of access and low risk of stimulating non-auditory regions. A1 stimulation may also serve as a model for other sensory cortical neuroprostheses and central neuroprostheses, where there are multiple cell types and intra-areal microcircuits, such as the cortical columnar microcircuits. To understand the potential for cortical prostheses and potential bases for perceptual variability, we examined interchannel discrimination in a rat behavioral model. Our data suggest rats can discriminate between stimuli presented on adjacent electrode sites separated by 125 microns (d’=2.15, s.d. 0.24) in layer 4. When repeated in layers 2-3, rats failed to discriminate between sites even up to 375 microns apart, which was the limit of our array (d’=0.32, s.d. 0.75). This result suggests that layer 4 cortical microstimulation has the potential to generate fine resolution across a stimulus dimension. Given this, careful consideration of local circuitry, stimulation parameters, and regions targeted by microstimulation can overcome many of the performance obstacles typically seen with central neuroprostheses.

27 Use of the post auricular muscle response for measuring pre-pulse inhibition of the human acoustic startle reflex.

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Gap-induced pre-pulse inhibition (PPI) of the acoustic startle (GPIAS: a behavioural test for tinnitus in animals) relies on a short gap in continuous background noise providing a cue to inhibit the response to a loud startling stimulus. Impaired GPIAS following tinnitus induction has been shown in a number of species, as well as in humans with tinnitus. Impairment of the GPIAS was originally thought to be caused by the tinnitus 'filling' the gap but recent studies have challenged this explanation. Preliminary work in humans measuring the eye blink reflex showed gap detection deficits in tinnitus subjects, but the underlying mechanisms of this effect were unclear (1). The eye blink response has a relatively long latency (>40ms) and therefore is not a simple primary reflex, nor is it specifically related to the auditory system.

We have developed a variation of the GPIAS method in which we measure the acoustic startle in guinea pigs using the simple pinna reflex. The post-auricular muscle reflex (PAMR) is the human analogue of the pinna reflex and may represent a metric for an objective tinnitus test. The PAMR is a short-latency (10-12 ms) response that involves only two or three synapses in the brainstem and provides a much tighter link between auditory input and motor output. However, gap-induced pre-pulse inhibition (PPI) of the PAMR has not previously been demonstrated.

In the present study, we measured gap-induced pre-pulse inhibition (PPI) of the PAMR in 38/48 normal-hearing subjects (subjects were excluded due to lack of PAMR response). PAMR responses were recorded electromyographically with a surface electrodes placed over the insertion of the post-auricular muscle to the pinna. Gaps were placed in a 1 kHz background tone, presented monaurally to the right ear at 70 dB SPL, and followed by startling stimuli comprising very brief 20ms broadband noise bursts presented at 105 dB SPL. Eye direction has been shown to have a dramatic effect on the amplitude of the PAMR reflex but although looking to the right increased the amplitude of the PAMR response it did not improve the detection of PPI. By optimising stimulation parameters we were able to observe reliable PPI using the PAMR response. We propose that measuring the PAMR response is a simple and reliable method for studying pre-pulse inhibition of the acoustic startle in humans."

28 Joint tuning to sound features emerges in superficial layers of human primary auditory cortex

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Electrophysiological recordings suggest there may be relevant transformations in sound processing taking place between thalamo-recipient primary auditory cortical (PAC) layers and superficial PAC [1,2]. Here we use ultra-high field fMRI (7 Tesla) to measure and compare sound responses at deep, middle and superficial cortical depths of human PAC.

We acquired high-resolution (f)MRI data, while volunteers listened to natural sounds. Cortical responses were analyzed inside and outside PAC with three encoding models, representing different hypotheses on sound processing. A first tonotopy model described sound processing by cortical frequency preference. A second independent modulation model hypothesized, in addition to frequency, preference to temporal and spectral modulations. A third joint modulation model described sound processing as the frequency-specific tuning of neuronal populations to combined spectral and temporal modulations [3,4].

In the PAC only, we observed a significant interaction such that the difference in model prediction accuracy varied with cortical depth (RM ANOVA; $p = 0.006$). Only at a superficial cortical depth, the joint modulation model performed significantly better than the other two models. In non-primary auditory regions, the joint modulation model significantly outperformed the other two models throughout the cortical depth.

In accordance with previous invasive animal studies [1,2], these results suggest a change in auditory processing throughout the depth of the PAC. That is, while neuronal populations in middle PAC layers are tuned independently to distinct sound features, neuronal populations in superficial PAC encode specific feature combinations. Joint tuning may be a first computational step for forming a complex representation of the physical input towards sound abstraction and perception.

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29 Investigating the functional organization of auditory pathway with high-resolution fMRI.

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Understanding how the human brain extracts behaviorally relevant information from sounds necessitates mapping sub-cortical and cortical processing levels simultaneously. So far, technical challenges have limited the coverage and/or resolution of functional magnetic resonance imaging (fMRI) studies of the human auditory pathway [1-3]. Here we investigate the topographic organization of the auditory pathway from the cochlear nucleus to the auditory cortex at high spatial resolution.

We collected anatomical (0.7 mm isotropic) and functional data (1.1 mm isotropic) at 7 Tesla. During functional imaging participants (N = 6) listened to natural sounds (1 s) presented in the silent gaps. FMRI encoding [4] was used to analyze the functional responses to natural sounds and investigate the spatial organization of preferences to acoustic properties for every subject independently. The consistency of the results across subjects was evaluated in a common cortical space (cortex based alignment) and a common sub-cortical space obtained through non-linear registration (FNIRT-FSL) of the anatomical data. A preliminary analysis of allowed identifying, in every subject, sub-cortical and cortical regions with a significant (FDR corrected q=0.05) response to the sounds. Cortical frequency preference showed tonotopic maps in accordance with previous studies [1].

These results show that high-field fMRI can be used to investigate the functional organization of the entire human auditory pathway at a resolution sufficient to highlight the topographic organization of acoustic features across all stages. The use of natural sounds and fMRI encoding will allow tracking the transformation of sound representations throughout the brain."

30 Adaptation in auditory cortex is actively shaped by somatostatin-positive and not parvalbumin-positive interneurons

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Adaptation to repeated stimuli is a ubiquitous property of cortical neurons that is thought to enhance the efficiency of sensory coding. In primary auditory cortex, the vast majority of neurons exhibit stimulus specific adaptation, i.e. firing rate attenuation dependent upon stimulus prevalence, which modulates neuronal frequency tuning properties. Such history-dependent adaptation is thought to support sensory-motor behaviors like stimulus habituation, discrimination and deviance detection, yet little is known about the neuronal mechanisms that control how adaptation is generated. In these experiments, we show how frequency tuning in A1 is differentially shaped by two inhibitory interneuron subtypes prior to and following adaptation. During tone pip trains that induce varying levels of adaptation across frequencies, we measured firing rates of putative excitatory pyramidal neurons (PNs), while using optogenetic manipulation to selectively suppress specific populations of interneurons. Prior to adaptation, i.e. during the first tone of each train, suppressing parvalbumin-positive interneurons (PVs) or somatostatin-positive interneurons (SOMs) each lead to increases or decreases in tone evoked responses in different PNs. Following adaptation, i.e. during the last tone of each train, PVs mediated inhibition increased modestly but continued to bi-directionally modulate tone evoked responses similarly to the first tone. In contrast, SOM mediated inhibition after adaptation increased dramatically and modulation became mostly uni-directional. Thus, SOM mediated inhibition appears to track the dynamics of adaptation more closely than that of PVs. In addition, we tested how inhibition and adaptation shape frequency tuning in PNs. First, we found that adaptation leads to a robust divisive suppression across the tuning curve for PNs, with stronger suppression for preferred frequencies. Matching the aforementioned findings, PV mediated inhibition across frequencies did not change during adaptation. In contrast, SOM mediated inhibition increased more strongly for preferred frequencies than off-peak frequencies, matching the pattern the pattern of suppression observed for adaptation. We further explore circuit mechanisms that may underlie this novel phenomenon. This study reveals a previously unknown functional mechanism of SOMs in generating adaptation.

31 Evolutionary origins of non-adjacent sequence processing in primate brain potentials

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There is considerable interest in understanding the ontogeny and phylogeny of the human language system. Language as a rule-governed system requires both sophisticated sensory processing and sequencing capabilities on the side of the receiver. Although, insights have increased on the development of auditory functions and non-adjacent rule sequencing operations in the infant brain, we lack knowledge on the interplay of these processes in the brains of our primate relatives. In the present primate study we used a paradigm initially developed to evaluate human infant and adult auditory processing and non-adjacent rule-learning abilities. We measured scalp-recorded event-related potentials (ERPs) from two macaque monkeys as they listened to syllable triplets. Frequent standard triplet sequences were interspersed with infrequent pitch or non-adjacent rule deviants. The monkey ERPs revealed similar early pitch and rule deviant mismatch responses (MMRs) that are more like the ones reported in infants. By comparison, in adults the rule deviant response occurs later and thought to be more independent of basic auditory processes. The results reveal the evolutionary origins of non-adjacent rule processes in the primate brain, showing evidence for conserved potentials that are evident at an early developmental stage in humans.

32 High-resolution intracranial recordings provide direct electrophysiological evidence for music and speech-selective neural populations in human auditory cortex

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The functional organization of human auditory cortex remains unresolved. Previously, we used 'voxel decomposition' to infer canonical components of the human cortical response to natural sounds, measured with fMRI. This analysis inferred distinct components selective for music and speech, which were localized to different non-primary regions of human auditory cortex. These components plausibly correspond to distinct underlying neural populations; but there is no direct electrophysiological evidence for such organization, and little is known about the temporal response properties of these putative neural populations. To address these questions, we recorded intracranial responses from a patient implanted with one of the highest resolution electrocorticographic (ECoG) arrays used to study auditory cortex to date (1 mm diameter electrodes, spaced 3 mm apart). We measured broadband gamma (70-140 Hz) responses to a diverse collection of 165 sounds. These sounds included many of the sounds people commonly hear, and have previously been used to characterize auditory cortex with fMRI. We then applied a decomposition method to infer canonical response time courses, whose weighted combination explained the ECoG response across all sound-responsive electrodes ($N = 52$, $p < 0.001$). This analysis revealed 5 reliable components, two of which exhibited clear selectivity for music and speech, respectively, despite the lack of any functional constraints used to infer them. Notably, we also observed clear evidence for music and speech selectivity in the response of individual electrodes. The degree of this selectivity substantially exceeded that typically observed in fMRI voxels. Responses in three other patients with lower-density grids (2.3-mm diameter, 4-mm spacing) were qualitatively similar, but the degree of category selectivity was reduced. Collectively, these findings provide some of the first direct electrophysiological evidence for distinct neural populations selective for music and speech, and demonstrate the utility of high-density electrode recordings in revealing cortical tuning in humans. Ongoing work is investigating the temporal properties of the different components revealed by our analysis and their relationship to acoustic and semantic properties of music and speech.

33 Foreground stimuli affect Neuronal Adaptation to Sound Level Statistics In The Inferior Colliculus Of Behaving Macaques.

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Neuronal activity might reflect the variety of stimulus regularities that characterize complex acoustic environments. Previous studies (e.g. Dean et al., 2005) suggested that neurons in the inferior colliculus (IC) of anesthetized guinea pigs adapt to stimulus statistics by shifting their firing rate towards the mean sound pressure level. However, it is still unclear how such neuronal adaptation may influence the masking effect of background noise in signal detection tasks, and affect the underlying neuronal responses in awake behaving subjects. To answer these questions, we measured the neuronal response in the IC of macaque monkeys performing a Go/No-Go tone detection task. Tones were 50 ms duration and were either simultaneously gated with a 50 ms burst of broadband noise or embedded within a continuous noise background, whose amplitudes were randomly sampled (every 50 ms) from probability distributions similar to those designed by Dean et al. (2005). Behavioral and IC neurometric threshold shifts to tones were not affected by background statistics. However, the magnitude of IC neuronal responses significantly varied as a function of the noise statistical properties. Simultaneously gated noise caused higher baseline responses and higher rate compression of rate vs. level functions compared to the noise distribution. Our results indicate that although IC neuronal responses were modified by the statistical regularities within the acoustic scene, neuronal adaptation to the background sound levels did not reduce the effectiveness of the masking noise. However, the addition of foreground signals to the acoustic environment significantly modified the adaptation process underlying sound perception.

34 ON THE EDGE OF YOUR EARS: INVESTIGATING THE NEURAL CORRELATES OF AUDITORY ANTICIPATORY ATTENTION.

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Anticipatory attention, i.e. biasing our attentional set towards upcoming stimuli, has been shown to operate by enhancing neural activity in cortical regions responsible for processing the upcoming stimulus, while suppressing activity in regions responsible for processing stimuli outside of the attentional focus. In the visual domain, the role of alpha oscillations in sustaining these modulations has been well demonstrated. However, only a handful of studies have succeeded to establish this role in the auditory domain.

EEG and MEG data were collected from fourteen healthy young participants performing an auditory pitch discrimination task of monaural tones. Anticipatory attention was triggered by a visual cue that was either informative, i.e. indicating the target side (either left or right), or uninformative. Behaviorally, participants were faster in the informative condition. EEG data showed that increments in anticipatory attention result in an increased contingent negative variation (CNV) and in an enhanced N1 and a reduced P3 to targets.

Furthermore, beamformer analysis of the sources of the alpha oscillations preceding the target revealed distinct effects of the two properties of the cue; informativity and directionality. Upon contrasting the informative to the uninformative conditions, we have found a significant decrease in alpha power in the left auditory cortex accompanied by an increase in alpha power in the visual cortices. However, contrasting informative right and informative left cues, we have found a significant increase in alpha power in the right auditory cortex following right cues relative to left cues.

Evidence of top-down modulation of auditory alpha has only been recently put forward (Frey et al., 2014). The present results corroborate this outgrowing literature and paint a clearer picture of the dynamics of the top-down modulation of alpha oscillations within the auditory cortices."

35 Using auditory brainstem responses to measure hearing loss-induced increases in neural gain and its implications with tinnitus

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The homeostatic plasticity model posits that tinnitus is triggered by an increase in neural gain due to a reduced input from a damaged periphery. Evidence for this mechanism in humans has come from auditory brainstem responses (ABR). ABRs recorded from tinnitus patients were found to show a reduced wave I amplitude but a normal wave V (Schaette 2011). This was interpreted as evidence of an increase in neural gain between the auditory nerve (wave I) and the upper auditory brainstem (wave V). However, a confound in this interpretation is that wave I is more dependent on contributions from high-frequency cochlear regions than wave V. High-frequency cochlear regions are also more affected by hearing loss. As a result, hearing loss may be expected to affect the wave I amplitude more than wave V, and this could be the driving factor behind the increased wave I/V ratio. Here, we aim to address this confound by measuring ABRs from restricted cochlear frequency regions.

Frequency-specific ABRs are obtained by restricting the response using high-pass masking noise with a variable cutoff frequency. Responses for different cutoff frequencies are subtracted to derive a response that only contains contributions from a specific cochlear region. This method has been used successfully to obtain frequency-specific click-evoked wave V responses. However, relative to wave V, the click-evoked wave I requires a high stimulus level to obtain an acceptable response. This means that uncomfortably loud HP noise would be required to obtain frequency-specific wave I responses. Furthermore, click stimuli are not optimal for eliciting wave I at high stimulus levels.

In this study we aim to address these problems by measuring chirp-evoked ABRs. We will use a rising chirp stimulus which starts at a low frequency and rises to a high frequency. Rising chirps have been used successfully in previous studies to increase the SNR of wave V (Fobel, 2004), as they compensate for the cochlear travelling-wave delay, causing the auditory nerve fibers to fire simultaneously and create a larger ABR. To further optimise frequency-specific chirps, we will use chirps that are weighted towards low-frequencies.

Once the optimal paradigm for measuring frequency-specific ABR wave I responses has been developed, we will measure the wave I/V ratio in normal hearing, tinnitus and matched hearing-loss groups. If there is a neural gain increase we will expect to see an increase in wave I/ V ratio in hearing loss regions in the tinnitus group compared to normal/hearing matched groups but not in regions where hearing is intact."

36 A computational model of temporal processing in human auditory cortex

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Temporal information in sounds is relevant for many general purpose and domain specific auditory functions, including amplitude modulation (AM) detection, extraction of temporal pitch and decoding of speech. Each of these functions has been extensively studied with a variety of methods (electrophysiology, non-invasive neuroimaging, psychophysics). The common neural coding mechanisms underlying these observations, however, remain unclear. Here we propose a computational framework to integrate available empirical information to derive a unified view of temporal information processing in human auditory cortex (AC).

We designed a simplified model of AC consisting of four functional units. These units approximately correspond to two core (AI, R) areas and two belt “streams” (Fast, Slow). Each unit was simulated using the Wilson Cowan Cortical Model (WCCM) of neural circuitry. The WCCM generates dynamic neural responses by interaction of excitatory (E) and inhibitory (I) populations. AI and R receive cochleotopic thalamic input, the belt streams receive cochleotopic input from AI (Fast) and R (Slow) respectively. We adjusted the main parameters of the four units, temporal and spectral integration windows, based on physiological evidence from monkeys , and recent human fMRI .

First, we explored the model’s coding of AM. For both noise and tones (0.125-8 kHz), we observed a switch from a temporal to a rate code for modulation rates above 50 Hz. The upper limit of temporal (but not rate) code was unit dependent, in accordance with electrophysiology2. Interestingly, estimated modulation transfer functions followed psychophysical modulation detection thresholds . Also, we observed a dependence of AM coding on carriers in agreement with psychophysics5. Second, we tested how this same model represents temporal pitch , with missing fundamental stimuli and iterated ripple noise (IRN). AI and Fast temporally decoded low (<300 Hz) missing fundamentals while the Slow area represented high frequencies as phase coherence across the network. IRN was coded temporally with comparative weaker strength matching its weaker pitch percept.

Using a simple network of E and I interactions and tuning of only two parameters, we modeled processing of temporal information in parallel cortical streams. Read out of population responses are in agreement with human psychoacoustics. Future use of the model, in particular, to simulate response to speech is planned."

37 Differential tuning of the low- and high-frequency components of the neurophonic spectrum reveals the spike contribution of barn owl's nucleus laminaris neurons

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In--vivo neural activity gives rise to trans--membrane currents that can be recorded as an extracellular field potential. These potentials are often challenging to interpret due to thousands of contributing sources. We aim at revealing the neural sources of the “neurophonic”. The neurophonic is a frequency--following extracellular potential that can be recorded in the network formed by the nucleus magnocellularis (NM) and the nucleus laminaris (NL) in the brain-stem of the barn owl. NL anatomy is well understood, and putative generators of the neurophonic are the activity of afferent axons from NM, the synaptic activation onto NL neurons, and spikes of NL neurons.

We recorded the neurophonic in response to binaural high--frequency tones (3--7 kHz) close to the recording site's best frequency, and we varied the interaural time difference (ITD). The mean activity of the monaural inputs to NL does not change with ITD. However, their relative phase does, causing cancellation or summation of input signals. The activity of the binaurally- sensitive output of NL, i.e., firing rate of NL neurons, strongly depends on ITD. Our recordings contained both of these signals, and we analyzed the broad--band power spectrum of the response (0.1--8 kHz).

The low--frequency component (LFc, 200--700 Hz) of the neurophonic spectrum depended on ITD. The spectrum of extracellularly recorded NL neurons' action potentials closely resembled this component. Thus, the LFc reflects the contribution of action potentials initiated in NL neurons. The spectral component at the stimulus frequency (SFc) was much stronger than the LFc. The SFc also depended on ITD, reflecting the activity of the inputs and their relative phase change with ITD. The power spectrum at other frequencies did not depend on ITD. We used the LFc as a proxy for NL neurons' local population activity, and the SFc as a proxy for NM axons' local population activity. We compared the ITD and frequency tunings of these proxies at each recording site. The best ITDs of the LFc and the SFc were independent. Also the tuning to stimulus frequency was different: LFcs showed typically a 400 Hz lower best frequency than SFcs. Both findings indicate that the LFc might originate from NL neurons' axons in the vicinity of the electrode. Related NL neurons can be located tens

to hundreds of micrometers away. The findings are consistent with the known anatomy of NL. Our analysis thus reveals the small contribution of NL neurons to the neurophonic, improving our understanding of the extracellular field potential in the auditory brainstem.

38 Can transcranial direct current stimulation (tDCS) modulate auditory cortical oscillations? Simultaneous acquisition of tDCS and magnetoencephalography (MEG)

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Abnormal neural oscillations in the auditory cortex have been implicated in the generation of tinnitus. This has been shown several times in both magento- and electro-encephalography (MEG/EEG) studies. Given the problems that people with tinnitus face such as increased anxiety and depression, and the lack of treatments and therapies, anything that could be capable of helping tinnitus should be considered of importance. tDCS has been shown to be able to proactively modulate certain neuronal oscillations. However, those oscillatory frequencies studied were not the same as the ones implicated in tinnitus. When combined with residual inhibition (the temporary suppression of tinnitus following presentation of a masking noise) tDCS has been found to have the potential to increase the suppression of tinnitus. However, it is unclear what neural effects the tDCS and white noise combination is having. Both tDCS and masking noise devices are becoming increasingly available to consumers so it is imperative to fully understand what effects tDCS is having on neuronal oscillations. This study aimed to investigate the effects of tDCS on auditory cortical oscillations using MEG. We carried out a combined tDCS and MEG experiment on 13 non-tinnitus participants. Participants were stimulated using either a sham tDCS or anodal stimulation on alternating trials in conjunction with a white noise masker known to induce residual inhibition. MEG data was recorded during this process using an Elekta Neuromag 306 channel system. The data presented are the results of this investigation, and show modulations in alpha and delta frequency oscillations. This would indicate that tDCS is capable of modulation oscillatory frequencies implicated in the generation of tinnitus. Further work is needed to assess how this would convert to a tinnitus population, but offers a promising avenue of exploration.

39 Characterization of a novel analysis method for single trial analysis of fluctuating neural responses

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Trial-to-trial variation in neural signals is known to be perceptually relevant, yet most analysis methods collapse data across many trials, obscuring the significance of this variability. Here, we characterize a novel analysis method for evaluating activity fluctuations at individual trial levels. The method was developed to test whether neural responses to combined stimuli reflect a mixture of the responses to the component stimuli, and was tested with both real neural data and synthetically-created spiking patterns drawn from representative response distributions. Responses to individual component stimuli were first fit with Poisson distributions. Then, a Bayesian model comparison was performed to determine whether combined responses were best explained by a mixture of these component Poisson distributions or several alternatives. These alternatives consisted of a winner take all model (a preference for one of the two component distributions), weighted averaging of components (a single distribution at an intermediate rate), or summation of component distributions. The model comparison was tested using synthetic data sets created to match each of these possibilities. That is, spike trains were generated as draws from a mixture of the two component distributions, a single component distribution, a single intermediate distribution, or distributions with higher mean rates than either component distribution. These data sets were correctly classified for more than 95% of cases when at least 20 trials worth of data were analyzed, demonstrating that the method is sensitive to each of these possibilities and has sufficient power for use with real data sets. Actual neural data from sound responses in the primate inferior colliculus were also analyzed using this method. Responses to combinations of sound spanned the range of models tested, but were often best described by the mixture model, a result obscured by across trial averaging methods. By characterizing neural response fluctuations on short timescales, the presented analysis reveals features which are not visible to methods that pool data across trials. This analysis is part of a growing family of short timescale analyses which provide a window into neural processing at biologically relevant timescales. Although here it is tested only on combinations of two components which are assumed to have Poisson variance, the method can in principle be extended other types of distributions and to any number of components.

40 The effect of language familiarity on the cortical analysis of speech-specific temporal structure

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Human speech is structured over multiple timescales. Phonemes, syllables and words carry information at scales ranging from a few tens of milliseconds to seconds, respectively (Rosen, 1999). Recently, we investigated the processing of such temporal structure in human auditory cortex by measuring BOLD signal changes to speech shuffled at different timescales in a foreign language (German); we showed that superior temporal sulcus (STS) is sensitive to temporal structure that is specific to speech but independent of linguistic lexical analysis (Overath et al., 2015). In the current study we addressed the role of temporal information in the transformation from speech-specific acoustic analysis to speech-specific linguistic analysis. We directly compared responses to English and Korean speech quilts to investigate the extent to which the previous findings are influenced by linguistic analysis.

We recorded four bilingual English-Korean speakers (all female) reading from a book. 4 s long speech quilts were then created with 30, 120, 480, and 960 ms segment lengths in English and Korean; we also included 4 s long original (unaltered) speech stimuli in either language. Imaging data was acquired on a GE MR 750 3T system using a high-resolution (2x2x2 mm) EPI sequence. Participants listened to the speech stimuli and identified which of the four speakers they heard via a button box.

We applied the bilateral group functional ROI in STS from Overath et al. (2015) to probe the responses to the English and Korean speech quilts as a function of segment length. Korean speech quilts showed a parametric increase similar to the one observed before (Overath et al., 2015), while the effect was significantly stronger and more left-lateralized for English speech. In addition, activity in inferior frontal gyrus (IFG) showed an increase as a function of segment length only for English speech quilts.

The results suggest a transition from speech-specific acoustic analysis to speech-specific linguistic analysis that arises in left STS and is mediated by frontal cortex (IFG).

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Rosen (1992) Phil Trans Royal Soc B 336: 367-373.

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41 The contribution of cognition in speech-in-noise perception in younger and older normal hearing adult listeners

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This study aimed to investigate the contributions of cognition in Speech-in-Noise (SiN) perception in a systematic way for a range of speech situations in a cross-section of younger and older adult listeners with age-normal hearing.

We hypothesised the strength of associations between intelligibility and cognition to vary depending on the choice of fore- and background sounds. For instance, sentences and words invoke semantic processing for intelligibility to different extents, and therefore might be expected to differ in their engagement of cognition. A similar reasoning may apply to informational and energetic maskers. Finally, by examining younger and older adults, we can investigate how cognitive contributions to speech perception change with age and hearing loss.

In the SiN tests, the target speech consisted of semantically low- and high-predicable (LP/HP) sentences, and of single words. Background noise was either speech-modulated noise or 3-talker babble. The speech conditions were chosen to vary the extent of semantic processing (words versus LP/HP sentences); the background noise was chosen to invoke more energetic (speech-modulated noise) or informational masking (3-tallker babble).

Cognitive assessments were selected to reflect the components of Baddeley's model of working memory: The central executive (Test of Everyday Attention subtests 1, 6 and 7, the Stroop test, reading span test, letter-number sequencing and digit span backward); the visual-spatial sketchpad (Corsi blocks forward and reverse); the episodic buffer (digit span forward and word list recall), and the phonological loop (two versions of a rhyme verification task).

Using principal component analyses, cognitive measures were reduced to four latent variables corresponding to the four subdomains of the Baddeley model. Individual differences in latent variable scores were then related to each SiN condition using linear mixed models.

Young adults showed no predictive effect of central executive processing for any SiN measures, but did show an overall predictive effect of phonological loop processing. They also showed a predictive effect for visuo-spatial sketchpad as a main effect and in interaction with masker type, and for the episodic buffer component in interaction with masker type. Data collection for the older participant group is ongoing, results will be available in the poster presentation.

For normal hearing younger adults the results indicate that non-executive cognitive processes are more important in speech-in-noise perception, and that underlying cognitive processes may differ between listening in energetic and informational masking.

42 Neurophysiologial manifestation and characterization of the causative gene in a mouse line carrying hereditary deafness

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Deafness is the most common disease in communication and sensory disorders. However, understanding on neurogenetics and neuropathy of many auditory disorders have been hampered because valuable animal models are desperately scarce. By applying mouse genetics, we anticipate to generating diseased mouse models and studying related neuropathy within the context of auditory neuroscience research. Here we report that a mouse line carrying a spontaneous mutation shows severe deafness. Genomic analysis suggests there is an intronic instead of an exonic mutation in gene Tu108, which implies a rather complicated gene modulation mechanim in tu108 mice. We then examined the neurophysiological impact with audiometry, which shows a profound deafness in Tu108 line as early as one month old. It was further confirmed that the tu108 line has impaired auditory transduction. However it seems that the hair cell mechanotransduction does not alternate obviously. Finally, our histological observation indicates this mutant line mainly carries a structural defect in the organ of Corti. In summary, Tu108 gene is linked to auditory transduction and mutated TU108 induce profound deafness by targeting the first order of the auditory pathways.

43 Early sensory experience directs the development of multisensory connections of primary sensory cortices

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Multisensory integration does not only recruit higher-level association cortex, but also primary sensory cortices like A1 (auditory), S1 (somatosensory), and V1 (visual). The underlying anatomical pathways include direct cross-modal thalamocortical and intracortical connections. Sensory loss from birth in humans results in functional recruitment of the deprived cortical territory by the spared senses. We investigated if the multisensory recruitment could be due to changes in the early development of thalamocortical and intracortical projections. Neuronal tracer injections into A1, S1, and V1 within the first postnatal month of normally developing Mongolian gerbils revealed that multisensory thalamocortical connections emerge before intracortical connections but mostly disappear during development. However, early auditory, somatosensory, or visual deprivation leads to an increase of these connections encompassing lemniscal, non-lemniscal, and multisensory pathways. The specific changes in the connectivity patterns are not due to a neurogenesis or apoptosis of projection neurons but rather to axonal remodeling. Consistent with our anatomical findings, functional single-photon emission computed tomography (SPECT) revealed altered stimulus-induced activity and higher functional connectivity specifically between primary areas in deprived animals. Together, we show that early sensory experience has a dramatic effect not only on the development of sensory thalamocortical and intracortical pathways underlying the deprived sense but also on pathways serving the non-deprived senses enabling a functional recruitment of deprived cortical areas by the spared senses.

44 Rate coding of high frequency amplitude modulations during behavior

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The fluctuating temporal structure of amplitude modulated (AM) sounds provides important cues for communication signals, as well as the perceptual qualities of rhythm, flutter, roughness, and pitch. Here, we examined cortical encoding across a broad range of modulation rates, as adult Mongolian gerbils (Merones unguiculates) performed an AM detection task. Freely-moving animals were tested on an appetitive Go-Nogo AM detection task while recordings were obtained telemetrically from a 16-channel array implanted in auditory cortex. “Go” stimuli consisted of amplitudemodulated signals (broadband noise carrier, AM rates: 4-1024 Hz, 100% modulation depth). The noise carrier was frozen, such that the same noise carrier was used for all animals across all sessions. The “Nogo” stimulus consisted of unmodulated (0% modulation) broadband noise. Correct responses on “Go” trials (“Hits”) were rewarded with water, and incorrect responses on “Nogo” trials were scored as false alarms (“FAs”). Task performance was quantified by a sensitivity metric, d’ = z(proportion of Hits) - z(proportion of FAs). Animals were capable of detecting AM rates up to 512 Hz (d’≥1). Performance for AM rates at or above 512 Hz, varied amongst animals. To determine whether animals were using an average level cue, we roved AM and unmodulated stimuli across a 12-dB range. Animals displayed robust AM detection under these conditions, suggesting that they were using a temporal cue. We also evaluated the decision process for AM detection by examining performance as a function of the duration of the modulating signal. AM duration thresholds for accurate AM detection were ~100 ms for fast modulation rates (128 and 256 Hz). To determine whether a common auditory cortical encoding mechanism could account for these behavioral results, we quantified neural sensitivity using both spike rate metrics. A neural template-matching classifier revealed that sensitivity to fast AM rates are sufficiently encoded by spike rate.

45 Anaesthetic choice modulates basic auditory processing: A combined EEG/LFP study in guinea pigs

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Anaesthesia is widely used in in vivo studies of sensory neural processing. Previous studies of the effects of general anaesthesia on neurons in the auditory cortex have shown significant changes to frequency tuning and responses to basic features within the stimulus such as onsets and offsets. Studies of this nature have typically used a single anaesthetic agent, comparing awake and anaesthetised states, and it remains unclear to what extent the choice of anaesthetic agent will affect basic response properties of cortical neurons to sensory stimulation.

Electrophysiological recordings were made with chronically implanted, extradural electrodes, positioned over auditory and visual cortices, and penetrating electrodes in auditory cortex. Recordings were made both while awake and under a range of anaesthetic regimes including opiates, NMDA antagonists and GABA potentiators.

Recordings of spontaneous oscillations replicate the results of previous human studies, showing a rapid increase in power of low-frequency (<10Hz) oscillations at loss of consciousness, suppression of high frequency activity and a shift toward criticality, with a higher proportion of unstable oscillatory modes being observed - effects which appear mostly independent of anaesthetic regime.

Responses to a range of basic sensory stimuli, such as auditory clicks and tones, display substantive differences in population level processing of even basic auditory stimuli between anaesthetic regimes. These modulations range from -20% to +50% changes in onset response amplitude, up to 25ms peak latency shifts and up to 600% increases in offset response amplitudes. Neural responses to visual flashes demonstrated universal suppression of visually evoked potentials under all anaesthetics and we also observed, under all anaesthetics tested, near total abolishment of auditory-visual cross-modal interactions.

Adapter-probe stimuli were also tested showing substantial modulation of adaptation recovery time constants, with diazepam slowing the release from adaptation and ketamine allowing faster recovery than when awake.

Local field potentials were used to isolate changes occurring in primary auditory cortex, helping to explain the phenomena seen in the EEG recordings and show changes in frequency tuning resulting from each anaesthetic.

In conclusion, we have demonstrated that anaesthesia has significant effects on systems level sensory processing and that the choice of anaesthetic used for recording can have grossly different effects on the response to even simple sensory stimuli."

46 Characterizing receptive fields in awake primate auditory cortex using principled correction of the spike-triggered average

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Characterizing auditory cortical receptive fields has been the subject of numerous studies, the majority of which have been conducted in anesthetized cats and ferrets. Comparatively little is known about auditory cortical receptive field structure in nonhuman primates. Considering the extensive homologies between human and nonhuman primate auditory cortex, characterizing auditory receptive fields in primates could serve as an important model of auditory cortical processing, with particular relevance for developing neural prostheses. Because anesthesia is known to affect response properties of auditory cortical neurons, studies using awake preparations are especially needed. The current study characterized spectrotemporal receptive fields (STRFs) in primary auditory cortex of two alert squirrel monkeys (Saimiri sciureus). Extracellular single- and multi-unit recordings were obtained using 16-channel linear multielectrode arrays (150 μm spacing), with neurophysiological traces sampled at 30 kHz. The spectrotemporal preferences of each unit were probed with a 30-m dynamic moving ripple (DMR) stimulus presented through a free field speaker from a central distance of ~40 cm. A novel 30-s DMR segment was subsequently presented (50 repetitions) to assess the prediction accuracy of the STRF estimates. STRFs were estimated by computing the average DMR spectrogram preceding each spike (spike-triggered average [STA]), at a resolution of 193 frequency bins and 200 time lags (1 ms). Although the STA can theoretically reflect an unbiased estimate of the STRF, we found that a two-step correction procedure nearly doubled prediction accuracy across units, presumably reflecting more accurate STRF estimates. First, a conventional amplitude threshold was used identify regions of the STRF that exceeded chance values obtained from simulated STRFs computed for each unit using circularly shifted spike times to preserve the spike rate and inter-spike interval distribution. Second, a cluster size threshold was used to limit clusters that survived the amplitude threshold to those that exceeded chance cluster size values obtained from simulated STRFs subjected to the same amplitude threshold. The amplitude and cluster size thresholds were optimized for each unit by cross-validation to maximize the correlation between predicted and observed responses to the repeated DMR segment. On average, this procedure resulted in a liberal amplitude threshold but a conservative cluster size threshold. The resulting corrected STRF estimates are used to provide a detailed

characterization of spectrotemporal response properties of awake primate auditory cortex.

47 Primate BOLD data demonstrating fundamental bases for auditory figure-ground analysis

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A critical aspect of auditory scene analysis is the ability to extract a sound of relevance (figure) from a background of competing sounds (ground) such as when we hear a speaker in a cafe. Previous work on this has used high-level stimuli with stochastic elements like speech in noise or deterministic stimuli like that developed by van Noorden. We have developed a stimulus based on the detection of elements in frequency space in a random background that are repeated over time – a form of sequential grouping of spectral patterns. Functional imaging in humans [1] demonstrates a network that includes auditory cortex and the intraparietal sulcus (IPS).

The stochastic figure ground stimulus we have developed examines fundamental mechanisms for figure ground perception that are equally relevant to the rhesus macaque, in which we can carry out both system level and systematic neuronal specification of the system. We investigated the neural bases of pre-attentive stimulus-driven auditory segregation in rhesus macaques using functional magnetic resonance imaging.

Stimuli were made of 5-15 randomly chosen pure tone components (ground) that change for every chord. This ground segment is overlaid with 10 additional components that are either coherent (figure) or incoherent (control), presented at the middle 2 s of the 6 s long exemplars. EPI images were acquired using a sparse acquisition protocol on 4.7T upright Bruker scanner (TR/TA/TE = 10s/2.01s/21ms) while the animal performed a stimulus irrelevant visual fixation task. 360 volumes (135 each for figure & control) were acquired per session per animal. Analysis was carried out using SPM software (SPM12). Single subject inference was carried out by applying a generalized linear model (GLM).

We observed significant activation in core auditory cortex, anterior superior temporal gyrus and posterior superior temporal sulcus (STS). Our results suggest that analogous to human IPS, macaque posterior STS is involved in mediating pre-attentive auditory segregation identified using an identical stimulus to that used in previous human study [1].

The data support the use of the macaque as a model for human auditory scene analysis that allows both system-level and neuronal characterisation.

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48 Direct human electrical recordings demonstrating fundamental bases for auditory figure-ground analysis

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The ability to detect a relevant sound by filtering out irrelevant sounds in the environment is crucial in day-to-day listening. This ability requires that the features of the relevant sound be grouped together as a single source (figure) and segregated from the features (background) of other competing sounds in the environment. How the auditory system performs this task is not completely understood. In the current experiment we recorded local field potentials (LFPs) from human subjects undergoing invasive ECoG monitoring for pre-surgical localization of their epileptic foci while they were listening to a stimulus in which the salience of the figure was varied systematically against a background. The subjects were implanted with depth electrodes in auditory cortex along the axis of Heschl's Gyrus (HG) and subdural grids covering the superior temporal gyrus (STG).

The subjects listened to a stimulus in which the salience of the figure was varied systematically against a background. We used a stochastic-figure-ground (SFG) stimulus developed in our lab that has been previously characterized using psychophysics and modelling. The SFG consisted of a sequence of simultaneously presented tones that were randomly distributed in log frequency space and varied from one 25 ms time frame to the next. During one time segment, a certain proportion of the tones remained the same over several consecutive time frames. This causes a figure to emerge from the background in which the salience is determined by number of tones kept fixed (the coherence) and the number of time frames over which this occurred (duration). In the current experiment, the first part (700ms) of the stimulus consisted of only the background with no figure, and in the second part the coherence of the figure was varied across trials (between 0, 2, 4 and 8). The overall duration of the figure was 28 individual 25ms time frames (700ms).

We measured event-related potentials (ERPs) and carried out single-trial time-frequency analysis using a wavelet transform. In HG responses to the figure when compared to the acoustically matched background were minimal or non-existent. In contrast, we observed a power change in the high gamma band (60-120 Hz) that peaked 200-300 ms and varied with the coherence of the stimulus on STG for all tested subjects.

The data demonstrate a neural correlate of auditory figure-ground segregation in the form of high-frequency local oscillations in human non-primary auditory cortex.

49 Mapping auditory information flow in the primate cortex: corticocortical and thalamocortical projections

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The flow of information in the primate auditory cortex follows a hierarchical processing scheme, with projections in the medial-lateral dimension from core, to belt, to parabelt. We recently showed that rostral auditory cortex in the rhesus monkey receives input via stepwise serial projections in the caudal to rostral dimension: through the primary, rostral, and rostrotemporal core areas (AI, R, and RT) on the supratemporal plane (STP), continuing to the rostrotemporal polar area RTp (Scott et al., Cerebral Cortex 2015). In addition to this serial cascade of corticocortical connections, every region of auditory cortex receives parallel thalamocortical projections from the medial geniculate nucleus (MGN), with the caudal core (AI and R) being the primary recipient of input from the ventral division (MGv, i.e. the lemniscal auditory pathway). Because few studies have placed tracer injections into the rostral STP beyond AI and R, we injected anterograde and retrograde anatomical tracers into AI, R, RT, and RTp to quantify the thalamic inputs to these areas and address several outstanding questions about the organization of auditory cortex. Whereas AI and R both receive nearly 90% of their thalamic inputs from the MGv, RT receives only ~45% from MGv, and an equal share from the dorsal subdivision, MGd. Area RTp receives ~25% of its inputs from MGv, but ~30% of its thalamic inputs arise from multisensory areas outside the MGN (e.g., medial pulvinar). In accord with the laminar patterns evident in corticocortical connections in the same cases, these thalamocortical connections support a model in which AI and R lie at the same hierarchical level, but RT and RTp lie at a higher level, perhaps between that of the core and belt. These results will be presented in the context of an expanded hierarchical model that aims to capture the complexity of the primate's ventral auditory stream, which may well exceed the complexity of the primate's ventral visual stream.

50 Two-Scale Processing in Human Auditory Cortex: A Scale for Detection and a Scale for Tracking

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The auditory system must be able to track sounds with irregular acoustic temporal dynamics, since natural sounds rarely have entirely regular modulation rates. Previous studies typically use regular sounds having modulation rates within a narrow frequency range, such as speech or amplitude modulated sounds. How does the auditory system actively track irregular temporal structure and detect salient acoustic changes embedded in a continuous acoustic stream? Here we use stimuli with 1/f modulation spectra of exponents at 0.5, 1, 1.5 and 2, which simulate the dynamics of environmental noise, speech, and some vocalizations. While undergoing magnetoencephalography (MEG) recording, participants listened to 3-sec stimuli and detected embedded tones. ¬–The tone detection rate differs across stimuli although the signal-to-noise ratio is held constant. The MEG results reveal that theta band oscillations surprisingly track all irregular sounds but were preferentially entrained by stimuli with exponent 1. To account for the results, we construct an auditory processing model, which incorporates comodulation and uses temporal Gabor filters, to quantify acoustic information on various timescales. By correlating the model outputs with behavioral and neural results, we observe that the auditory system extracts fine-grained acoustic changes on a scale less than ~ 40 ms to help detect tones; in contrast the cortical oscillations in the auditory cortex are entrained by acoustic structures on a scale larger than ~ 200 ms. The results suggest a general algorithm for temporal processing – a short scale (< 40 ms) for processing detailed acoustic changes and a large scale (> 200 ms) for tracking acoustic structures.

51 Ongoing dynamics of frequency-specific large-scale brain networks predict the speed of auditory decisions

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To what extent do neural processes involved in auditory perception rely on the connectivity of brain networks? To answer this question, we combined human magnetoencephalography (MEG) and source localization with large-scale network analyses. Twenty young listeners judged brief (400-ms) acoustic textures along one of two feature dimensions in two distinct, difficulty-matched tasks. The stimuli consisted of densely layered tone sweeps and varied in the proportion of coherent tones (up/downwards; local feature), and also their overall pitch (high/low; global feature). Power of the MEG source signals were derived within -0.5–1.5 s around stimulus onset at frequencies 1–32 Hz. To assess neural interactions using graph-theoretical measures, power envelope correlations between all pairs of sources were computed, and binary brain graphs were constructed per trial. To predict trial-by-trial decision speed from the ongoing brain network states, we used a general linear model while controlling the effects of the acoustic features. The regression weights of this model were averaged over subjects and compared with a null distribution. On the whole-brain level and for both tasks, faster decisions were correlated with higher topological segregation of dynamic brain networks. This effect was found prominently in the beta band (~21 Hz; false coverage-statement rate corrected). Interestingly, we also found task-specific effects: higher local efficiency at right supramarginal gyrus predicted faster decisions in the pitch task. In contrast, higher local efficiency within the right anterior cingulate and left middle frontal gyrus predicted faster decisions in the coherence task. Our results suggest that higher segregation of brain connectivity networks in mainly extra-temporal cortices speeds up auditory decisions. Depending on the task, this network configuration can emerge in distinct areas within the parietal and frontal cortices.

52 Chronic calcium imaging reveals strong suppressive effects of anaesthesia on spontaneous and sound-evoked responses in dorsal inferior colliculus

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The inferior colliculus (IC) is a major auditory processing center, which receives input from major brainstem auditory nuclei. The non-lemniscal regions of the IC, dorsal cortex (DCIC) and lateral cortex (LCIC), are major targets for feedback projections from the cerebral cortex, making them likely susceptible to anaesthetic effects. Moreover, a large part of the DCIC lies superficially, making it a favorable structure for chronic in vivo two-photon imaging. Using calcium imaging, we measured spontaneous and sound-evoked activities of the same IC neuronal population in mice when the animals were awake and during anaesthesia with ketamine/xylazine. GCaMP6s was expressed in IC neurons through the injection of AAV-vector. Pure-tone stimuli of various frequencies and intensities were presented while fluorescence of GCaMP6s was recorded by two-photon imaging. In an awake animal, a substantial portion of cells showed inhibitory response to pure tone stimuli, as indicated by a decrease in GCaMP6s fluorescence. We also observed excitatory responses to tone offset in some cells. Upon ketamine/xylazine anaesthesia, we noticed a decrease in baseline GCaMP6s fluorescence, which we interpret as a decrease in spontaneous activity. Inhibitory and offset responses were greatly diminished. Onset excitatory responses often showed an increase in threshold or a decreased amplitude. Some cells showed a shift in their characteristic frequency during anaesthesia. The same neurons were imaged after the animals recovered from anaethesia to confirm that the changes were temporary and due to anaesthesia. Pupil size, whisker movement and body movement of the animals were recorded to further probe the effect of alertness. Post-hoc histology was performed on imaged cells to relate their neurochemical properties to their response characteristics. Our findings suggest the presence of tonic excitation on IC neurons in awake animals, which is suppressed during anaesthesia.

53 Contribution of correlated neural activity in the auditory cortex to the cocktail-party problem

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One of the fundamental functions of the auditory system is to transform acoustic stimuli into discrete perceptual representations (sounds). However, often, because we listen in noisy environments, our auditory system needs to extract and segregate a “target” stimulus (e.g., your friend’s speech) from a noisy background (e.g., the sounds that are formed by other talkers in a restaurant). This ability is often referred to as figure-ground segregation or, more informally, as the cocktail-party problem. However, it is unknown whether and if coordinated correlated auditory contributes to the computations underlying the cochtail-party. To address this issue, we recorded from the auditory cortex while rhesus monkeys simultaneously reported whether or not they heard a target stimulus that was embedded in a noisy background. The target stimulus was a tone burst, whose frequency was set to the best frequency of the recording site, and the noisy background was comodulated broadband noise. On a trial-by-trial basis, we varied the “target-in-noise” ratio (TNR) between 0 and 25 dB. On approximately 50% of the trials, we presented the noise alone; these trials served as catch trials. We recorded with Plexon u-probes and were able to isolate several neurons in each recording session. In general, we did not identify any changes in correlated activity with changes in TNR level. However, changes in correlated activity did emerge as a function of the monkeys’ performance. In particular, we found that signal correlation was modulated as a function of task performance (hits versus misses). Similarly, noise correlation was modulated as function of whether the monkeys’ reported a hit versus a miss. Finally, we found that the Fano factor (an index of spiking variability) was smaller on hit trials than on miss trials. These findings suggest changes in coordinated population activity may limit a listener’s performance on tasks like foreground-background segregation. They also suggest that changes in Fano factor may be an underlying mechanism.

54 Mechanism and Function of Physiologically Heterogeneous Cell Types in Caudolateral Mesopallium

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The avian caudal mesopallium is one of the first regions in the auditory system responsible for selective, invariant representations of learned conspecific song. Using whole-cell electrophysiological recordings from caudolateral mesopallium (CLM) in zebra finches (Taeniopygia guttata), we have identified several putative classes of neurons by spike shape, frequency-current relationships, and firing patterns. A small proportion of cells had narrow spikes (NS; 9%) and little to no frequency adaptation, characteristics of inhibitory interneurons. The remaining putatively excitatory cells exhibited broad spikes and a range of phasic and tonic firing patterns that could be clustered into separate groups. Some neurons were regular-spiking (RS; 16%), with tonic, moderately adapting spiking responses to prolonged depolarizations. The predominant majority of neurons displayed a phasic firing pattern, responding only at the onset of depolarizing step currents. Within this group of cells we distinguished transient-spiking neurons (TS; 29%), which fired 3-5 action potentials at depolarization onset, followed by subthreshold oscillations, and onset-spiking neurons (OS; 46%), which fired only a single action potential at depolarization onset. Some neurons were filled with biocytin to reconstruct cell morphology; phasic neurons tended to have smaller, less elaborate dendritic trees. All four classes of neurons were present in adults and juveniles, but TS and OS neurons were more common in adults. Birds reared in an impoverished auditory environment had a much larger proportion of regular spiking neurons (70%), suggesting that excitability of CLM neurons changes over the course of development in an experience-dependent manner. Firing patterns are intrinsic, as they persisted in the presence of fast synaptic transmission blockers. Some TS and OS cells became regular-spiking when treated with 4-AP and alpha-dendrotoxin but not other potassium-channel blockers, suggesting that a low-threshold outward current is responsible for phasic firing in these cells. Based on linear and dynamical systems models fit from responses to complex, broadband current stimulation, phasic neurons are likely to function as coincidence detectors in processing complex auditory stimuli such as birdsong.

55 A high-frequency tonotopic reversal in marmoset parabelt auditory cortex

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The current working model of primate auditory cortex comprises the hierarchical arrangement of a series of functionally distinct information processing stages: a primary 'core' region, a secondary 'belt' region, and a tertiary 'parabelt' region. Combined anatomical, physiological, and imaging experiments in monkeys have subdivided core and belt into multiple tonotopic subfields (Kaas & Hackett 2000). Human fMRI investigations have attempted to find homologues of the primate core fields A1 and R by looking for a low-frequency tonotopic reversal near Heschl's gyrus (HG), the histologically-identified site of human primary auditory cortex. While many studies have found such a reversal, a long-standing contradiction exists between results supporting an auditory cortex oriented parallel to HG, and others perpendicular to HG (Baumann, Petkov & Griffiths 2013; Moerel, de Martino & Formisano 2014). Using a single neuron mapping technique in awake and behaving marmosets, we have identified a previously unrecognized high frequency tonotopic reversal in putative parabelt auditory cortex, immediately lateral to the previously known low frequency reversal in lateral belt. Such a spatial arrangement of high and low frequency regions in adjacent fields could conceivably be mistaken for a single field with a tonotopic axis perpendicular to the true cortical configuration. Thus this high frequency region may explain the mutually contradictory patterns of results observed in human imaging studies. Neurons in this high frequency region exhibit long response latencies, strong selectivity for acoustic parameters, such as bandwidth, intensity, temporal modulation, and spatial location, as well as response modulation by behavioral engagement.

56 Distinct timescales for neural discrimination of sound envelope shape in three auditory cortical fields

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Mammals discriminate sounds based on perception of timbre and loudness due to temporal shape cues including duration and rate of change in sound envelope amplitude (Iverson and Krumhansl 1993; Irino and Patterson 1996, Drullman, Festen et al., 1994; Geffen et al., 2011). Mammals need cortex to detect temporal sound cues but the underlying cortical circuits and coding mechanisms for this ability remain unknown. Here we propose that cortical neuron spike timing patterns can be used to discriminate differences in sound envelope shape cues in three auditory cortical fields of the rat.

Single neuron response spike trains were recorded from layer 4 neurons in surgically exposed primary (A1), ventral (VAF) and caudal suprarhinal (cSRAF) auditory cortical fields of the rat as the physiology and corresponding thalamocortical pathways have been well described (Polley et al., 2007, Storace et al., 2010, 2011, 2012, Higgins et al., 2010). Spiking responses were probed with fifty-five unique noise burst sequences that varied in noise burst duration but had fixed noise burst repetition rate. To evaluate temporal patterns, spike trains were convolved with an exponential kernel having an evaluation window or time constant, Tc (van Rossum, 2001). A sound sequence discrimination index (d-prime) was computed from the evaluated spike train responses (Zheng and Escabi, 2012, Gai and Carney, 2008). Next, for each pair of spike trains, the Tc was varied between 1 and 256 ms to determine time window yielding optimal (aka maximal) sound sequence discrimination.

In all fields, we find a rank order increase in the synchronized response duration with A1 < VAF < cSRAF to any given sound shape (Lee et al., 2016). Similarly, here we find a rank order increase in Tc yielding best discrimination with: A1 < VAF < cSRAF (logarithmic means: A1: 33 ms (1.03), VAF: 39 ms (1.02), cSRAF: 44 ms (1.03), $p < 0.001$). A1 neurons discriminate small differences in sound envelope shape (e.g. 2Hz vs 4Hz). Whereas, VAF and SRAF are better than A1 at discriminating large differences in sound envelope shape (e.g. 2Hz vs 64Hz). These results indicate that cortical neuron spike-timing patterns can be used to discrimination of sound envelope temporal shape cues. Furthermore, distinct response timescales allow for complementary sound shape discrimination in primary versus non-primary auditory cortices. The multi-scaled organization could in theory provide a behavioral advantage to mammals for discriminating temporal shape cues in the sound envelope."

57 Activity of medial prefrontal and striatal neurons in primates while remembering faces and vocalizations.

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Our previous work has shown that ventrolateral prefrontal cortex (VLPFC) integrates face and vocal information and is necessary for audiovisual working memory. However, visual working memory relies on many cortical and subcortical regions including the medial prefrontal cortex (mPFC) and dorsal striatum. Moreover, mPFC is involved in conflict detection, audio-vocal control and receives strong inputs from higher order auditory processing regions within the temporal lobe. There are few studies which have examined the roles of these regions in audiovisual processing and memory. Here, we recorded from mPFC and striatal neurons while macaques performed an audiovisual nonmatch-to-sample task. Subjects attended an audiovisual movie clip of a face-vocalization as the Sample and detected the occurrence of a Nonmatch (when the face or vocalization differed from the Sample movie). Neurons within the mPFC and striatum were task related and were active for key periods of the task including the sample, the delay, the match, and the nonmatch epochs. In contrast to previous findings from VLPFC, both mPFC and striatal neurons were more active during decision-related epochs of the task, such as detecting the Nonmatch or suppressing a response during a Match presentation than during the Sample or Delay. This data suggests mPFC and the striatum are part of a neuronal circuit underlying audiovisual working memory in the primate brain.

58 Pitch perception in marmosets

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The mechanisms of pitch perception have been one of auditory neuroscience's central questions due to the importance of pitch in music and speech perception. Yet the evolutionary origins of pitch perception, and whether its underlying mechanisms are unique to humans, is unknown. It has been shown that humans perceive pitch of harmonic sounds through spectral or temporal features. Previous studies have described three primary features of human pitch perception: (1) Lower resolved harmonics have a stronger pitch strength compared to a pure tone at the fundamental frequency (F0) and also to higher unresolved harmonics; (2) pitch of resolved harmonics is sensitive to the quality of spectral harmonicity; (3) pitch of unresolved harmonics is sensitive to the salience of temporal envelope cues. Among these features, the first two have never been demonstrated in any non-human species. We have conducted a series of psychophysical experiments to explore pitch perception behaviors in the marmoset (Callithrix jacchus), a highly vocal New World monkey species separated from humans by about 30 to 40 million years. Our results showed that, for a standard musical tuning fundamental frequency of 440Hz (ISO 16), the marmoset exhibits all three primary features of pitch perception mechanisms as found in humans. Combined with previous findings of a specialized pitch processing region in both marmoset and human auditory cortex, this finding suggests that the mechanisms for pitch perception, which have long been thought unique to humans, may have originated early in primate evolution, before the separation of New World and Old World primates. Additionally, one remarkable property of human pitch perception is that it is largely intact in the absence of the fundamental frequency component, the so-called "missing fundamental" phenomenon. Our recent experiments have provided new evidence that the marmoset perceives missing fundamental in a pitch discrimination task, even when the pitch change is as small as one semitone (the smallest pitch step in Western music). Together, our findings demonstrate that the marmoset has the capability to process pitch information similar to humans and suggest that these animals may be able to discriminate notes in a human musical scale, which is crucial for any music melody perception.

59 Electrophysiology of the human superior temporal sulcus during speech and language processing

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The superior temporal sulcus (STS) is a crucial hub in the cortical system subserving speech perception. To date, this area has been primarily examined with non-invasive functional neuroimaging (e.g. fMRI). Electrocorticography (ECoG) offers a unique opportunity to study this region with both high spatial and temporal resolution. Here, we examined ECoG activity evoked in the STS by a variety of stimulus classes under multiple task conditions. Our goal was to identify fundamental electrophysiological properties of this region.

Subjects were neurosurgical patients undergoing chronic invasive monitoring for medically intractable epilepsy. All procedures were approved by the University of Iowa Institutional Review Board and NIH, and all subjects gave informed consent for this study. Direct recordings from middle and anterior portions of the STS were made using multicontact depth electrodes that targeted mesial temporal lobe structures (amygdala and hippocampus). ECoG data were simultaneously acquired from the auditory cortex in Heschl's gyrus (HG) and lateral superior temporal gyrus (STG) using penetrating depth and subdural grid electrodes, respectively. Stimuli were non-speech and speech sounds, presented in passive-listening and target detection tasks. Additional data were acquired during performance of the Mini Mental State Exam (MMSE; Folstein et al., J Psychiatr Res, 1975, 12:189-98) and other cognitive tasks. ECoG frequencies between 4 and 150 Hz were examined.

The STS exhibited response profiles distinct from those in auditory cortex. The STS was less responsive to non-speech stimuli compared to speech. Prominent activity occurred in low gamma (30-70 Hz) and beta (14-30 Hz) bands. Responses had longer onset latencies than those in HG and on STG, except its most anterior portion. Activity within the STS preceded subjects' behavioral responses during active tasks. In a minority of sites, activity preferentially increased to target stimuli, including complex tones. Responses increased with intelligibility when speech was manipulated using a noise vocoder. Comparable degrees of activity were elicited in the language-dominant and non-dominant hemispheres. Finally, a conversation-based paradigm (MMSE) revealed sites in STS that preferentially responded to the subject's own speech over that of the interviewer's, reflecting their possible involvement in the dorsal audiomotor processing pathway.

We conclude that human STS can be effectively probed with ECoG, offering unique insights into its response properties and the transformations that occur from earlier processing stages in auditory cortex.

60 Associative plasticity in the auditory cortex induced by fear conditioning

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The sensory cortex is able to modify its function based on preceding experience in order to optimize processing of behaviorally relevant stimuli. In the auditory cortex, tonotopic reorganization follows various types of learning. Fear conditioning leads to expansion of the regions representing the conditioned stimulus. However, the extent of this plasticity as described by classical electrophysiological approaches has been unclear at the level of subpopulations of neurons. We used two-photon calcium imaging in vivo to elucidate functional plasticity in the auditory cortex with single-cell resolution. Further, we wanted to differentiate the plastic changes in receptive fields of somatostatin-positive interneurons (SST), because SST cells can influence tuning of principal cells by inhibitory inputs to their distal dendrites. In somatostatin/tdTomato mice with an implanted chronic cranial window and neurons expressing an ultrasensitive calcium indicator GCaMP6 in the auditory cortex, we measured coding properties of exactly reidentified neurons before and after fear conditioning. In subsets of SST-negative neurons, both shifts towards the CS+ and CS- were present. The shift direction was dependent on neuron´s best frequency (BF) before fear conditioning. In some neurons no tuning shifts were observed, even when they were spatially intermingled with the retuned neurons. This evidence contradicts the view of simple expansion of CS+ tuned regions. SST+ cells retuned in a different manner with an upward BF shift independent on initial best frequencies. Behaviorally, these changes were accompanied by selective spatial attention towards the conditioned stimuli. The adaptive purpose of these learning-induced physiological and behavioral changes can be possibly explained as an information processing optimization, improving the ability to discriminate between threatening (CS+) and non-threatening (CS-) stimuli. The orienting responses towards CS+ were more often followed by escape behavior, instead of conventional freezing reactions.

61 Slow rhythms in conspecific vocalizations are over-represented in the primary auditory cortex of common marmosets

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A 3- to 8-Hz rhythm is a typical feature of human speech and is known to be critical for speech comprehension. Interestingly, macaque monkeys communicate with a rhythmic oral gesture within this range and they prefer a gesture produced in the natural rhythm over unnatural ones. These findings suggest the importance of rhythm perception in primate social communications and that the neural representations of vocal rhythm are fundamental to elucidate neural mechanisms of social communication. To address this issue, we conducted electrophysiological recordings from the primary auditory cortex (A1) of anesthetized marmosets, a New World monkey known to have various rhythmically modulated calls. We synthesized sounds having rhythms spectro-temporally matched to three representative marmoset call types and examined neural responses to the real and synthetic calls.

We found that the A1 neurons were largely divided into two groups; one that responded both to the real and synthetic calls and the other that responded only to the real calls. The responsiveness to the synthetic calls was dependent on the best frequencies of the cells, which were defined by the frequency tuning peak of the units, suggesting that the frequency is an important feature of sounds that evokes the A1 neurons. For the former cell group, we further examined their sensitivities to the rhythmic modulations by manipulating the rhythms in amplitude and frequency of the synthetic sounds independent from each other. The A1 neurons showed various types of tunings to these rhythm combinations and they covered entire parametric space of our stimulus set as a population. However, a large proportion of the cells (~40% of units) preferred the combinations of slow rhythms <8 Hz, which is naturally found in marmoset calls.

These results indicate that the marmoset A1 neurons over-represent temporal rhythms that are commonly observed in conspecific vocalizations and human speech. Our findings suggest common neural mechanisms underlying vocal communications in humans and an ancestral primate and the usefulness of marmosets as a primate model for speech comprehension."

62 Egocentric and Allocentric Representations in Auditory Cortex

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A key function of the brain is to provide a stable representation of an object's location in the world. Auditory cortex is necessary for sound localization, with auditory cortical neurons encoding sound azimuth and elevation. However the coordinate frame in which neurons in the central auditory pathway, including auditory cortex, represent space remains undefined: classical spatial receptive fields in head-fixed subjects can be explained either by sensitivity to sound source location relative to the head (egocentric) or relative to the world (allocentric). We dissociated these reference frames by performing the first recordings of spatial receptive fields in freely moving subjects. We found two distinct populations of spatially tuned neurons in auditory cortex. While the majority (~80%) of spatially tuned neurons represented sound source location relative to the head, we describe a novel group of neurons in which space was represented in an allocentric world-centered reference frame. Our findings argue that auditory cortex is involved in the representation of both sound source location relative to ourselves and in the world independent of our own position. Allocentric neurons illustrate that the auditory system can distinguish between acoustic changes resulting from self-motion and sound-source motion, and may play a critical role supporting perceptual stability during movement.

63 Sensory coding properties predict selective attention effects on single units in primary auditory cortex

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Auditory selective attention is required to discern behaviorally relevant information in crowded acoustic environments. Studies of attention and related behaviors during single-unit recording in animals have revealed diverse behavior-related effects, which have yet to be integrated into a coherent theory of how attention influences neural coding. In order to better understand the diversity of behavioral effects, we asked whether the baseline sensory coding properties of neurons in auditory cortex predict whether they will be modulated by attention.

We trained three head-fixed ferrets to perform an auditory selective attention task. Animals responded to a target tone embedded in one of two simultaneous narrowband noise streams and ignored catch tones in the other. The target stream was switched between blocks, and selective attention was verified by comparing responses to targets versus catch tones.

After training, we recorded single-unit activity in primary auditory cortex (A1) during behavior and during passive presentation of task stimuli (n=52). One noise stream was centered at neural best frequency and contralateral to the recording site. Thus, the task alternated between attention directed into the receptive field (attend RF) and away from the RF (attend away). Identical noise stimuli were played in all behavioral conditions.

We compared spiking activity evoked by the noise and tone stimuli in each behavioral condition. During the attend RF condition, the average noise-evoked response decreased ($p<0.001$, sign test). Tone responses did not change. Because only the RF stream evoked neural activity, this change represents a suppression of noise responses at the locus of attention.

Distractor responses were suppressed in only about half of recorded units. To test whether a neuron’s sensory coding properties predicted modulated by attention, we computed a nonlinear spectro-temporal receptive field (STRF) for each unit. The STRF included a nonlinear input term that accounted for short-term plasticity (STP) of sensory inputs. Neurons that showed evidence for STP were less likely to undergo attention-mediate changes. Thus the nonlinear temporal integration properties of A1 neurons predict whether they will undergo changes in tuning during selective attention."

64 Independent attentional modulation of compound auditory feature integration and segregation.

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Attention plays a significant role in sensory detection. Although auditory scene analysis relies largely on the preattentive segregation and grouping of features based on their temporal and spectral attributes (Bregman 1990), attention also plays an important role in focusing on particular sound sources or streams (Cherry 1953). Auditory perceptual grouping and segregation depend on Gestalt-like rules (such as similarity and proximity along one or more dimensions), however little is known of attention's effects on perception in feature integration or segregation, when the differences between features are held constant. Intuitively it would seem that, the more readily that features may be segregated or independently processed, the greater their resistance to integration and grouping.

To address this question, we assessed human subjects' (n = 4; 1 female) sensitivity for detecting one or two acoustic features presented simultaneously, using psychophysical methods. The features, broadband sinusoidally amplitude-modulated (AM) noise and spectral bandwidth (bandwidth restricted noise) (SB), were chosen for minimal physical interaction. In an experiment designed to assess feature segregation, subjects were required to selectively attend to either AM or SB during a session while ignoring the other feature. In the experiment designed to evaluate feature integration, subjects were required to detect a feature compound. Sensitivity in both cases was compared to single feature (SF) detection under either mixed (randomly interleaved trials) or blocked (SF only) sessions. A yes-no procedure was used: The subjects indicated using a joystick whether a test stimulus was different than a previously presented standard stimulus (400-ms stimulus duration and interval).

Thresholds for feature detection were estimated from psychometric function fits using percentage of correct responses at seven levels of modulation/bandwidth, normalized for comparisons across condition. All subjects in the SA experiment were able to detect the attended feature with relatively low losses in accuracy (~0-25%), relative to SF stimuli, which appeared independent of the unattended feature magnitude. However, most (3/4) subjects in the FI experiment displayed relatively large drops in relative threshold (~10-70%) when detecting compound as compared to SF stimuli. Our results support that, for relatively independent compound acoustic features, feature integration and segregation operate largely independently and are subject to attentional modulation.

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65 Contrast gain control in auditory thalamus

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Contrast gain control has been identified in the visual, auditory and somatosensory systems. Gain control is beneficial because the statistics of the sensory environment are constantly changing, meaning that neurons may not be able to accurately represent the range of stimulus values that occur at any moment unless they are able to adapt their dynamic ranges to match that range. Furthermore, adaptation to sound contrast may also provide a useful mechanism for generating noise-invariant neural representations of complex sounds. In the auditory system, previous work has demonstrated robust contrast gain control in ferret auditory cortex (Rabinowitz/Willmore et al., 2011), and limited contrast gain control in the auditory midbrain (Rabinowitz et al., 2013). It is currently unknown whether the robust contrast gain control seen in cortex is computed locally in the cortex or whether it reflects a thalamic computation which is relayed to cortex. To determine the site of robust contrast gain control in the auditory system, we recorded with extracellular electrode arrays from auditory thalamus in anesthetized mice. We presented dynamic random chord stimuli at two different contrasts, and similar mean sound level. We fitted the neuronal responses with a linear spectro-temporal receptive field and sigmoid output nonlinearities for each contrast. To estimate the gain of each unit, we examined the parameters of the sigmoid output nonlinearities. We found that the auditory thalamus exhibits robust auditory contrast gain control, similar to that previously found in cortex, suggesting that the thalamus does indeed have a role in computing contrast gain control. We are currently conducting similar recordings in auditory thalamus while inactivating auditory cortex, to investigate whether the contrast gain control seen in auditory thalamus arises through cortico-thalamic feedback from primary auditory cortex or is implemented within the thalamus itself.

66 Task engagement induces shift from sensory to behavioral representations in primary auditory cortex

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Primary sensory cortical areas are commonly conceived of as early processing stages that faithfully represent the physical attributes of the stimuli, in contrast to higher cortical areas that associate behavioral meaning with the sensory representation, and generate an appropriate response that is maintained until a motor command is executed. Thus, within this purely sensory framework, responses of the primary cortices during task performance are not expected to reflect the behavioral significance of the stimulus features as do higher sensory, association, motor and frontal cortices. Here instead, we demonstrate that the neuronal population response in the early primary auditory cortex (A1) strongly reflects both the behavioural state of the animal and the behavioral meaning of the stimulus. This A1 activity was recorded in awake ferrets while they were either passively listening or actively discriminating two periodic click trains of different rates. We found that task-engagement induced a shift in the nature of the encoding from a sensory-driven to a behavioral, asymmetric representation of Go and No-Go stimuli. Moreover, information about the behavioral meaning of the stimulus was maintained during the silent period after the stimulus presentation and until the behavioral response, forming a memory trace that was strongly correlated with the animals' performance. This sustained, asymmetric representation of behavioral meaning was found in a variety of other discrimination tasks that shared the same basic Go/No-Go structure, but employed different acoustic stimuli and reinforcement paradigms. We show that the behavioral representation of stimuli in A1 population activity bears strong similarities with the activity of single cells in the frontal cortex, but appears earlier following stimulus presentation. These findings indicate that primary sensory cortices play a highly flexible role in processing incoming stimuli and implement a first step in extracting task-relevant information.

67 Investigating the cortical encoding of phonological features of continuous speech in dyslexia

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Developmental dyslexia is characterised by difficulties in learning to read despite normal intellectual functioning, normal hearing and vision and an adequate learning environment. This has been suggested to be consequence of a cognitive impairment in the phonological representation and/or processing (ie, inability to attend to and mentally manipulate speech sounds). Importantly, a recent study (Di Liberto et at., Current Biology, 2015) demonstrated that cortical processing at the level of phonological units can be measured using non-invasive electroencephalography. Here we investigate a possible neural basis for phonological deficit in children with dyslexia by applying this framework based on EEG and natural speech. Participants with dyslexia between 8 and 12 years of age and age-matched control children listened to 9 minutes of an audio-story while non-invasive EEG was simultaneously recorded. Measures of low-frequency cortical entrainment to the acoustic spectrogram and to phonological features of speech were derived and used to quantify neural activity at the level of phonemes. Enhancement of cortical activation is interpreted as a higher quality of speech encoding while temporal and topographical differences would suggest an alteration in the mechanism that underpins the cortical processing of specific features of speech. Here we investigate these effects in children with developmental dyslexia to test the hypothesis of phonological deficit in the processing of speech.

68 A System Identification Approach for Rapid Characterization of the Auditory Evoked Potential (AEP)

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Background

The event-related potential (ERP) has long been the canonical technique for conducting electrophysiological analyses of the human auditory system, and for good reason. As is apparent from the auditory evoked potential (AEP), ERPs can index processing along the auditory hierarchy with excellent temporal resolution. One shortcoming of the traditional ERP approach however is the relatively time-consuming nature of its acquisition, which can limit its clinical utility.

An alternative approach which seeks to circumvent these limitations focuses on deriving what is known as a Temporal Response Function (TRF; Theunissen et al., 2001; Lalor et al., 2009). Typically this is done by regressing neural data against some feature of a continuous stimulus. In the context of EEG/MEG this has been done, for example, by regressing the data on each electrode against the envelope of an amplitude modulated carrier signal (Lalor et al., 2009), or even speech (Lalor & Foxe, 2010; Ding & Simon, 2012). This has been shown to elicit ERP style responses and, due to the continuous nature of the stimuli being presented, has facilitated research which could not easily be conducted using a traditional ERP approach (Power et al., 2012). However, the SNR of these TRFs is typically not as high as those of a traditional ERP. Also, it is unknown whether this approach can facilitate the resolution of ABR components.

Method

Here, we present a novel approach to deriving EEG TRFs using a stimulus that consists of an amplitude modulated broadband noise carrier.

Results

We characterize the components of these TRFs through comparison with AEPs derived using standard approaches.

Conclusion

This novel stimulus paradigm could be useful in many subdomains of both clinical and cognitive auditory neuroscience research.

69 The relation between neural entrainment and speech intelligibility

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Objectives: We investigate the relation between speech intelligibility and neural entrainment using EEG measurements while avoiding confounds such as language knowledge and cognitive capabilities. Speech understanding is currently measured using behavioural responses to natural running speech. These results not only reflect neural coding of the speech signal, but also language processing, memory and attentional effects. Using EEG measurements we want to eliminate those effects.

Methods: 33 normal-hearing adults participated in a first experiment. The subjects listened attentively to the Flemish Matrix speech material combined with speech weighted noise at different signal-to-noise ratios (SNRs from -12.5 dB to -1 dB) while their EEG was recorded. By decoding the speech envelope from the EEG signal and correlating it with the original speech envelope, we estimated the neural entrainment of the stimulus envelope. By choosing the frequency range and investigating the effect of the decoder temporal integration window, we were able to find monotonically increasing speech entrainment as a function of stimulus SNR and we were able to focus on pre-attentive processing. In a second experiment, we compared the results between attentively listening and being distracted by watching a movie.

Results: We show that the correlation between decoded and actual envelope monotonically increases with stimulus SNR, and that with subject-specific decoders individual speech intelligibility is strongly correlated with the electrophysiological measure. When the subjects were distracted, we were still able to find an increasing entrainment with SNR.

Conclusion: Using EEG measurements we were able to estimate the speech understanding of a subject even when the subject was not attentive. This is the first step towards automatically and objectively estimating speech perception measures, such as the speech reception threshold.

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70 Auditory analogues of simple and complex cells: linearity of responses to periodic stimuli

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Recently, S and C neurons were described in macaque auditory cortex based on segregation of “on” and “off” responses in the frequency domain, i.e. in cochlear space (Tian et al 2013). These cell types were proposed to correspond to simple and complex cells of the visual cortex, which are distinguished based on segregation of “on” and “off” responses in retinal space. This suggests a similarity of cortical computational mechanisms across sensory modalities, whereby cortical receptive fields (RFs) are generated from aligned thalamic inputs in their respective sensory epithelium space.

Another way to distinguish simple and complex cells in the visual cortex is by testing the linearity of their responses to sinewave drifting gratings (Skottun et al 1991): the response of simple cells varies linearly with the spatial frequency of the grating (indicated by a high response at the stimulus frequency normalized to DC, F1/F0), while complex cells respond non-linearly (low F1/F0). If auditory cortical neurons show a similar distinction, it would provide further support for the generalized RF model above.

We recorded 189 cells from areas A1 and CM of rhesus auditory cortex. Neurons classified as S based on the difference between “on” and “off” frequency-rate curves, compared to those classified as C, showed smaller distances between “on” vs. “off” best frequency, narrower tuning range and higher frequency selectivity, consistent with Tian et al (2013). In contrast to that study, we found longer response latencies in S cells vs. C cells. However, this was due to a subset of long-latency S cells; in an analysis restricted to latencies <40 ms no difference was found between S and C neurons.

To test linearity of S and C cell responses, we recorded responses of 91 cells to auditory “moving ripple” stimuli, which are equivalent to drifting sinewave gratings. We show that the F1/F0 ratio in auditory S cells is significantly higher than in C cells. This provides new evidence for correspondence between visual simple/complex and auditory S/C neurons. The reported effects were robust against changes in the method of S/C classification, and against restricting the analysis to A1 cells or to cells with confirmed driven responses in both “on” and “off” segments.

Tian et al (2013) proposed that S cells might serve as detectors of boundaries between two successive sounds with different spectra, a mechanism that could be important for speech and music processing. However, we did not detect increased firing rate at such boundaries in S cells (n=24). On the other hand, C cells (n=66) decreased their firing rate at boundaries between two different sounds, compared to boundaries between repeated identical stimuli."

71 Interactions of simultaneous sound representations in the primate inferior colliculus

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When multiple stimuli activate overlapping populations of neurons, it is unclear how the brain preserves information about each stimulus. Two possible mechanisms that might support the accurate perception of multiple stimuli involve sorting neurons into subpopulations either across time or based on their tuning properties. Such mechanisms limit the number of stimuli encoded by any given neuron at any given time, thereby, enhancing the degree to which different stimuli are encoded by different neurons.

We have previously found evidence of the sorting-across-time mechanism in the inferior colliculus (IC) by using multiple simultaneous sounds of similar frequencies, so that each individual sound activated similar populations of neurons (Caruso et. al, 2015, Soc. Neuro Abstr DP07.04/DP04). Here, we tested whether this sorting-across-time mechanism (time-division multiplexing) also occurs for more dissimilar sound frequencies eliciting a lower degree of overlap in neural representations. In this case an alternative coding mechanism could involve the refinement of the tuning of individual cells, leading to separate populations of neurons representing each sound. Thus, we investigated the responses of individual neurons in the IC in the presence of multiple sounds drawn from a larger range of frequencies.

Single neurons were recorded in an awake, behaving rhesus macaque during a dual sound localization task. The monkey was required to make either a single saccade to the location of one sound or a sequence of saccades to the locations of two simultaneously presented sounds. Frequency tuning was measured by presenting a fixed set of eight bandpass filtered noise frequencies alone or in combination with either a lower or higher frequency noise. As in our previous study, spike counts on single sound trials were modeled by Poisson distributions. The spike counts on dual sound trials were tested to see if they were best described by a mixture of the Poisson distributions observed on single sound trials, consistent with a sorting-across-time coding mechanism vs. other possibilities consistent with averaging, winner-take-all, or summation.

We found that sorting-across-time was evident in some neurons even for sounds that were quite different from each other in frequency. Additionally, we found sharpening in neural tuning supporting an increased separation between representations of

simultaneous sounds. Overall, these data suggest the IC could be using multiple mechanisms to increase encoding efficiency.

72 Information processing by synchronized neuronal ensembles in the primary auditory cortex

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The primary auditory cortex (AI) contains interconnected populations of neurons that are responsible for auditory information processing. Most studies of information processing in AI involve either single unit spectrotemporal receptive field (STRF) estimation or paired neuronal correlation analyses, and thus assume that AI neurons filter auditory information either as individual entities or, potentially, as pairs. However, mounting evidence suggests that sensory stimuli are processed by interconnected, co-activated populations of neurons. Therefore, determining how AI encodes information will require an integrated approach that combines receptive field and multi-neuronal ensemble analyses.

To assess multi-neuronal information processing in AI, we performed multi-electrode extracellular recordings in rat AI while presenting dynamic, broadband stimuli, which allowed us to construct STRFs. We then used dimensionality reduction techniques to identify distinct groups of AI neurons (neuronal ensembles, or NEs) that reliably fired synchronously in AI. Via multiple models, we verified that neurons in the same NE had higher rates of coincident firing than would be by chance or by having similar stimulus preferences. For each NE, we then identified synchronous spiking events, and used the events to assess spectrotemporal information processing. For neurons that were members of an NE, the spikes associated with the NE conveyed greater information than the spikes that were not associated with the NE.

These findings challenge the classical idea that AI neurons produce a homogeneous set of spikes that may be equally weighted to estimate a single STRF. Instead, spikes of AI neurons may represent different pieces of information, and equally weighting all neuronal spikes to form a single STRF ignores this. Therefore, by taking into account the stimulus preferences associated with each NE, we may gain a more complete evaluation of information processing in A1.

73 Neural asymmetries demonstrate the influence of spectral cues on sound externalization

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Sound sources in natural environments are usually perceived as externalized auditory objects that are located outside the head. In contrast, when listening via headphones or hearing- assistive devices, sounds are often heard inside the head, presumably because the acoustic filtering of incoming sound becomes inconsistent with normal experience. Although it is well- known that the high-frequency spectral cues mainly induced by the pinnae encode the sound direction, it is less clear how the salience of these cues affects sound externalization. The present study was targeted to evaluate the consequence of changes in spectral cue salience on sound externalization and to identify neural correlates of the perceptual changes by means of electroencephalography (EEG). Normal-hearing listeners were monitored with EEG while judging differences in externalization between two noise bursts filtered with listener-specific head-related transfer functions (HRTFs) that were parametrically modified to vary spectral contrast. Behavioral results showed strong individual differences, but, on average, HRTFs with less spectral contrast evoked less externalization. Event-related potentials (P2) were significantly larger after stimulus changes evoking externalization decreases, as compared to changes evoking externalization increases. The fact that approaching sounds lead to larger neural responses than retreating sounds is consistent with previous reports on the perceptual salience of looming auditory objects, whereby an increase in sound intensity is perceptually more important than a decrease in sound intensity. Here we show a similar asymmetry for spectral cues, demonstrating the perceptual equivalence between intensity-based distance perception and sound externalization based on spectral cues.

74 Reward expectation influences the activity of auditory striatal neurons during decision making

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Animals constantly adapt their behavior based on environmental conditions to optimize reward and avoid punishment. To understand how neural circuits implement flexible sound-driven choices, it is necessary to identify the brain regions involved in these behaviors, and how neural activity is influenced by the outcome of a choice. The rodent caudal striatum receives direct inputs from the auditory cortex and the auditory thalamus, as well as outcome-related signals from midbrain dopaminergic innervation. This region is therefore ideally situated to integrate sensory information with feedback about the outcome of an action (i.e., reward or punishment), and potentially plays a key role in action-selection. In this study, we investigated the effects of the expected magnitude of reward on neuronal activity in the auditory striatum. Water-restricted mice were trained in an auditory categorization task where they learned to associate different sound frequencies with different reward ports to obtain water. We changed the amount of water delivered on each reward port every 150-200 trials. Isolated single units from extracellular recordings displayed frequency-selective sound-evoked responses as well as movement-related activity. A comparison of neuronal activity from trials with different amounts of expected reward revealed that a subset of striatal neurons were modulated based on reward expectancy at different time periods during the task. Our findings pave the way for future investigation of the neural circuits underlying sound-driven choices based on reward.

75 The influence of frequency on perceived temporal rate is larger in demanding listening situations

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Acoustic features co-vary in natural environments (e.g., a sound's pitch changes with changes in the sound's temporal rate). Such structural covariations provide redundancy in fast-changing, acoustically complex soundscapes and might support hearing in difficult listening situations. The current study investigated how changes in frequency induce (illusory) temporal rate change percepts. The illusion is thought to arise from expectations matching the learned structural covariations in natural acoustic environments. However, it is unknown whether reliance on learned structural covariations depends on situational task demands or whether structural covariations are stably utilized. Here we ask whether the magnitude of the perceptual illusion increases in unpredictable listening situations and when perception occurs under distraction.

Participants listened to amplitude-modulated sounds with modulation rates (~5 Hz) either decreasing or increasing over time, and identified the direction of the rate change. Sounds also either decreased or increased in carrier frequency (~1300 Hz) over time, but participants were instructed to ignore such changes. Experiment 1 confirmed that perception of the sound's temporal rate was biased by frequency such that sounds were perceived as speeding up when frequency increased and as slowing down when frequency decreased (temporal rate-change illusion). In experiments 2 & 3, frequency and temporal rate changes were small or large, and participants were cued either to expect an easy or difficult rate change (Exp2) or frequency change (Exp3), or were given an uninformative neutral cue. The magnitude of the illusion increased when participants were uninformed (neutral) about the difficulty of the upcoming sound. In experiments 4-6, participants listened to the amplitude-modulated sounds and performed a congruent distractor task at different difficulty levels. Memory load in the distractor task (Exp4 and Exp5) only weakly affected the illusion magnitude, whereas the illusion magnitude increased with increasing number of objects to be tracked in a multiple object tracking task (Exp6).

In sum, when the difficulty of a sound's temporal rate change is unpredictable or sound perception is demanding because of a congruent distractor task, the influences of frequency changes on a sound's perceived temporal rate change are increased, leading to a magnified illusion. The results suggest that in difficult listening situations, listeners might rely more strongly on learned structural covariations for sound perception than in less demanding situations.

76 Two types of cortical interneurons differentially modulate behavioral frequency discrimination acuity

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The ability to discriminate between tones of different frequencies is fundamentally important for everyday hearing. Primary auditory cortex (A1) regulates behaviors that rely on frequency discrimination (Aizenberg and Geffen, 2013), but the underlying neural mechanisms are poorly understood. Frequency tuning of cortical excitatory neurons are thought to be shaped by the interplay of excitatory and inhibitory inputs. In the cortex, the two most common classes of inhibitory interneurons are parvalbumin-positive (PV) interneurons and somatostatin-positive (SOM) interneurons. PVs target the soma and initial axon segment, while SOMs target distal dendrites. Therefore, these two interneuron classes may differentially affect responses of excitatory neurons. We recently found that photo-activation of PVs enhanced tone-evoked responses of excitatory neurons, which was correlated with an improvement in behaviorally measured frequency discrimination acuity (Aizenberg et al., PLoS Biology, 2015). We now find that photo-activation of SOMs diminished tone-evoked responses in the excitatory neurons, by suppressing tone-evoked responses more strongly than spontaneous activity. Interestingly, photo-activation of SOMs also increased the frequency selectivity of excitatory neurons, but had mixed effects on behaviorally measured frequency discrimination acuity. These findings are consistent with the interpretation that PVs and SOMs carry out differential roles in shaping frequency selectivity in the auditory cortex.

77 Learning Mid-Level Codes for Natural Sounds

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Auditory perception depends critically on abstract and behaviorally meaningful representations of natural auditory scenes. These representations are implemented by cascades of neuronal processing stages, where neurons at each stage recode outputs of preceding units. Explanations of auditory coding strategies must thus involve understanding how low-level acoustic patterns are combined into more complex structures. While models exist in the visual domain to explain how phase invariance is achieved in V1 by complex cells, and how curvature representations emerge in V2, little is known about analogous grouping principles which could govern mid-level auditory representations.

To generate intuitions and predictions about mid-level codes in the auditory system we developed a hierarchical probabilistic model that learns combinations of spectrotemporal features from natural stimulus statistics. The first layer of the model forms a sparse, convolutional code of spectrograms. Features learned on speech and environmental sounds resemble spectrotemporal receptive fields (STRFs) of mid-brain and cortical neurons, consistent with previous findings. The second layer of the model encodes combinations of STRF activations. To generalize across specific STRF activation patterns, the second layer encodes time-varying magnitudes of the first layer coefficients. High-level units pool first layer features, thus becoming selective to STRF combinations. The resulting representation is partially invariant to specific instances of spectrogram patterns, and it constitutes a more abstract representation of sound.

To test the validity of the model, we compared its properties to experimental measurements of auditory neurons. When interrogated with simulated neurophysiology experiments, the model exhibited trends similar to those reported in the auditory thalamo-cortical hierarchy, including a decrease in preferred spectral and temporal modulation rates between the first and second layers of the model. The model also gives rise to new predictions about cortical representations of sound. We found that second-layer units often encode two ""opposing dimensions"", i.e. groups of STRFs which do not become activated together at the same time. For instance, some of them are "excited" by presence of temporally modulated STRFs (such as clicks) and "inhibited" by presence of temporally stable features (such as harmonics).

Taken together, our results suggest that mid-level auditory codes may be derived from high-order stimulus dependencies present in the natural acoustic environment."

78 Extraction of task-relevant events from acoustic stream in ferret frontal cortex

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The frontal cortex is often associated with enhancement of relevant information for goal-directed behavior. Neuronal responses in the frontal cortex (FC) of the behaving ferret have been shown to be behaviorally gated and highly selective for target stimuli during auditory and visual discrimination tasks (Fritz et al., 2010). This suggests a selection of sensory information in tasks in which ferrets rapidly categorize reference and target tokens. However, in natural and cluttered environments, sounds are not necessarily presented in token-based sequences. Instead relevant events are embedded in continuous sound streams and their detection demands to dynamically update the representation of the incoming stimulus. Here, we attempt at characterizing the extraction of relevant sensory information in complex continuous stimuli performed by sensory cortices and frontal areas. To address this question, we trained ferrets on a change detection paradigm where animals have to constantly monitor a stochastic and continuous acoustic stream to detect subtle statistical changes. We then gathered electrophysiological data in the primary auditory (A1) cortex and the FC (dlFC/Premotor) of the behaving ferret. A1 neurons exhibited strong onset responses and reduced change-related discharges, whereas dlFC neurons presented an enhanced response to change-related events during behavior, possibly being the signature of accumulation of sensory evidence. These area-specific responses to sound are consistent with EEG recordings done in humans performing a similar task. All together this suggest a behavior-dependent sensory 'gating' mechanism leading to decision making.

79 A coactivation model to explain detection of audiovisual vocalizations at different intensities and delays

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Combining sensory cues improves the perception, detection, and discrimination of sensory stimuli (Chandrasekaran et al., 2011), and allows for more efficient interaction with the world. Sensory cues vary widely in intensity and are often delayed with respect to one another (Cluff et al., 2015). How behavioral benefits of multisensory integration depend on these stimulus properties is unclear.

We trained monkeys to detect audiovisual vocalizations presented across a large range of intensities and delays in between the visual and the auditory signals and embedded in noise. Monkeys benefited from combining these visual and auditory cues, responding faster and more accurately for audiovisual compared to auditory- and visual-only vocalizations. The dependence of behavioral benefits on stimulus properties was complex, inconsistent with the predictions of a race model (Miller, 1982), and not easily explained by seminal principles of inverse effectiveness and the temporal window of integration (Stein and Meredith, 1993).

Instead, we show that extending a classical coactivation model that assumes additive superposition of visual and auditory evidence and integration of this combined signal to a bound (Schwarz, 1994; Diederich, 1995) provides a better description of the behavioral patterns. Specifically, we show that by restricting the classical coactivation model to accumulate within some limited time interval (a deadline) provides an excellent prediction of the response times and accuracy of the monkeys in this task. Moreover, simulations of the model with various stimulus intensities and delays could explain discrepancies between our measured behavior and the seminal principles of multisensory integration. Together, the model fits, simulations, and prior success of similar models in multisensory discrimination tasks, suggest that superposition and integration to a bound provides a candidate mechanistic framework for understanding how behavioral benefits from multisensory integration emerge.

80 Dynamic faces suppress and reset local field potential responses in the macaque auditory cortex

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Humans and monkeys integrate the visual cues from the motion of the mouth and other parts of the face with the auditory components of speech and vocalizations to improve their behavioral accuracy and speed up their reaction time (RT) (Chandrasekaran et al., 2011). These behavioral benefits in RT are paralleled by reductions in spiking response latencies in monkey auditory cortex for audiovisual compared to auditory-only vocalizations (Chandrasekaran et al., PNAS, 2013), and EEG response latencies in humans (van Wassenhove et al., 2005). How these behavioral and neural benefits come about from integrating visual and auditory cues is currently unclear.

One theoretical framework, predictive coding, proposes that these benefits arise because visual cues generate predictions about the forthcoming auditory components of vocalizations and thus improves the efficiency of neural processing resulting in faster behavioral RTs and reductions in response latency (Arnal and Giraud, 2012). Currently, we lack intracortical evidence for the hypothesis that predictive coding explains the responses in auditory cortex during the processing of audiovisual communication signals. The mechanism by which predictions are set up is unclear as well.

Using a naturalistic audiovisual vocal detection task in macaque monkeys and electrophysiological recordings in auditory cortex, we investigated if the spectral structure of local field potential (LFP) activity triggered by auditory and audiovisual vocalizations were consistent with the postulates of predictive coding. We found that phase organization in the 15-60 Hz band of the LFP was suppressed for the audiovisual versus auditory-only stimuli. That is when visual cues set up a prediction about an impending auditory vocalization, the responses in auditory cortex are suppressed—a result consistent with other experimental studies of predictive coding in auditory cortex (Todorovic et al., 2011). Facial motion also resets ongoing auditory LFP in low frequencies suggesting that it may be a candidate mechanism for setting up predictions (Schroeder et al., 2008). Together, our results support a predictive coding framework that involves a phase resetting mechanism to generate the behavioral benefits of audiovisual vocal perception.

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81 Neural representation and hierarchical processing of phonemes in temporal cortex revealed by intracranial EEG

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A finite set of phonetic units is used in human speech. How our brain recognizes these units from speech stream, as we do in visual object recognition, is still largely unknown. The revealing of this neural mechanism may lead to the development of speech brain computer interfaces and intelligent speech recognition systems. In this study, epilepsy patients undergoing intracranial EEG (iEEG) monitoring were instructed to listen to short stories containing 3974 Chinese phonemes. 2939 recording electrodes from 28 patients were used to decode phonetic units during the perception of continuous speech. We identified neural populations over Heschl gyrus (HG), superior temporal gyrus (STG) and superior temporal gyrus (STS) that showed selective response to specific Chinese vowel complex or its constituent parts. The high-gamma activity of all these electrodes was further combined to separate sets of phonemes into clusters. The clustered organization largely coincided with phonetic categories defined by place of articulation, similar as that has been found in English (Mesgarani et al, 2014). The neural clustering organization over STG and HG are more similar with the clustering in acoustic feature space, especially along the lower dimensions of the principle component space of formant pattern (mainly correspond to place of articulation and manner of articulation). Meanwhile, in the neural space of posterior STS electrodes, phonemes tend to be separated along the higher dimensions of principle components related to short-time features in formant pattern decomposition. STS areas also showed stronger speaker invariance in their selective response. These findings suggest that the distinct formant patterns of phonemes (analog to the contour of visual objects) were hierarchically processed along the auditory pathway, giving rise to the phoneme identity represented at STS and further stations.

82 Implicit discrimination of embedded auditory regularities in mesio-temporal regions

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Extracting regularities from our environment is posited to depend on a hierarchy of prediction errors such that violation detection of single events relies on pre-attentive mechanisms, while for more complex ones conscious access to the incoming stimuli is required. Recent work has challenged this view by providing evidence of neural detection of rule violation over groups of sounds (global violation) in unconscious patients. However, the neural correlates of implicit global violation detection remain under-explored as previous studies have focused on active tasks or cortical circuits. Here, we hypothesised that detection of global auditory regularities can occur without explicit awareness and investigated its neural correlates.

We recorded local field potentials (LFPs) in 8 epileptic patients undergoing pre-surgical monitoring, 7 of which had implanted electrodes in mesio-temporal regions and 1 cortical grids. Patients were watching a silent movie and were presented with an auditory local-global paradigm, including embedded regularities of single sounds and groups of five sounds (1000Hz tones, 100/150ms). LFPs were analysed by contrasting global standard vs. deviant sequences, using non-parametric tests and corrected for multiple comparisons with cluster-based permutations ($p<0.05$).

We found evidence of differential responses to global standard/deviant sounds in several mesio-temporal and cortical contacts for all patients: in 5 of them, these were observed in subcortical regions, during an early window, starting already at ~30ms post-deviance onset. Four patients showed effects at late intervals, after 200ms post-deviance onset. No patient reported knowledge of the sequence structure at the end of the experiment.

Our results suggest that global violation detection can occur pre-attentively, and is mediated by mesio-temporal structures.

83 Stimulus-Specific Adaptation in Distinct Inhibitory Populations in Auditory Cortex

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Neurons in primary auditory cortex exhibit stimulus-specific adaptation (SSA), the decrease in responses to a common (standard) stimulus that does not generalize fully to another, rare stimulus (deviant). Here we use in vivo two-photon targeted loose-patch recordings in mice to investigate how inhibitory populations shape SSA. We recorded in primary auditory cortex from identified neurons of the three main inhibitory populations, parvalbumin- (PV), somatostatin- (SST) and vasointestinal polypeptide-(VIP) positive neurons. PV neurons, which form the major inhibitory population in the cortex, exhibited early-onset SSA with responses that terminated about 30 ms after stimulus onset. Responses of VIP neurons lasted up to 150 ms following stimulus onset, i.e. substantially beyond stimulus offset, maintaining SSA for nearly the whole time. SST neurons were less responsive to sound stimuli. Those that did respond to pure tones showed SSA, but with somewhat weak deviant responses. Our findings of SSA in all inhibitory populations suggest that the temporal dynamics of inhibitory responses are important in shaping the dependence of cortical responses on stimulus history. In particular, different populations of interneurons can control deviance sensitivity during different temporal windows following stimulus onset. In addition, as inhibitory neurons are a main locus of top-down and neuromodulatory regulation, modulation of their deviant responses can be a means for controlling the level of deviance detection according to the behavioral state.

84 Bridging the gap: stimulus-reinforcement plasticity emerges in the basal forebrain and drives Hebbian plasticity in the auditory cortex

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The mammalian cortex updates its representation of sensory stimuli to reflect past experience and behavioral utility. For instance, learning that a specific stimulus predicts food or punishment magnifies the cortical representation of the conditioned stimulus (CS), providing higher perceptual sensitivity for future encounters. Cholinergic (ACh) inputs from the basal forebrain are believed to perform a key role in this learning-induced receptive field plasticity. The prevailing model holds that basal forebrain neurons respond to the unconditioned reinforcement stimulus (US) such as reward or punishment by flooding the cortex with acetylcholine, which temporarily disables the inhibitory ‘brakes’ that limit adult receptive field plasticity. Thus, the bottom-up CS sensory trace ‘mixes’ with the cholinergic US reinforcement trace in primary sensory cortex and the reduced inhibitory tone permits stimulus-specific remodeling of the CS.

However, in the real world, predictive stimuli often occur and disappear seconds before reinforcement, imposing a temporal gap between the CS and US. Any stimulus-specific cortical plasticity observed when animals are conditioned using long delays between the CS and US would be difficult to reconcile with the current conceptual model. We tested whether learning and cortical plasticity could “bridge the gap” by training mice on a trace fear conditioning task where the CS (narrow band noise) preceded the US (foot shock or air puff) by 5 seconds. We found that mice could easily learn the CS-US association. Recordings from primary auditory cortex (A1) revealed a clear over-representation of the CS frequency, much like traditional conditioning paradigms where the CS and US overlap.

How and where did the system find a way to bridge the 5s gap between the CS and US to enable stimulus-specific A1 plasticity? We identified a potential mechanism by performing simultaneous multi-channel extracellular recordings from A1 and basal forebrain in awake, head-fixed ChAT-Cre:Ai32 transgenic mice during CS-US conditioning. We used an optogenetic approach to antidromically activate ACh+ neurons in the basal forebrain that project to A1. Antidromically phototagged ACh-A1 projection neurons in nucleus basalis not only respond to the US, as previous studies suggested, but also had robust, short-latency (~10 ms) responses to auditory stimuli. This implied that bridging the CS-US gap in A1 was trivial because nucleus basalis neurons could encode both punishment and sound. Thus the crucial ‘handshake’ between the CS and US trace need not bridge a 5s gap, but rather could occur during the CS response period itself. Accordingly, we found that A1-projecting ACh neurons rapidly enhanced their responses to the CS frequency during conditioning. Interestingly, we noticed that non-ACh neurons in nucleus basalis, many of them putatively GABAergic, also responded to auditory cues but showed reduced responses to the CS frequency during conditioning. These findings challenge the prevailing model by suggesting that learning-induced plasticity in A1 does not result from the convergence of the sensory and reinforcement neural signals in A1, but rather a stimulus-specific plasticity in A1-projecting nucleus basalis neurons that multiplex acoustic and nociceptive signals.

85 Electrophysiological correlates of speaker separation and foreground-background selection in ambiguous listening situations

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In everyday listening environments (e.g., in a busy cafeteria), a main task for our auditory system is to follow one out of multiple speakers talking simultaneously. The present study was designed to find electrophysiological indicators of two central processes involved - separating the speech mixture into distinct speech sequences corresponding to the two speakers (sound source segregation), and then attending to one of the speech sequences (sound source selection). We generated multistable speech stimuli that were set up to create ambiguity as to whether only one or two speakers are talking. Thereby we were able to measure neural correlates of the foreground versus background versus inseparable representation of speech material without any confounding stimulus changes. Participants listened to a continuously repeating sequence of six consonant-vowel syllables (ti-te-ko-ti-te-to-…), which were uttered alternately by two human speakers, and indicated via button presses whether they perceived the sequence as an inseparable mixture (‘integrated percept’) or as originating from two separate speakers. In the latter case, they distinguished which speaker was in their attentional foreground (‘segregated-speakerA percept’ or ‘segregated-speakerB percept’). Our data show a long-lasting event-related potential (ERP) modulation starting at 130 ms after stimulus onset, which can be explained by the perceptual organization of the two speech sequences into attended foreground and ignored background streams. Our paradigm extends previous work with pure tone sequences towards more ecologically valid speech stimuli and adds the possibility to obtain neural correlates of the difficulty to separate a speech mixture into distinct streams.

86 Discrimination of Frequency Modulation in Artificial Vocalizations in CBA/CaJ Mice

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Mice often produce ultrasonic vocalizations (USVs) that sweep upwards in frequency from around 60 kHz to around 80 kHz, and similarly sweep downwards in frequency from 80 kHz to 60 kHz. Whether or not these USVs are used for communication purposes, or whether vocalizations with different spectrotemporal shapes have different meanings is still unknown. Determining the discrimination abilities for synthetic upsweep and downsweep frequency-modulated stimuli will expand the current knowledge about acoustic communication. Mice were trained and tested using operant conditioning procedures and positive reinforcement to discriminate between upsweeps and downsweeps. The stimuli varied in bandwidth, duration, and direction of the sweep. The animals responded when they heard a change in the repeating background, indicating that they could discriminate background from target. The mice performed significantly worse discriminating between background and targets when the stimuli occupied the same bandwidths. Further, the mice's discrimination performance became much worse when the duration approached that of their natural vocalizations. When the sweeps occupied different frequency ranges and longer durations, discrimination performance improved. These results collected using artificial stimuli created to mimic natural USVs indicate that the bandwidth of vocalizations may be much more important for communication than the frequency contours of the vocalizations. Supported by NIH DC012302.

87 The role of auditory thalamo-striatal and cortico-striatal neurons in amplitude modulation frequency discrimination

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Multiple parallel neural pathways link information about sounds with behavioral responses. The striatum, a brain structure involved in movement and reward-related learning, receives neuronal projections from both the auditory thalamus and the auditory cortex. It is unclear whether sound information that reaches the striatum through these two parallel pathways is redundant or complementary. To test whether both pathways are required for auditory discrimination of amplitude modulated sounds, we first performed transient pharmacological inactivations of auditory cortex in mice trained to perform a two-alternative choice auditory task. We then used optogenetic techniques to tag neurons in the thalamo-striatal and cortico-striatal pathways, allowing us to identify them during extracellular recording. We characterized the responses of identified neurons in each pathway to pure tones and to amplitude-modulated noise stimuli. Consistent with previous studies, we found that inactivation of auditory cortex largely impaired the ability to discriminate between different amplitude modulation frequencies. We also found that neurons in the thalamo-striatal and cortico-striatal pathways have largely overlapping tuning for sound frequency, but display different coding strategies for amplitude modulated sounds. These results suggest that the thalamo-striatal pathway carries sufficient information to support discriminations of sound frequency, but that fundamental differences exist between the cortico-striatal and thalamo-striatal pathways with respect to their contribution to discrimination of temporal modulations in amplitude.

88 Coordination of vocal interactions by marmoset monkeys in naturalistic social environments

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Vocal communication is important in day to day life, and plays a key role in maintaining group cohesion and social bonds. Successful vocal communication, however, requires coordination of vocal interactions with group members according to the social context. Marmosets (Callithrix jacchus) exhibit many human-like social vocal behaviors including a rich vocal repertoire. Previous experiments in isolated laboratory conditions have revealed rule-based antiphonal vocal interactions between marmosets. However, marmosets' interactive vocal communication in complex social environments remains largely unstudied. In this study, we asked what social rules marmosets use for vocal communication in complex, naturalistic social contexts. We recorded vocalizations from an entire group of marmosets housed in a colony environment and tracked their vocal interactions in order to determine which animals or groups responded to other's vocalizations and in what order. The pattern and frequency of vocal interactions was measured using Markov chain analysis, focusing particularly on the marmoset twitter call which is presumed to have a role in social communication. We found that twitter call production is non-random, but rather produced as part of interactive vocal exchanges. Surprisingly, we also found that co-housed family groups participate in twitter exchanges no more often than individual animals, suggesting the role of twitter calls as an inter-group communicative signal. We also found that individual animals exhibited biases to which animals they responded to. These results are the first quantitative measurements of marmoset vocal interaction in the social environment of a marmoset colony and demonstrate complex social communication. These findings will have important implications for future studies of vocal communication, and can potentially be paired with physiologic studies to determine the neural basis of interactive social behaviors.

89 Neural decoding of attentional selection in multi-speaker environments without access to separated sources

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In a natural auditory environment, most people can easily attend to a particular speaker out of many. However, this task remains challenging for those suffering from peripheral and central auditory pathway disorders. Recently, it has been shown to be possible to decode which speaker a person is attending to, by monitoring their neural activity via both invasive and non-invasive electrophysiological recordings. This has led to an upsurge in attention-aware brain-computer interfaces (BCIs) that can control smart hearable devices capable of selectively amplifying one speaker and suppressing all others in crowded environments.

Current attention decoding algorithms require explicit access to the isolated sound sources in the environment, which is not realistic. Techniques such as beamforming have been used in an attempt to isolate each speaker. However, not only do these techniques fail when there is an inadequate spatial separation between speakers, their reliance on multiple microphones has drawbacks with regards to hardware complexity and user comfort. Here, we address these challenges by using state-of-the-art single microphone automatic speech separation algorithms in which deep neural network (DNN) models are used to separate the sound sources. The output of the speech separation algorithm can then be used to decode the attentional state of the listener, and subsequently, to amplify the attended source.

Using invasive electrocorticography (ECoG) data, we successfully decoded the attention of a user in seconds. Subjects were presented with two stories: one read by a male, and the other by a female. There was no spatial separation between the two. Subjects were instructed to attend to one speaker, and to periodically switch their attention between the two.

We used a method known as stimulus-reconstruction to estimate the stimulus spectrogram that the patient was attending to. By assessing the similarity of this reconstruction and the separated sound sources provided by the DNNs, we obtained decoding-accuracies in excess of 90% when using 4 seconds of test data. Switches in attention could be determined between 5 and 15 seconds after the transition point.

The decoder output can then be used to amplify the attended source relative to the background to assist the listener. We show that the separation algorithm used produces a speech signal that is objectively cleaner (8.97 dB increase in Signal-to-Distortion-Ratio (SDR), 40% relative increase in Perceptual Evaluation of Speech Quality (PESQ) score). Such an improvement has shown to significantly improve the subjective experience for the hearing impaired.

90 Mind the Gaps: Neural Coding of Species Identity in Birdsong Prosody

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In the animal kingdom, vocal communication is used to establish social identity and to exchange information. In bird song, these functions are transmitted in prosodic melodies composed of syllables punctuated by silent gaps of variable length. Species-specific vocalizations of songbird are thought to be learned primarily through auditory exposure of juveniles to adult tutors. However, this hypothesis remains untested because the developmental mechanisms governing neuronal coding of own species' song remain unclear. We recorded neuronal responses from the primary auditory forebrain in zebra finches and identified two types of neurons. One encodes durations of silent pauses between syllables, called temporal gaps, that are unique to each species, whereas the other was responsive to song morphology, acoustic features of syntactic elements. Remarkably, gap-encoding and morphology-sensitive neurons showed functional dissociation, and the former were even responsive to temporal gap structures in white noise. Moreover, both behavioral learning of song gap durations and their neuronal encoding properties in juvenile birds were resistant to abnormal auditory experiences with other tutor species or no tutor experiences during development. Interestingly, young zebra finches cross-fostered by Bengalese finch parents, learned Bengalese finch song morphology transposed onto zebra finch temporal gaps. Collectively, these results demonstrate innate neuronal encoding of prosody in birdsong and reveal distinct acoustic processing channels for phonology and morphology in vocal communication learning. Innate encoding of silent gaps in birdsong suggests a species-specific neuronal bar code for song learning that may contribute to formation and maintenance of conspecific social networks in highly speciose acoustic environments.

91 Primate frontal cortex neurons predict the outcome of natural conversations

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Communication is an inherently interactive process that weaves the fabric of society together for both human and nonhuman primates alike. Yet much of what is known about the neural basis of communication in our simian cousins has been limited to studies of static signals. To investigate the properties of the primate brain during active social signaling, we recorded the activity of frontal cortex neurons as freely-moving marmosets engaged in natural conversations. The responses of all neurons (n=258) to vocalization stimuli were compared in two behavioral contexts during conversations with a Virtual Marmoset (VM): when subjects produced a response following hearing a vocalization stimulus (Antiphonal) and when no response occurred (Independent). Across three subjects, PCA indicated that the greatest source of variance in firing rate was explained by these two behavioral contexts. Furthermore, we observed that frontal cortex activity could reliably predict whether a conspecific's vocalization would elicit a vocal response with 92% accuracy. In fact, correct classification was not stimulus-driven, as neural activity preceding the stimulus could still reliably predict the behavioral outcome. This finding was surprising for at least the following two reasons. First, this population of neurons did not exhibit robust changes in firing rate to vocalization stimuli. Second, the PCA analysis included all neurons, not just those that were modulated by the conversational behavior. These data suggest that the state of the brain prior to hearing a conspecific vocalization determines whether marmosets will produce a response and engage in a conversation. The close coupling between brain state and behavioral context is further evidenced by analyses of extended conversations, as brain and behavior exhibit a near perfect correlation. These data suggest that active social signaling may have a profound effect on the neuronal processes and lend unique insight into facets of the primate social brain.

92 Coding Loudness by Pulse Amplitude or Pulse Duration in cochlear implant: Does It Matter for Cortical Neurons?

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Improving the coding strategies in cochlear implants (CI) is still the subject of intense investigations: the stimulation mode, the pulse shape and grounding schemes can lead moderate to important effects on the spread of excitation, electrode discriminability and nerve excitability. For example, several strategies are currently used to code loudness such as increasing the pulse amplitude, the pulse duration or the pulse rate. This study aims at comparing the responses obtained from the eighth nerve and the auditory cortex to stimulations delivered through a cochlear implant and for which increases in sound loudness were coded either by pulse amplitude or by pulse duration.

Experiments were performed in urethane anesthetized guinea pigs (6-18months old). A map of the primary auditory cortex (AI) was first established by inserting an array of 16 electrodes (2 rows of 8 electrodes separated by 1mm and 350µm within a row) and quantifying the tonotopic gradient in AI based on multiunit recordings. A dedicated electrode-arrays (400µm) was then inserted in the cochlea (4 electrodes inserted in the 1st basal turn) and its connector was secured on the skull. The electrode array was placed back in the auditory cortex at the exact same location. A dedicated stimulation platform developed by Neurelec/Oticon was used to generate electrical current delivered by the implanted electrode. The eight nerve fibers were then stimulated with 20 levels of pulse amplitudes or 20 levels of pulse duration generating similar charges.

The patterns of activated cortical sites corresponded to the CI stimulating electrode. Furthermore, little differences in the cortical responses were found when the pulse duration was used rather than the pulse amplitude. The cortical responses evoked by electrical stimulations were often of shorter duration than the acoustic responses; the firing rate evoked by both the pulse duration and pulse amplitude strategies was usually higher than the one evoked by pure tones. These data suggest that, at the level of the primary auditory cortex, equivalent cortical activation can be achieved by coding sound loudness with pulse amplitude or with pulse duration.

93 Does Long Lasting Exposure to Non-Traumatic Industrial Noise Affect Differentially the Auditory Cortex in Adult vs. Immature Rats?

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Over the last decade, an increasing number of studies have reported that noise exposure at non-traumatic sound levels (<85dB) can lead to important alterations in the responses of auditory cortex neurons. For example, studies have described reduced neuronal responses in the noise frequency band, alterations of tonotopic maps and even behavioral deficits (Norena et al 2006; Zhou & Merzenich 2012, Zheng 2012). Here, we evaluated the consequences of long-lasting exposures (3 months, starting at 2 months old) to an industrial ("realistic") non-traumatic noise (80dB SPL, 8h/day) on the rat auditory system. We compared these data with those obtained from rats exposed for 3 months at the age of P5. Based upon Auditory Brainstem Responses, thresholds were higher for the young exposed animals compared with the young non-exposed ones, an effect that was no longer present 1 month later. This suggested that a potential TTS occurred after 3 months of exposure in young rats exposed at the age of P5. This potential TTS effect was not observed in adult rats. Analyzing the cortical evoked responses revealed several differences between the P5 exposed rats and the control rats, but only when the exposed P5 rats were tested in less than 24h after exposure. These differences were: First, the tuning was broader as quantified by the Q10dB, Q20dB and by the bandwidth at 75dB. Second, within the receptive field, the firing rate of auditory cortex neurons was higher in the exposed animals than in the control animals. Third, the percentage of neurons responding to a short gap of silence in a vocalization was much higher in exposed P5 rats than in control rats. In contrast, in the auditory cortex of adult animals (exposed at 2month old), there was no effect of the 3-months exposure whatever the stimulus (artificial or natural stimuli) and the parameter used to quantify the neuronal responses. Altogether, these results suggest that exposure to non-traumatic industrial noise has a larger impact when occurring at hearing onset than when occurring in adult animals. However, these effects do not seem to persist over time, they dissipated within a month.

94 Characterizing Auditory Cortical Responses to Multidimensional Stimuli.

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Auditory objects typically contain multiple dimensions of interest, e.g., frequency, intensity, bandwidth, amplitude modulation and location. Given its importance in encoding auditory objects, and its position in the sensory hierarchy, auditory cortex may play an important role in integrating information across these dimensions. Thus, probing cortical responses with multidimensional stimuli may reveal novel aspects of cortical coding. Evolutionary algorithms (EAs) provide a powerful tool for investigating cortical responses to multidimensional stimuli. EA's have been successfully applied to find highly effective multi-dimensional stimuli for cortical neurons. However, visualizing and quantifying the resulting multidimensional data remains a computational challenge. Here we develop computational methods to address this problem, and apply them to neural responses to five dimensional stimuli in mouse A1. First, we apply a Self Organizing Map (SOM) to visualize the regions of multidimensional space sampled by the EA. We then apply a Generalized Additive Model (GAM), a non-linear extension of the linear model, to make quantitative predictions of cortical responses to multidimensional stimuli. We find that the GAM provides a good model for predicting cortical responses to multidimensional stimuli in the neighborhood of regions that are well sampled by the EA. Taken together, the EA, SOM and GAM provide a powerful computational toolbox for characterizing auditory cortical responses to multidimensional stimuli.

95 Responses to sinusoidal frequency modulation in the guinea pig ventral cochlear nucleus

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Background

Many psychophysical studies have investigated the detection of sinusoidal frequency-modulation (SFM) and on the type of sensory information it predominantly relies on: temporal-envelope (ENV) resulting from cochlear filtering, or temporal fine-structure (TFS) cues conveyed by changes in the neural phase-locking pattern over time, or a combination of both. Few neurophysiological studies have addressed this issue and data is still lacking regarding the coding of SFM in the early stages of auditory processing (below inferior colliculus). This work aimed at characterizing the responses of ventral cochlear nucleus (VCN) neurons to SFM tones presented at various modulation depths and sound levels.

Methods

Single-units in normal-hearing anaesthetized pigmented guinea pigs were recorded extracellularly using tungsten-in-glass microelectrodes. Stimuli were 1-second SFM tones played at the unit’s best frequency (BF), at modulation rates of 2, 5 and 10 Hz and modulation depths of 2, 4, 8, 16, and 32 % relative to BF. All stimuli were presented at positive and negative polarities and at several sound levels.

Results

VCN responses to SFM varied as a function of sound level, bandwidth and unit type. Shuffled correlogram analyses were carried out in order to assess the relative strengths of ENV and TFS coding for the different unit types in the VCN. For small modulation rates (≤5Hz) and small modulation depths (≤16%), low-CF units showed weak temporal ENV coding but high phase-locking to TFS. In comparison, high-CF units generally followed the stimulus ENV for most conditions. The transition region over which temporal coding changes from being dominated by TFS coding to ENV coding was around 1-2 kHz.

Conclusion

The results provide physiological evidence that SFM is encoded via neural phase-locking to TFS cues for low carrier frequencies and modulation rates, and via neural phase-locking to ENV cues at high carrier frequencies. The results also suggest weaker phase-locking to TFS in guinea pigs compared to other species. Further work will be carried out in order to assess the strengths of these two coding mechanisms in the presence of a hearing deficit.

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96 Different spatio-temporal EEG features drive the successful decoding of binaural and monaural cues for sound localization

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It is well established that sound source location in the horizontal plane is dominantly inferred from binaural acoustic cues while monaural (spectral) cues are used for vertical plane localization and in situations where binaural cues are ambiguous. However, how these cues are processed in human auditory cortex is poorly understood. In particular, it is still a point of contention whether binaural and monaural cues are processed by the same or distinct cortical networks.

In this study, we aimed to investigate the neural underpinnings of spatial cue processing using realistic free-field sound stimulation together with advanced multivariate EEG analysis. We show for the first time that it is possible to decode horizontal and vertical sound source location from the recorded EEG signal. Notably, the spatio-temporal pattern of EEG features that facilitated decoding differed based on the availability of binaural and monaural cues. In particular, we identified neural processing of binaural cues at around 120 ms post-stimulus and found that monaural cues are processed later at between 150 and 200 ms. Furthermore, different spatial activation patterns emerged for binaural and monaural cue processing. These spatio-temporal dissimilarities suggest the involvement of separate cortical mechanisms in monaural and binaural acoustic cue processing.

The finding that we can decode sound source location using EEG has potential applications in the development of brain-computer interfaces, future hearing aids, and in measuring the fidelity of virtual acoustic environments.

97 Decoding cocktail party attention using EEG signatures of hierarchical speech processing

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The cocktail party problem refers to the ability of humans to selectively focus on a single speaker in noisy environments. Exactly how the auditory system performs this feat remains incompletely understood. Progress has been made with the realisation that cortical activity entrains to the amplitude envelope of speech. By employing a stimulus-reconstruction approach where neural activity is mapped back to the envelope, it has been shown that attentional selection can be decoded to a high degree of accuracy, even from single-trial electroencephalography (EEG) data.

The reliance on the amplitude envelope as the representation of speech is nonetheless almost certainly suboptimal. Speech is processed by a hierarchical cortical network with multiple stages performing specialized, but interrelated roles. Thus, a mapping of EEG to the speech envelope may be to conflate the multi-stage processing of many speech features into a single aggregate measure. Indeed, recent research has shown that EEG responses to natural speech are best predicted when that speech is represented in terms of both its low-level spectrotemporal acoustics and a higher-level categorical labelling of phonetic features, rather than simply as its envelope (Di Liberto et al., 2015).

Here, we sought to explore the efficacy of decoding attentional selection when relating cortical activity to different low- and high-level representations of natural speech. EEG data were collected as subjects engaged in a listening task where they were cued to attend to a story in one ear whilst ignoring a different story in the other ear. We perform stimulus-reconstruction with speech represented in the form of a so-called AI-gram, which reflects the spectrotemporal features of speech necessary for articulation and intelligibility, as well as in terms of pitch measures and sentences. Finally, we leverage the complementary information provided by these various representations to further improve decoding of attentional selection.

98 The impact of visual gaze direction on human auditory scene analysis

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In everyday life, we constantly change the direction of our visual gaze, depending on our current tasks and goals. Animal research has suggested that neural responses in auditory cortex are increased to sounds coming from the direction of gaze, as compared to another direction. How this direction of gaze influences auditory processing in humans is not well understood. Here, we recorded Electroencephalography (EEG), eyetracking and behavioural data to investigate how gaze direction impacts the processing of either attended or unattended sounds from different locations. We presented rapid (~4 Hz; random inter-tone-interval) streams of pure tones from three speakers (left, central, right). Participants (N=19) gazed at one of the speakers, and responded to occasional targets from either the same or a different speaker. We found significantly faster response times when gaze and attention were directed towards the same location, as compared to when they were directed to different locations. In addition, both spatial attention and gaze modulated EEG activity in the alpha-band (8-12 Hz). In conditions where gaze and attention were not spatially aligned, alpha-band activity was significantly increased contralateral to the direction of gaze, indexing a suppression of distracting sensory input. Interestingly, auditory spatial attention but not gaze direction modified event-related potentials to individual sounds. In summary, our data suggest that gazing towards the source of a sound facilitates processing of that sound. When spatial attention and gaze are not spatially aligned, alpha-band activity acts to suppress task irrelevant input, resulting in similar event-related neural responses to gazed-at and non gazed-at sounds.

99 Electrocorticographic delineation of human auditory cortical fields based on effects of propofol anesthesia

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Functional organization of human auditory cortex remains poorly defined. While the posteromedial portion (two thirds) of Heschl's gyrus (HG) is considered part of core auditory cortex (e.g. area A1), its further subdivisions are unknown. Anterolateral HG has been considered to be part of core auditory cortex (e.g. area R) and/or surrounding belt (e.g. area AL). Propofol, a sedative agent used for induction of general anesthesia, has been shown to affect auditory cortical activity (e.g. Plourde et al., Anesthesiology 2006, 104:448-57; Davis et al., PNAS 2007,104:16032-7). This study tested the hypothesis that auditory fields defined by anatomical criteria and acoustic response properties could also be characterized by their sensitivity to the effects of propofol.

Subjects were neurosurgical patients undergoing removal of intracranial electrodes placed to identify locations of epileptic foci (electrocorticography, ECoG). All procedures were approved by the University of Iowa Institutional Review Board, and each subject gave informed consent for this study. Stimuli were 50 Hz click trains (0.5 s duration, 1.5 s interstimulus interval). The stimuli were presented continuously during induction of general anesthesia, which included a 10-minute baseline followed by propofol infusion rate increasing from 50 to 150 ug/kg/min in 25 ug/kg/min steps every 10 minutes. ECoG recordings were made simultaneously from depth electrodes implanted in HG and subdural grid electrodes implanted over superior temporal gyrus (STG). Depth of anesthesia was monitored using spectral entropy (Viertio-Oja et al., Acta Anaesthesiol Scand 2004, 48:154-61). Auditory cortical activity was measured and characterized averaged evoked potentials (AEPs), frequency-following responses (FFRs) and high gamma (70-150 Hz) event-related band power (ERBP).

Posteromedial HG could be divided into two subdivisions based on changes in AEP and FFR during induction. In the most posteromedial aspect of the gyrus, the earliest AEP deflections were preserved, and FFRs increased during induction. In contrast, the remainder of the posteromedial HG exhibited attenuation of both the AEP and the FFR. Anterolateral HG exhibited weaker activation characterized by broad, low-voltage AEPs and no FFRs. Lateral STG could exhibit FFRs which would dissipate during induction.

Differential patterns of auditory cortical activity during induction of propofol anesthesia are useful physiological markers for field delineation. In contrast to previous interpretations, posteromedial HG is not uniform in its basic response properties and can be parcellated into at least two subdivisions. Preservation of the earliest AEP

deflections and FFR likely reflect persistent synaptic activity initiated by the ventral division of the medial geniculate nucleus. Absence of the FFR in anterolateral HG and its presence on the lateral STG is not consistent with synaptic flow from lateral HG to more lateral auditory cortex on the lateral convexity. Instead, it suggests that portions of the lateral STG reflect a relatively early stage in the auditory cortical hierarchy.

100 Persistent activity in auditory cortex during passive listening

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Persistent activity, the elevated firing of a neuron after the termination of a stimulus, is hypothesized to play a critical role in working memory. This form of activity is therefore typically studied within the context of a behavioural task, which includes a working memory component. Here we investigated whether persistent activity is observed in primary sensory cortex in the absence of any explicit behavioural task. We recorded spiking activity from single units in the auditory cortex (A1, R and RT) of awake, passively-listening marmosets. We observed persistent activity that lasted from a few hundred milliseconds to many seconds following the termination of the acoustic stimulus, in the absence of a task. Phasic persistent activity primarily occurred in units that showed strong phasic onset responses while sustained offset responses primarily occurred in units that showed sustained responses during the stimulus. Long duration persistent activity, on the order of seconds, was observed primarily in units that showed dramatic suppression in during the stimulus. Given that these responses were observed in passively listening animals, persistent activity in sensory cortex may have functional importance beyond storing behaviourally relevant information in working memory. These findings also indicate that, despite the prevalence of balanced excitation and inhibition observed in A1 neurons, a range of unbalanced excitation-inhibition dynamics may exist in marmoset auditory cortex.

101 HDAC3 dynamically regulates discrimination learning and information storage in primary auditory cortex

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Epigenetic mechanisms that modulate gene expression – such as histone modification – are key for regulating neuroplasticity. Blocking histone deacetylases (HDACs) has been shown to facilitate various forms of memory by releasing the brakes on neuroplasticity (e.g. McQuown et al., 2011; Stefanko et al., 2009). Recent work in the auditory system shows that inhibition of HDAC3, a class I HDAC, enhances representational plasticity in primary auditory cortex (A1) by facilitating unusually specific retuning to highly specific auditory features of learning experiences (Bieszczad et al., 2015). Here, we set out to determine if HDAC3-mediated specificity of A1 reorganization for sound frequency would enable performance in tasks that require frequency discrimination. Thus, we designed a two-tone frequency-discrimination (2TD) task: Adult male rats were trained to discriminate between two spectrally-distant frequencies (5.0 vs. 11.5 kHz; both 70 dB SPL). Because these sounds are spectrally different, any HDAC3-mediated effect could be attributed to associative memory processes per se rather than purely perceptual processes. Bar-presses (BP) to the CS+ tone were rewarded by access to water; BPs to the CS- resulted in an extended inter-trial delay ("time out"). The first three training sessions included post-training injection of the HDAC3 inhibitor, RGFP966 (10 mg/kg; s.c.), or Vehicle. We found that three days of RGFP966 treatment significantly enabled rats to acquire the 2TD more rapidly, reaching asymptotic levels of performance two days before vehicle-treated animals. These data support the hypothesis that A1 is under epigenetic regulation by HDAC3 to enable auditory associations to become better consolidated during incremental learning experiences with sound. This prompts a novel investigation into the temporal dynamics of epigenetic regulation that may convert the sensory details of transient experiences into long-term memory by releasing the brakes on representational plasticity.

102 Prefrontal and sensory correlates of auditory spatial attention in the macaque

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Auditory spatial attention is critical for everyday interactions, especially hearing in noisy environments. In addition, attention is thought to be a largely "amodal" resource, but to test this assumption it is important to understand whether spatial attentional mechanisms differ across modalities (e.g. vision vs audition), particularly at the single-neuron level. Though fundamental to our understanding of attention and auditory processing, the neural correlates of spatial auditory attention remain poorly understood. This is due in part to the lack of a robust animal model, particularly one that shares key similarities with humans.

To address this, we have developed a novel spatial auditory selective attention task for macaques (n=2), based closely on human paradigms. In this task, a macaque monkey is cued to a particular side and must report the presence of a difficult-to-detect auditory target (embedded in noise) only if it appears on the cued side. If it appears on the uncued side, he must ignore it. In this way, we are able to compare attention effects under identical auditory conditions.

We have begun collecting single neuron data from from two key areas implicated in the control of auditory spatial attention: prefrontal cortex (caudal principal sulcus; n = 449) and caudal auditory cortex (A1/CM/CL/TPT; n = 477) in one monkey during this task. In both areas, attention deployed to contralateral space significantly affected baseline firing rates in about 20% of the responsive neurons and also significantly affected 20-40% of responses to the masking noise. These early results are consistent with some of the hypothesized mechanisms reported during visuospatial attention, suggesting at least some attentional mechanisms are truly amodal.

103 Social consequences of interrupting marmoset conversations.

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Social living is an integral feature of primate societies. As such, social rules emerge that regulate individual and group behaviors. The ability of group members to recognize and follow these rules is critical to their survival and reproductive success, and violations to these rules may have a significant behavioral impact. Common marmosets, like other primates, follow rules during social and communicative interactions. However, it is unknown how violations to these rules impact the communicative exchange and the social treatment of the violator. Here, we examined the social consequences of interruptions during their natural conversations, known as antiphonal calling. We used a novel, multi-speaker interactive playback design with two 'Virtual Monkeys' (VMs) that simulated individual marmosets to test how interruptions impacted the dynamics of the conversation. One VM was denoted VM-Norm, as it produced normal responses to subjects' vocalizations, and the other was denoted VM-Int, as it occasionally interrupted subjects' own phee calls. Two types of phee calls were produced by the VMs: 1) antiphonal phee calls were broadcast in response to subjects' vocalizations, and 2) when subjects were vocally inactive for a period of time, one VM was selected to broadcast a spontaneous phee call to attempt to engage the subject in communication. This design afforded subjects the opportunity to learn about the individual behaviors of each VM and make decisions about whether or not to interact with those VMs based on that information. We recorded subjects' responses to each VM's different phee call types. We found that subjects were significantly less likely and slower to respond to an interruption from VM-Int than an antiphonal call from VM-Int or VM-Norm. Interruptions effectively ended the vocal exchange between subjects and VM-Int for that bout of calling. However, interruptions had no effect on subjects' decisions to respond to either VM when the VM initiated the vocal exchange (i.e., a VM's spontaneous call). We repeated this experiment with familiar and non-familiar stimuli, different age groups, and an increased rate of interrupting and found that these results persist regardless of these conditions. We are currently examining how interacting with the same interrupter over multiple days influences subjects decisions in conversations.

104 Synaptic or intrinsic, that is the question; parsing out synaptic currents in mapping the auditory corticocollicular inputs with glutamate uncaging

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In the auditory cortex, a subset of neurons in layers 5 and 6 project to the inferior colliculus. These projections have been shown to have a wide variety of effects when stimulated in vivo. Very little is currently known about nature of the inputs from the rest of the auditory cortex onto these cells. To investigate these inputs, we use laser photo-uncaging of glutamate to stimulate the cells that synapse onto the layer 5 and layer 6 corticocollicular cells in brain slices taken from adult mice. Pre-identified cells were recorded in a whole cell patch configuration then stimulated with a larger grid covering the area from the white matter to the pia. In this preparation we use a low calcium artificial cerebral spinal fluid method to isolate synaptic responses, and contrast this method with the more commonly used time window method. In identified layer 5 and layer 6 corticocollicular recordings, cells show spatial differences in their respective input maps with layer 5 having inputs coming from various layers compared to layer 6 which almost exclusively receives input from layer 6. Previously, layer 5 and layer 6 have been shown to have different electrophysiological properties and we find evidence that they differ in the nature of their inputs. Differences in these properties will likely then play different roles in modifying ascending information at the IC. These differences may explain the varied results seen in the inferior colliculus during in vivo stimulation of the auditory cortex.

105 First formant context information modulates speech segregation

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Perceptual grouping of auditory stimuli including separating consecutive speech sounds from one another resulting in distinct auditory representations are crucial in language comprehension. Previous studies suggest that this complex streaming process relies on interactions between stimulus-driven processing and centrally sustained temporal-context information. However, only a few studies have used speech stimuli to induce stream segregation yet, aiming at how speech-specific properties (e.g., formant transitions) may assist in the successful process.

In the present study, we investigated neural activity associated with the perceptual organization of speech sounds differed in Δf1. We recorded event-related potentials (ERP) while patterns of three vowel sounds (/ee/-/ae/-/ee/) were presented. Each trial started with an adaptation sequence, which could have either a small, intermediate, or large difference in first formant (Δf1) followed by a test phase, in which Δf1 was evenly intermediate. During the adaptation phase grouping process of speech sounds was sensitive to first formant transition: Δf1-related brain activity was found between 100-250 ms after the /ae/ vowel over fronto-central and left temporal areas, consistent with generation in auditory cortex. ERPs recorded during the test phase indicated that perceptual context results in transient changes in neural activity as well: prior stimulus modulated ERP amplitude between 20-150 ms over left fronto-central scalp region. According to our results perceptual organization of speech utilizes first formant information and modulation of vowels relying on a widely distributed neural network."

106 Convergence of excitatory and inhibitory projections in the mouse medial geniculate body

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The medial geniculate body (MGB) is the target of excitatory and inhibitory inputs from several sources. Among these, the inferior colliculus (IC) is an important nucleus in the midbrain that acts as a nexus for many auditory pathways and projections, ascending and descending, throughout the rest of the central auditory system and provides both excitatory and inhibitory projections to the MGB. In addition, the thalamic reticular nucleus (TRN) is a major source of inhibition to the MGB, particularly in rodents. Finally, the auditory cortex (AC) is a major source of descending input to the MGB, providing direct excitation and indirect inhibition via the TRN. In our study, we assessed the relative contribution from these excitatory and inhibitory projection sources to the MGB of the auditory system. Using retrograde tract tracing with CTbeta-Alexa Fluor 594 injected into the MGB of the mouse, we quantitatively mapped the projections from both ICs, the TRN, and the AC to the ipsilateral MGB. Our results indicate significant GABAergic projections from the IC and TRN to the MGB and excitation from the AC that play a significant role in shaping auditory processing. These results complement prior studies in other species, which suggests that these pathways are important factors in the regulation of neuronal activity in the auditory forebrain.

107 Spatial representation of speech in human auditory cortex

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Sound localization is an important ability that allows an organism to monitor its surroundings. While the neural mechanisms of sound localization have been studied extensively in nonhuman mammals, auditory spatial selectivity in human primary and nonprimary brain areas remains largely speculative. Moreover, it remains unclear how the auditory cortex jointly encodes spatial cues with the spectrotemporal features of speech that carry linguistic and non-linguistic information. In this study, we used invasive neurophysiological recordings in humans while they listened to speech from five different directions to study the organization of responses in human auditory cortex. We found differential responses to spatial cues at the level of single electrodes in primary cortical areas where the majority of electrodes responding to the contralateral side. Moreover, a linear decoder was able to predict the direction of speech stimuli based on neural population data significantly higher than chance. We characterized the joint encoding of spectrotemporal and spatial information and found a dissociated encoding of these cues, meaning that spectrotemporal feature selectivity was largely independent of the direction of the sound. Instead, we observed that the stimulus direction modulates the gain of the spectrotemporal tuning properties. These findings reveal the encoding properties of neural responses to spatial cues in human auditory cortex with implications for neurophysiological models of speech processing in the auditory pathway.

108 Changes of inhibitory and excitatory input to Layer 2/3 auditory cortex induced by developmental exposure to polychlorinated biphenyls.

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Polychlorinated biphenyls (PCBs), a family of compounds once used as dielectric fluids in capacitors and transformers, are carcinogenic and affect function of multiple systems, including the nervous and endocrine systems. Due to their toxicity and resistance to degradation, production of PCBs was banned in the 1970s. However, humans continue to be exposed, primarily through ingestion of contaminated food, and PCBs can be transferred to infants through the placenta or through breast milk. Developmental exposure to PCBs has been associated with hearing impairments in humans and rats.

Here, we ask whether hearing impairments induced by developmental PCB exposure are associated with changes in the central auditory system. We have previously shown that developmental PCB exposure alters thalamocortical transmission (Sadowski et al. 2016), and hypothesize that PCB exposure may change inhibitory and excitatory drive to layer 2/3 auditory cortex. Female breeding rats were dosed with 0 or 6 mg/kg/day of an environmental PCB mixture from 4 weeks prior to breeding until weaning on postnatal day 21. Auditory brainstem responses (ABRs) were recorded from adult offspring. Brain slices were then prepared and auditory cortex layer 2/3 pyramidal neurons inhibitory or excitatory postsynaptic currents were recorded under whole cell configuration. PCB exposed subjects showed elevated ABR thresholds, and changes in the frequency and amplitude of spontaneous inhibitory postsynaptic currents, as well as alterations in the amplitude of spontaneous excitatory postsynaptic currents, and the amplitude of miniature inhibitory postsynaptic currents. Together, these findings provide evidence for changes of both inhibitory and excitatory input to layer 2/3 auditory cortex associated with developmental PCB exposure.

109 Unsupervised learning and recognition of vowel sequences in the auditory cortex

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The ability to recognize and predict patterns in sensory input is a fundamental feature of the brain. Learning to process sequential information is particularly important in audition, and underpins speech recognition and language acquisition.

In this study, we aimed to examine the neural representation of repeated auditory sequences in the auditory cortex of the ferret, following the experimental paradigm reported by Gavornik and Bear (2014). A sequence of four artificial vowels (Bizley et al., 2009), termed ABCD, with each letter denoting a unique fundamental frequency was presented to awake passively listening (as well as anesthetized) ferrets that were implanted with multi-electrode arrays in the primary auditory cortex. After the exposure phase, the trained sequence as well as novel sequences, obtained by reordering the same elements (e.g. DCBA), and presenting the same sequence ABCD but with a different timbre were presented to examine transfer learning and generalization.

Gavornik and Bear (2014) observed enhanced field potentials and multiunit spiking activity in response to the repeated sequence (ABCD) relative to the novel sequence (DCBA) in an experimental group of mice but no difference in responses to the two stimuli in the control group. The present set of experiments aim to examine whether auditory cortical responses to repeated sequences show enhancement as observed by Gavornik and Bear (2014) in the primary visual cortex or whether they are suppressed, in line with previous reports of stimulus-specific adaptation in the auditory cortex (Ulanovsky et al., 2003).

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110 A low cost platform for large scale auditory behavioral experiments in mice

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To understand the neural basis of complex behavior, animals are often trained to perform carefully controlled tasks, which is often difficult, labor intensive and costly. This limits both the complexity of behaviors that animals can be trained to perform, as well as the diversity of environments learned behaviors are probed in. These factors can impede progress in understanding complex behavior and in turn its neural bases. To avoid these problems, we developed a low cost, high-throughput system for conducting behavioral experiments in mice, which is easy to implement and use, together with associated analysis methods. Our system is based on the Python programming language and the Raspberry-Pi series of micro-controllers. Here, we present the architecture of the system, and proof of concept behavioral data from frequency and level discrimination tasks as well as tone in noise detection. We envision that the platform will prove useful in a variety of domains: training mice to perform complex tasks, fast screening of transgenics on standardized tasks, and systematic exploration of parameter spaces of simple tasks. Together these advantages should allow us to address more effectively the mechanisms underlying learned behavior and thereby their neural bases.

111 Avalanche dynamics during spontaneous and sound evoked activity in the auditory cortex of awake mice

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In sensory cortical areas, thalamic afferents synapse primarily on mid-cortical layer neurons (L4) which in turn project to neurons in upper (L2/3) and lower (L5/6) cortical laminae. Within L2/3, neurons incorporate ongoing cortical activity, usually in the form of reverberating activity from within or distant cortical regions that reflect the state and behavioral context of the animal. These features, among others, may contribute to the heterogeneous organization of stimulus preference in L2/3. A well-established hypothesis is that cortical activity, especially in L2/3, reflects a complex system operating at or near criticality in order to maintain network stability while optimizing information processing. Prior studies have shown that spatiotemporal patterns of spontaneous neuronal activity organize into neuronal avalanches that exhibit signatures of critical dynamics; that is, the probability distribution of avalanche sizes can be fit with a power law of specific parameters. Here we study neuronal avalanche dynamics preceding as well as during sensory stimulation in primary sensory cortex. We investigate neuronal avalanches using in vivo 2-photon Ca2+ imaging of ongoing and sound evoked activity of primary auditory cortex (A1) in awake mice using GCaMP6s. We explore the relationship between properties of sensory stimuli, single cell responses, and population responses with respect to avalanches. We investigate the spectral tuning properties of neurons participating in avalanches in order to probe the relationship between criticality and sensory coding. On the single cell level, many neurons were tuned to a particular sound frequency but responded unreliably. On the population level, we found that avalanche statistics varied depending on the stimulus frequency and intensity of the presented sound. We speculate that stimulus frequency and intensity dependence reflected in avalanche size suggests that stimuli are encoded in distinct local subpopulations; not just single neurons. Furthermore, stimulus-evoked avalanches often contained neurons that are not overtly tuned to the presented stimulus. The role of these neurons in sensory coding is unclear. Our investigation provides insight into how neural networks containing differing populations of neurons with varying firing rates stably encode information about sensory stimuli in the context of self-organized criticality.

112 Inactivation of primate dorsolateral prefrontal cortex during auditory working memory

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We have previously shown that inactivation of the ventrolateral prefrontal cortex (VLPFC), including areas 12/47, 45, and ventral 46 results in impaired performance during audiovisual working memory with dynamic vocalization movies as the memoranda. We have also demonstrated that VLPFC inactivation impairs performance when only the auditory stimulus, the vocalization has to be remembered. These experiments demonstrate that VLPFC is crucial in auditory and audiovisual working memory. However, it is also possible that our inactivation may have included portions of the dorsolateral prefrontal cortex (DLPFC). Furthermore, DLPFC may also be involved in these working memory paradigms due to its general role in the process of working memory, and goal directed behavior. We therefore trained animals to perform an auditory match-to-sample task using 3 categories of complex sounds: macaque vocalizations, other vocal sounds and non-vocal auditory stimuli. Cylinders were aligned over the DLPFC in order to allow for the use of cortical cooling which inactivates the area within the cylinder. For each experimental session the monkeys were brought to the testing room and the auditory match to sample task was started. The subjects performed 100 trials to establish the baseline prior to cooling (WARM trials) then the cooling process was started and the brain was cooled to 20 degrees Celsius in order to reduce synaptic activity and temporarily inactivate the cortex. After 100 trials during cooling (COLD trials) the temperature was returned to normal and the subject was returned to their home cage. Warm and Cold trials were compared in order to determine if cooling of DLPFC has an effect of auditory working memory.

113 Auditory streaming of speech: acoustics, lexicality and neural signatures

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To make sense of the acoustic mixture arriving at the ears, the auditory system must establish which sound elements arise from the same source and should therefore be grouped together perceptually. Billig et al. (Curr. Biol., 2013) demonstrated that a spoken sequence of repeated syllables (e.g. “stome stome stome …”) can be perceived as two separate streams: one of the initial fricative (“s s s …”) and another of the remainder (“dome dome dome …”). The percept is bistable, alternating between this segregated form, and the full integrated syllable. Acoustic differences between the initial fricative and the syllable remainder contribute to this streaming effect. However, lexical information can also play a role: the non-word “stome” is more likely to stream apart than the acoustically similar word “stone”. To test whether these findings generalise beyond the stimuli and British English speaking participants in Billig et al. (2013), similar sequences were constructed from a larger set of syllables and played to speakers of North American English. Syllables beginning with “sw” (e.g. “swim”, “swoon”) streamed less than those beginning with “s” followed by a stop consonant (e.g. “stem”, “scour”). This may be due to the presence of formant transitions in the former case only. The lexical status of the syllable also affected perception, with words being perceived as integrated for longer than acoustically similar non-words. Work is in progress that uses these bistable stimuli in conjunction with fMRI and electrocorticography to probe the neural processes underlying perceptual organisation and lexical processing.

114 Rapid Adaptation to Changing Signal Conditions in human auditory Cortex

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Humans are experts at perceiving spoken language, even in the presence of interfering sound sources. However, the dynamic neural mechanisms required to understand speech in noise are largely unknown. To understand how the auditory system adapts to extract speech during irregular additive and reverberant distortions, we used invasive technology to record auditory cortical responses in neurological patients as they listened to continuous speech stimuli while the background noise changed every three seconds. Analysis of the neural responses to the speech signal as the background noise changed revealed an adaptation phase after the onset of a novel noise. Directly after noise onset, the neural representation of speech features degraded, then adaptation gradually restored these features. We quantified the degradation of the neural representation using discriminative analysis of phonetic features and stimulus reconstruction techniques. To explore possible mechanisms that could contribute to this dynamic response property, we constructed a neural network model to map the speech stimulus to the neural responses. A simple feedforward network model failed to replicate the temporal adaptation of neural responses to the changes in the background. We then incorporated feedback mechanisms into the model based on 1) synaptic depression models and 2) the statistical structure of neural co-activation patterns. We found that these mechanisms allowed the model to replicate the temporal dynamic properties of the neural response at noise transitions. The proposed model thus offers insight into biologically plausible computational mechanisms that can explain the robust speech perception observed in real-world hearing conditions.

115 Eye movement-related eardrum oscillations (EMREOs) suggest visual-auditory spatial integration begins in the auditory periphery

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Visual and auditory signals that arise from coincident locations in space often fuse to produce a combined visual-auditory percept, such as lip reading cues that facilitate speech comprehension. A critical problem for this process is that the visual and auditory systems employ different methods of determining the locations of stimuli. The visual system relies on the site of retinal activation and the auditory system evaluates interaural timing and intensity differences as well as spectral cues. In species that move their eyes with respect to the head/ears, there is no fixed relationship between these cues, and representations must be adjusted with each change in eye position if the brain is to determine whether a visual and an auditory stimulus coincide in space.

Eye movements have been shown to modulate auditory activity in a number of brain regions such as the inferior colliculus, auditory cortex, parietal cortex, frontal eye fields, and the superior colliculus, but where eye movement-related signals first contribute to auditory processing is not known. One possibility is the auditory periphery. Active mechanisms in the ear comprise the outer hair cells, or motile neurons in the cochlea, and the middle ear muscles. Both systems are under descending control from the brain, providing a possible route of transmission of information about eye movements to the auditory periphery.

To test this hypothesis, we used a microphone to record movements of the eardrum in human subjects (n=10, 16 ears) performing saccades to visual targets. We found that the eardrums oscillated in conjunction with eye movements, despite the absence of any delivered sound. These oscillations began at least 10ms before the eye had traveled 5% of the total angular distance of any given saccade. The initial phase and magnitude of these eye-movement related eardrum oscillations (EMREO) was dependent on saccade origin, direction, and length. The dependence of the EMREO on all three of these factors suggests it contains the necessary information to facilitate visual-auditory spatial integration, although the exact means by which it does so remains uncertain."

116 Motor system excitability fluctuations during rhythm and beat perception

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Humans synchronize movements with the perceived, regular emphasis (the beat) in musical rhythms. Neural activity during beat perception is dynamic, time-locked, and heavily based in the motor system. Neural oscillations synchronize to regularities, such as the beat, in auditory rhythms (Fujioka, et al., 2012; Nozardan, et al., 2011). Excitability in the motor system fluctuates during beat perception, as indexed by the amplitude of motor-evoked potentials (MEPs) evoked by transcranial magnetic stimulation (TMS). In a previous study, MEP amplitude was greater when listeners heard rhythms with a strong beat vs. a weak beat, but only for MEPs elicited 100 ms before the beat, not for MEPs generated at random time points relative to the beat (Cameron, et al., 2012). Thus, motor system excitability may not be uniform across the entire rhythm, but instead may fluctuate, rising at particular times on or before the beat. Here, we sought to characterize the dynamics of motor system excitability during beat perception.

Participants (n=23) listened to strong beat, weak beat, and nonbeat auditory rhythms (35s each). TMS was applied to left primary motor cortex at 100 time points in the beat interval of each rhythm type. MEP amplitudes were recorded with electromyography from the right hand (first dorsal interosseous muscle).

Motor system excitability dynamics differed for strong beat vs. weak beat and nonbeat rhythms: Excitability ncrease linearly over the beat interval (in anticipation of upcoming beat positions) in strong beat rhythms, but not weak or nonbeat rhythms. Additionally, excitability fluctuated at the rate of individual events (the beat rate subdivided by four) to a greater extent in strong beat rhythms than in the other rhythms.

These results suggest that during beat perception, motor system excitability 1) anticipates upcoming beats, and 2) tracks subdivisions of the beat.

117 The relationship between perceptual timing and language skill in early and middle adolescence: the St Thomas More School Project

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We have previously tested the relationship between auditory analysis and language skill in children in a series of experiments based on the systematic examination of multiple auditory domains (pitch, time and timbre) from simple features in single sounds or time intervals to complex sequences. The work demonstrated a relationship between pitch or temporal sequences and language skill in a large cohort of eleven-year-old school children [Grube et al: PMID 22951739]. The present study examined the specific relationship between time-sequence and language skill and how this changes over adolescence. Specifically, our previous data from eleven-year-old children demonstrated a relationship between the analysis of short isochronous rhythms and language skill whilst in young adults the analysis of longer more abstract, beat-based timing was important [Grube et al: PMID 24168197]. Here, we examined the relationship of both types of auditory skill and language skill in large cohorts of eleven- and fourteen-year-old children.

237 eleven year olds and 234 fourteen year olds each underwent 3 hours of testing in total (including both auditory and language). The groups represent complete year groups from a non-selective government-funded school. The four timing tasks comprised discrimination of single time intervals, deviation from isochronous rhythm, regularity detection (the ability to detect a ‘roughly’ regular beat) and metrical rhythm discrimination [Grube et al: PMID 20534501 and 22951739]. Language assessment included rhyme decision, spelling, word reading, non-word reading, rapid automated naming (digits and objects), and spoonerisms. Pairwise correlation analysis was carried out on data from ~ 190 eleven year olds and ~ 200 fourteen year olds.

In the eleven years olds a limited but significant and consistent correlation between isochronous sequence analysis and language skills was demonstrated after accounting for non-verbal intelligence [average rho before: 0.23, and after: 0.19; $p < 0.05$, Bonferroni-corrected]. In the fourteen year olds a moderate to large and significant correlation was found between isochronous sequence analysis and language skill [average rho before: 0.33, and after: 0.22; $p < 0.05$, Bonferroni-corrected], and also between regularity detection and language skill [average rho before: 0.31, and after: 0.22; $p < 0.05$, Bonferroni-corrected].

The data confirm an important relationship between rhythmic and language skill consistent with the notion of a ‘temporal scaffolding’ mechanism common to generic

auditory and speech domains. This specific nature of this relationship is not fixed but evolves over adolescence.

118 Perceptual boundaries for species-specific vocalizations in the common marmoset (Callithrix jacchus)

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One of the most basic questions in cognitive neuroscience concerns how continuous, variable sensory inputs are organized into discrete, behaviorally significant perceptual categories with clearly defined boundaries. This phenomenon was first described, and remains best characterized, for human speech, although there is a wealth of evidence showing that many species display categorical perception of their own species-specific communication calls. The common marmoset (Callithrix jacchus) is a small, arboreal New World primate with a rich vocal repertoire. While several different classes of vocalizations have been described for this species (i.e., “twitter”, “phee”, “trill”, etc.), we know surprisingly little about how these vocalizations are actually perceived by these animals, including the perceptual boundaries for classifying particular call types. Further, almost nothing is known about the neural underpinnings of categorical perception for species-specific vocalizations in marmosets. We began to address these questions by training marmosets using operant conditioning techniques to discriminate among several variants of synthesized (“virtual”) vocalizations. We created a series of virtual vocalizations for each call type that progressively deviated away from the mean population value for single, or pairs of, acoustic parameters (e.g., dominant frequency, FM rate, etc.). Results from behavioral experiments utilizing these stimuli showed that marmosets appear insensitive to changes along one acoustic parameter axis for a given call type over a range of up to 2 SD of the population mean for that call type. Furthermore, marmosets showed less sensitivity to variations in their species-specific vocalizations compared to similar variations in simpler acoustic stimuli (e.g., pure tones, sFM tones, etc.). These findings suggest potential categorical specializations for vocal perception by marmosets. Finally, we examined changes in neural activity in several regions of auditory cortex (core and lateral belt) while marmosets engaged in the above discrimination tasks. [Supported by NIH grants DC003180 to XQW and DC013150 to MSO]

119 Dissociation of knowledge and performance during sensorimotor learning

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Sensorimotor learning allows animals to make critical associations for survival. Animals learn to navigate environments in search of nutrition; they link sensory features to predators and they improve motor coordination to enable skilled movements. We know from humans, however, that learning is intimately connected with context. In basketball, the same shot that is easy in practice can be challenging during a game. To mitigate this, coaches "simulate" the in-game context during practice and train players to operate under pressure. Coaches recognize that learning encompasses both the skilled movements required to shoot but also the mental training to operate in pressure-packed conditions. Can we separate what an animal "knows" (i.e. the sensorimotor skills to discriminate two tones) versus how it "performs" (i.e. the effectiveness of executing on that knowledge)? During a stimulus recognition task, animals must discriminate between target and non-target sounds (sensitivity, d') and make a decision to respond (criterion, c). Rodent learning models often use sensitivity (d') to measure performance, thereby becoming the key correlate for neural data. This approach assumes that neural circuit dynamics during learning reflect improvements in knowledge (sensitivity) under conditions of a stable decision criterion (c). Alternatively, knowledge may dissociate from performance because the decision criterion is also shifting. To date, however, it has been difficult to behaviorally distinguish knowledge from performance. We found that by introducing probe "practice" trials (by removing the licktube for 20-40 trials) during predominantly active training (presence of licktube), we could behaviorally reveal that mice can discriminate target and non-target sounds at expert levels well before the performance data indicated. Head-fixed mice licked to the target tone (i.e. 4.7 kHz) and withheld from the non-target tone (i.e. 8 kHz) within 5 days during the probe practice trials; it took 6-8 more days to achieve similar performance during active trials (n=7 mice). Interestingly, network decoding of neural data acquired with two-photon calcium imaging of excitatory neurons tracked these two phases. First, there was a rapid improvement in discrimination accuracy by days 3-5. Second, there was a more gradual stabilization whereby neuronal weights from previous days could be used to decode future days, tracking the implied response criterion. Surprisingly, single-neuron analysis showed that the neurons driving these two features were distinct and spatially interspersed. Thus, dissociation of knowledge and performance suggests that learning encompasses simultaneous, but separable, neural dynamics for sensory discrimination and state control.

120 Feature Selective Attention Enhances Population Coding in Primary Auditory Cortex

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Sensory environments often contain an overwhelming amount of information competing for perceptual resources. Attention mediates this competition by selecting the sensory features that form a percept. How attention affects the activity of populations of neurons to support this process is poorly understood because population coding is typically studied through simulations in which one sensory feature is encoded without competition. Here, we test the prediction that attention enhances population coding of a “target” sensory feature in the presence of a competing “distractor”. We recorded from populations of auditory cortical neurons while rhesus macaques performed a novel feature selective attention task. We found that attention adaptively re-shapes the joint response distributions between neurons in a population to enhance the neural representation of the target feature, while simultaneously suppressing the distractor. These findings present a novel mechanism by which attention modulates neural populations to support sensory processing in cluttered environments.

121 The significance of nominally non-responsive cell activity in auditory perception and behavior.

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Single-unit activity recorded from behaving animals can often have heterogeneous response profiles. A fraction of recorded cells typically exhibit trial-averaged responses with obvious task-related features, such as pure tone frequency tuning in the auditory cortex, or ramping activity in secondary motor areas. However, a substantial number of cells do not appear to fire in a task-related manner and require different analytical methods. We analyzed single-units recorded from rats during a frequency recognition task in order to identify to what extent task variables are reflected in individual spike trains of every recorded neuron – independently or as part of small ensembles of cells. Adult rats were trained on a go/no frequency recognition task that required them to nosepoke to a single target tone for food reward and withhold from responding to multiple nontarget tones. Using multielectrode arrays we recorded from 75 single-units in the auditory cortex and 57 single-units in the frontal cortex (FR2). While the trial-averaged responses of some cells exhibited obvious and statistically significant task-related features, many cells were nominally non-responsive (41/75 AC cells and 35/57 FR2 cells from six animals had neither significant tone-modulated activity or ramping activity; $p < 0.05$, 5,000 bootstraps). This variable activity is the only information available to downstream cells and circuits and must be decoded by other brain regions in real time on single trials. Accordingly, we devised a novel spike-timing based algorithm for trial-by-trial decoding. We found that: 1) Nominally non-responsive neurons represent behavioral variables. Our analysis shows that, in fact, the activity of cells that seem unresponsive when trial-averaged can and often do reflect basic differences in sensory stimulus encoding and decision-making. 2) We identified many ‘multiplexed’ neurons that simultaneously represented both the sensory input and the upcoming behavioral decision (43% of cells were multiplexed, with accuracy index ≥ 0.05 for both stimulus category and choice). 3) Frontal cortex has a better representation of task-relevant auditory stimuli than auditory cortex. Auditory cortex reliably responds to pure tones in untrained animals. However, when tones take on behavioral significance, this information is encoded more accurately in frontal cortex, suggesting that this region is critical for identifying the appropriate sensory-motor association.

122 Frequency contour tuning reveals neural tolerance for vocal category variation in mouse A2

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How a sound's pitch changes over time can hold communicative significance for humans, from informing affect of an utterance to distinguishing words in tonal languages. Frequency contours in the vocalizations of many species are in fact features that are used to discriminate variants of one sound category from another. Indeed, in cases where some sound features overlap between categories, frequency contours can play a decisive role in acoustically separating sounds with distinct meaning. Indeed, in the mouse, variants of ultrasonic pup isolation calls and adult mating calls overlap along basic acoustic dimensions, like duration or onset frequency. However, the responses of a subset of putative pyramidal neurons in the Core auditory cortex of pup-experienced females can still discriminate between their frequency contours, potentially enabling better call categorization in downstream auditory fields (Shepard et al, J Neurosci, 2015). To better understand whether auditory cortical neurons can actually attune to specific frequency contours, we modeled mouse vocalizations using tones with frequency modulated by sine waves (sFM). Six parameters were fit to a library of calls: duration, onset frequency, sFM amplitude (sFMA), sFM frequency (sFMF), sFM phase, and linear FM slope. Natural calls, sFM call models, and sFM stimuli optimized around each neuron's best frequency and intensity were presented to mice during awake head-fixed single unit recording. We observed in Core and A2 fields of mouse auditory cortex that approximately half of tone-excited neurons could be tuned to sFMA and sFMF values differing from pure tones. In some cases, best sFMA could be as small as 1/25th of an octave, suggesting a fine sensitivity to subtle frequency contour modulation. Such sensitivity often could not be explained simply by the response to spectrally-matched noise models. Furthermore, we found that tuning widths for sFMA were larger in A2 compared to Core auditory cortex, consistent with greater tolerance for acoustic variability in frequency contours in a higher-order auditory cortical field. Additionally, best-sFMA values in A2 were significantly higher when sFM stimuli were centered around adult versus pup calls, in congruence with adult calls typically having higher sFMA than pup calls. Taken together, these results demonstrate that sFM stimuli provide a useful basis to systematically investigate the frequency contour tuning of Core and higher-order auditory cortical neurons, which enables the assessment of how more

categorical representations of sounds, such as species-specific vocalizations, emerge along the auditory cortical hierarchy.

123 Learning to hear with cochlear implants: role of noradrenaline

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Cochlear implants are neuroprosthetic devices that can provide hearing to deaf patients, but outcomes and acoustic learning are highly variable. Learning with the cochlear implant is believed to require plasticity within the central auditory system, but the mechanisms by which behavioral training enables plasticity and improves outcomes are poorly understood.

Recent work in our lab has established a cochlear implant model in rats that allows the animal to freely behave while using a multi-channel device (King et al., J Neurophysiol 2016). This provides a new opportunity to study neural plasticity related to auditory perception and hearing restoration with cochlear implants. The cochlear implant is inserted using a modified dorsal approach via a basal turn cochleostomy. This method optimizes the insertion depth of the implant and spares the stapedial artery. Animals are trained on a self-initiated frequency detection/recognition task prior to deafening and implantation, and then tested after implantation on frequency detection capability.

In this project, we have focused on the effects of norepinephrine, which has shown to be important in learning and synaptic plasticity in the rat auditory cortex (Martins and Froemke, Nat Neurosci 2015), on training with cochlear implants. The locus coeruleus (LC) is the main producer of norepinephrine in the brain (Sara, Curr Opin Neurobiol 2015). Previous work from the lab showed that a single episode of LC stimulation induces changes in the primary auditory cortex and improves auditory perception in normal-hearing animals. Here we asked if LC stimulation could accelerate cochlear implant use and/or enhance peak performance in deaf rats. Some animals were wild-type rats expressing ChETA channelrhodopsin-2 in the LC; other animals were TH-Cre rats selectively expressing ChETA in noradrenergic LC neurons. We are currently examining whether optogenetic LC stimulation improves performance in normal-hearing and cochlear implant-using deaf rats, as well as performing fiber photometry after GCaMP6s expression in LC neurons. By combining LC optogenetic stimulation and cochlear implants, we hope to further elucidate the role of norepinephrine and synaptic plasticity in cochlear implant learning.

124 Learning and Performance Variability in A Rodent Model of Multi-Channel Cochlear Implant Use

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Cochlear implants (CIs) are neuroprosthetic devices that can restore meaningful hearing to the profoundly deaf. However, asymptotic speech recognition and time to reach asymptotic levels are variable, ranging from 0 to 100% speech recognition and from <6 months to >2 years, respectively (Tyler et al., 2000; Chang et al., 2010). To determine neural mechanisms that underlie individual differences in the time course of adaptation to CI stimulation as well as in steady state outcomes, we developed a rat model of CI use.

Female Sprague-Dawley rats are first trained on a self-initiated broadband (half-octave pure tone spacing) and narrowband (quarter-octave pure tone spacing) frequency detection task. Once animals have learned both tasks (d'>1.7), they are bilaterally deafened with a combination of ototoxic drugs and intracochlear trauma (>50 dB hearing loss), and unilaterally implanted with an 8-channel array in the scala tympani. Following surgical recovery and objective sound processor programming, the animals are initially tested on the broadband frequency detection task using CI stimulation as their exclusive input; this is their first day of stimulation. They then receive further targeted training to improve their behavioral performance. Day 1 initial performance is highly variable (n=3; d': -0.18, 0.21, and 0.86) but overall relatively poor; over a period of weeks, while learning trajectory and peak performance differ across animals (n=3; d': 0.94, 1.15, and 2.38), all animals improve significantly compared to their initial performance (p<0.01). This model of initial and learning variability captures some key features of clinical outcome variability with regards to vowel and word recognition with a CI in post-lingually deaf users.

In order to explore the neural correlates of these phenomena, we are using chronic micro-electrocorticography (uECoG) in CI animals throughout the behavioral testing and learning period with the CI. In collaboration with the Viventi lab, the Froemke lab has developed a uECoG system for recording from auditory cortex in awake, freely moving animals (Insanally et al., 2016). The 60-contact arrays can record stable tonotopic maps over a period of weeks to months. We are expanding this setup to include chronic cortical recordings within the behavior boxes during CI learning and performance. We expect that cortical representations of CI channels will be overlapping or indistinguishable in the initial phase, correlating with relatively poor initial performance, and that the CI channel representations will become more defined with training and experience, correlating to improved behavioral performance with the CI.

125 A physiological and behavioral system for hearing restoration with cochlear implants.

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Cochlear implants are neuroprosthetic devices that provide hearing to deaf patients, although outcomes are highly variable even with prolonged training and use. The central auditory system must process cochlear implant signals, but it is unclear how neural circuits adapt - or fail to adapt - to such inputs. Understanding these mechanisms is required for development of next-generation neuroprosthetics that interface with existing neural circuits and enable synaptic plasticity to improve perceptual outcomes. Here we describe a new system for cochlear implant insertion, stimulation, and behavioral training in rats. Animals were first ensured to have significant hearing loss via physiological and behavioral criteria. We developed a surgical approach for multi-channel (2-channel or 8-channel) array insertion, comparable to implantation procedures and depth in humans. Peripheral and cortical responses to stimulation were used to objectively program the implant. Animals fitted with implants learned to use them for an auditory-dependent task that assesses frequency detection and recognition, in a background of environmentally- and self-generated noise, and ceased responding appropriately to sounds when the implant was temporarily inactivated. This physiologically-calibrated and behaviorally-validated system provides a powerful opportunity to study the neural basis of neuroprosthetic device use and plasticity.

126 Contribution of population activity in the auditory cortex to the cocktail-party problem

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One of the fundamental functions of the auditory system is to transform acoustic stimuli into discrete perceptual representations (sounds). However, this task is often complicated by our listening conditions: rarely do we listen to sounds against silence. Instead, our auditory system often must extract and segregate a “target” stimulus from a noisy background (e.g., isolating your friend’s speech from the rest of the sounds in a restaurant). This ability is frequently referred to as figure-ground segregation or, more informally, as the cocktail-party problem. The neural underpinnings of this ability, specifically those in the auditory cortex, have not yet been fully elucidated. To address this issue, we recorded from the auditory cortex while rhesus monkeys simultaneously reported whether they heard a target stimulus that was embedded in a noisy background. The target stimulus was a tone burst, whose frequency was set to the best frequency of the recording site, and the noisy background was comodulated broadband noise. On a trial-by- trial basis, we varied the “target-in-noise” ratio (TNR) between 0 and 25 dB. On approximately of 50% of the trials, we presented the noise alone; these trials served as catch trials. Although most auditory-cortex neurons were driven by the auditory stimuli, only a small fraction of neurons was significantly modulated as a function of TNR levels. Further, we could not identify a significant population of neurons that was modulated by the monkeys’ choices (detection versus no detection of the target stimulus). Because of these two sets of findings, it seemed that very few individual neurons contributed sensory evidence to the task’s perceptual decision. However, the heterogeneity of neural responsivity suggested that population activity might provide more stimulus- and/or task-related information. To test this hypothesis, we constructed a support vector machine and tested how well neural activity in response to different stimulus and/or task attributes couldbe discriminated using a linear-decision- boundary. With populations as small as ~100 neurons, this classifier could reliable decode TNR level, discriminate between the target and noise stimulus, and discriminate between variability that was modulated by the monkeys’ choices. Overall, these findings are consistent with the hypothesis that auditory cortex does contribute directly to the cocktail-party problem. However, this contribution is not seen in individual neurons but the overall activity of the population.