Tucker-Davis Technologies Symposium on Advances and Perspectives in Auditory Neurophysiology (APAN)

8:00 – 9:00 Registration and Poster Set-up

9:00 – 9:05 Opening Remarks and Announcements

9:05 – 10:00 **Keynote Lecture**

"Auditory Cortical Structure at the Molecular Level: New Challenges for Neuroanatomy"

Troy A. Hackett, Vanderbilt University

10:05 – 10:20 **Four 3-minute Poster Teasers** (Chairs: Christopher I. Petkov and Mitch L. Sutter)

- **The role of ventral prefrontal cortex in auditory, visual and audiovisual working memory (76),** *B. Plakke,* J. Hwang, M.D. Diltz, L.M. Romanski
- **Rapid task-related plasticity of spectrotemporal receptive fields in the auditory midbrain (34),** *S.J. Slee,* S.V. David
- **Recovery of central auditory function in mice following profound peripheral deafferentation: a combined behavioral and neurophysiological study (50),** *A.R. Chambers,* Y. Yuan, A.S. Edge, M.C. Liberman, D.B. Polley
- **Characterizing central auditory neurons in Drosophila (8),** *A.E. Baker,* A.G. Vaughan, B.S. Baker, R.I. Wilson

10:20 – 11:20 **Morning Poster Session** and Coffee Break

11:30 – 12:30 **Slide Session I** (Chairs: Cory T. Miller and Jennifer F. Linden)

11:30 – 11:45 **Behavioral and neural effects of silencing the auditory cortex in adult ferrets using optogenetics,** *V.M. Bajo,* C. Korn, K. Reynolds, E.S. Boyden, F.R. Nodal, A.J. King

11:45 – 12:00 **Nonauditory task-related modulations of neuronal activity in auditory thalamus and cortex in freely moving rat,** *K. Borges,* S. Jaramillo, A.M. Zador

12:00 – 12:15 **Direction selectivity mediated by adaptation in the owl's inferior colliculus,** *Y. Wang,* J.L. Peña

12:15 – 12:30 **Tonotopic organization in monkey and human auditory cortex using phase-encoded functional MRI,** *O. Joly,* N. Ghazaleh, S. Kumar, S. Baumann, G. Chapuis, W. van der Zwaag, A. Thiele, T.D. Griffiths, M. Saenz

12:30 – 2:00 **Lunch** on own (posters stay up during meeting). Check APAN website for dining suggestions.

2:15 – 3:15 **Slide Session II** (Chairs: Daniel B. Polley and Heather L. Read)

2:15 – 2:30 **Task engagement selectively modulates noise correlations in primary auditory cortex,** *J. Downer,* M. Niwa, M.L. Sutter

2:30 – 2:45 **Modulation of spontaneous and sensory-evoked synaptic dynamics in A1 during auditory discrimination tasks in mice,** *M.J. McGinley,* S.V. David, D.A. McCormick

2:45 – 3:00 **The critical period of recovery for me-IPSC inhibitory transmission within the auditory cortex closes prior to postnatal day 23,** *T.M. Mowery,* V.C. Kotak, D.H. Sanes

3:00 – 3:15 **Phonetic feature representation in human superior temporal gyrus,** *N. Mesgarani,* C. Cheung, K. Johnson, E.F. Chang

3:15 – 3:30 **Four 3-minute Poster Teasers** (Chairs: Daniel B. Polley and Heather L. Read)

- **Cortical oscillations and spiking activity associated with Artificial Grammar Learning in the monkey auditory cortex (54),** *Y. Kikuchi*, A. Attaheri, A. Milne, B. Wilson, C.I. Petkov
- **Causal role of primate auditory cortex in auditory perceptual decision-making (25),** *J. Tsunada,* A. S. Liu, J.I. Gold, Y.E. Cohen
- **Oxytocin-based neuromodulation of mammalian social behavior (74),** *B.J. Marlin,* R.C. Froemke
- **Enhanced cognitive flexibility in reversal learning induced by removal of the extracellular matrix in auditory cortex (26),** *M.F.K. Happel*, H. Niekisch, L.L. Castiblanco, F.W. Ohl, M. Deliano, R. Frischknecht

3:30 – 5:50 **Afternoon Poster Session** and Refreshments

5:50 – 6:00 Travel Awards (Jennifer F. Linden) and Other Announcements (Yale E. Cohen, Xiaoqin Wang)

6:30 – 9:30 After-party at Basic (http://www.barbasic.com) – Pay $15 to Cory Miller during APAN.

Supported by funding from: NIDCD, Tucker-Davis Technologies, Wellcome Trust

1. **Distinct roles of anterolateral and posteromedial Heschl's gyrus in coding human voice fundamental frequency,** *R. Behroozmand,* J. Greenlee, C. Larson, D. Hansen, H. Oya, H. Kawasaki, M. Howard, J. Brugge
2. **Spatial hearing capabilities of the adult guinea pig (*Cavia porcellus*),** *N.T. Greene,* A.T. Ferber, K.L. Anbuhl, P.D. Allen, D.J. Tollin
3. **Predicting benefits of multisensory memories,** *A.T. Thelen,* M.M. Murray
4. **Organization of human auditory cortex: modulation of response patterns on the posterior lateral superior temporal gyrus during a target detection task,** *M. Steinschneider,* K.V. Nourski, H. Oya, H. Kawasaki, M.A. Howard III
5. **Plasticity in hierarchical auditory cortical processing of behaviorally relevant vocalizations revealed by Arc/Arg 3.1 mRNA expression,** *T.N. Ivanova,* R.C. Mappus, C. Gross, G.J.Bassell, R.C. Liu
6. **Neural correlates of consciously-perceived, unattended sounds,** *A.R. Dykstra,* A. Gramfort, A. Gutschalk
7. **Spatial processing of cortical neurons in the primary auditory cortex after cholinergic basal forebrain lesion in ferrets,** *F.R. Nodal,* N. Leach, P. Keating, J. Dahmen, A.J. King, V.M. Bajo
8. **Characterizing central auditory neurons in Drosophila,** *A.E. Baker,* A.G. Vaughan, B.S. Baker, R.I. Wilson
9. **Spectro-temporal receptive field models of inferior colliculus neurons,** *S.Z. Enam,* M.R. DeWeese
10. **Neural signature of inattentional deafness,** *K. Molloy,* M. Chait, N. Lavie
11. **Differential neuronal responses in ferret frontal cortex during performance of positive and negative reward versions of an auditory long-term memory task,** *J.B. Fritz,* S.A. Shamma, P. Yin
12. **Duration of acoustic experience shapes development of auditory cortex cartography,** *C. Wong,* D. Kühne, A. Kral, S.G. Lomber
13. **Defining harmonic resolvability in the common marmoset (*Callithrix jacchus*),** *M.S. Osmanski,* X. Song, X. Wang
14. **Learning the stimulus space geometry from auditory neural population responses,** *B. Englitz,* S. Shamma
15. **Amplified cortical, but not thalamic, somatosensory and visual projections to the anterior auditory field following early- or late-onset deafness,** *N. Chabot,* M.A. Kok, S.G. Lomber
16. **Physiological but not anatomical abnormalities in the auditory thalamus of ectopic BXSB/MpJ-Yaa mice,** *J. Mattley,* L.A. Anderson, J.F. Linden
17. **Neural mechanisms underlying the coding of time-varying stimuli in primary auditory cortex of awake marmoset studied by intracellular recording,** *L. Gao,* X. Wang
18. **Human depth electrode recording of auditory cortex responses to different pitch values,** *P.E. Gander,* S. Kumar, K.V. Nourski, H. Oya, H. Kawasaki, M.A. Howard III, T.D. Griffiths
19. **Activity of auditory cortical neurons in monkeys performing a short-term memory task,** *B.H. Scott,* P. Yin, M. Mishkin
20. **Representation of periodic sounds in the inferior colliculus of the gerbil - periodotopy revisited,** *J.W.H. Schnupp,* J.A. Garcia-Lazaro, N.A. Lesica
21. **Electrophysiological correlates of intra-categorical discrimination training,** *R. De Meo,* N. Bourquin, J.-F. Knebel, M.M. Murray, S. Clarke
22. **Stimulus expectancy influences auditory detection by selective cross-modal phase reset of different frequencies: evidence from EEG and behavior,** *S. ten Oever,* N. Van Atteveldt, A.T. Sack
23. **Schizophrenia-associated microdeletion dynamically disrupts communication to the auditory cortex through microRNA-dependent mechanisms,** S. Chun, I. Bayazitov, J. Blundon, *S.S. Zakharenko*
24. **Neural representations of background speakers at the cocktail party,** *K.C. Puvvada,* J.Z. Simon
25. **Causal role of primate auditory cortex in auditory perceptual decision-making,** *J. Tsunada,* A. S. Liu, J.I. Gold, Y.E. Cohen
26. **Enhanced cognitive flexibility in reversal learning induced by removal of the extracellular matrix in auditory cortex,** *M.F.K. Happel*, H. Niekisch, L.L. Castiblanco, F.W. Ohl, M. Deliano, R. Frischknecht
27. **Microstimulation of frontal eye field in concert with saccades to visual or auditory targets,** *V.C. Caruso,* D.S. Pages, J.M. Groh
28. **Neural correlates of auditory discriminations in the auditory cortex of behaving macaque monkeys,** *C.W. Ng,* J.A. Overton, G.H. Recanzone
29. **Intracranial recordings reveal spatial and temporal differences in the processing and categorization of speech,** *A.E. Rhone*, B. McMurray, H. Oya, K.V. Nourski, H. Kawasaki, M.A. Howard III
30. **Auditory-tactile integration in temporal frequency discrimination,** *J. Huang,* Y. Zhang, M.E. Reinhardt, S. Hsiao, X. Wang
31. **Neural correlates of musical memory: an ECoG study on musical imagery,** *Y. Ding,* B. Hong, J. Huang, X. Wang
32. **Neural discrimination of sequences of sounds during acute coma,** A. Tzovara, A. Simonin, N. Cossy, A.O. Rossetti, M. Oddo, *M. De Lucia*
33. **Spectral templates for encoding harmonic structure in marmoset auditory cortex,** *L. Feng,* X. Wang
34. **Rapid task-related plasticity of spectrotemporal receptive fields in the auditory midbrain,** *S.J. Slee,* S.V. David

Supported by funding from: NIDCD, Tucker-Davis Technologies, Wellcome Trust

35. **Nonlinear spectro-temporal and spatio-temporal integration of natural stimuli in primary auditory cortex,** I. Thorson, *S.V. David*
36. **High-resolution fMRI phase-mapping of azimuth space in rhesus monkey auditory cortex,** *M. Ortiz,* T. Steudel, N.K. Logothetis, J.P. Rauschecker
37. **Oxytocin receptor expression in the rodent central nervous system,** *M. Mitre,* S. Norden, R.C. Froemke, M.V. Chao
38. **The song in your head: identifying tonal frequency patterns in auditory cortex,** *J.M. Thomas,* I. Fine, G.M. Boynton
39. **Auditory streaming in rhesus macaques,** *K.L. Christison-Lagay,* Y.E. Cohen
40. **Regional tuning to interaural time and level difference in human auditory cortex,** *N.C. Higgins,* S.A. McLaughlin, G.C. Stecker
41. **Cortical neurons segregate competing sound sequences with high spatial acuity,** *J.C. Middlebrooks,* P. Bremen
42. **Investigating auditory processing in conscious awake marmosets using fMRI,** *C.R. Toarmino,* C.T. Miller, C.C.-C. Yen, D.A. Leopold, A.C. Silva
43. **Monkeys can localize more than one simultaneous sound, but how they do it is mysterious: behavior and neural activity in the inferior colliculus,** *J. Lee,* R. Estrada, S. Tokdar, J.M. Groh
44. **Streams of sound: a synfire sequence detector that performs auditory grouping,** *S. Steele,* J. Rinzel
45. **Neural representations of visual stimuli in human auditory cortex correlate with illusory auditory perceptions,** *E. Smith,* S. Duede, S. Hanrahan, T. Davis, P. House, B. Greger
46. **Pre-stimulus phase affects auditory perception during continuous-mode processing,** *M. Henry,* B. Herrmann, J. Obleser
47. **Neural oscillatory dynamics reveal distinct mechanisms underlying auditory perception of time,** *B. Herrmann,* M. Henry, M. Grigutsch, J. Obleser
48. **Neural correlates of hearing in noise in macaque auditory cortex,** *S. Bennur,* Y.E. Cohen
49. **Neural correlates of proactive interference in primate A1 during auditory short-term memory,** *J. Bigelow,* B. Rossi, I. Zdilar, A. Poremba
50. **Recovery of central auditory function in mice following profound peripheral deafferentation: a combined behavioral and neurophysiological study,** *A.R. Chambers,* Y. Yuan, A.S. Edge, M.C. Liberman, D.B. Polley
51. **Sensitivity of macaque auditory cortical neurons to amplitude modulation as a function of modulation frequency and duration,** *K. O'Connor,* J.A. Verhein, M. Niwa, M.L. Sutter
52. **Stimulus quality modulates primate auditory recognition memory and PFC activity,** *B. Rossi,* J. Bigelow, B. Plakke, A. Poremba
53. **Evidence of voluntary vocal control by the common marmosets (*Callithrix jacchus*),** *L. Zhao,* S. Roy, X. Wang
54. **Cortical oscillations and spiking activity associated with Artificial Grammar Learning in the monkey auditory cortex,** *Y. Kikuchi*, A. Attaheri, A. Milne, B. Wilson, C.I. Petkov
55. **Cellular and laminar specificity of stimulus-specific adaptation in the primary auditory cortex,** *R.G.Natan,* L. Mwilambwe-Tshilobo, M.N. Geffen
56. **Neural correlates of sensory memory in auditory cortex,** *S. Akram,* B. Englitz, C. Chambers, D. Pressnitzer, J.Z. Simon, S.A. Shamma
57. **Independent or integrated processing of interaural time and level differences in human auditory cortex?** *C.F. Altmann,* S. Terada, M. Kashino, T. Mima, H. Fukuyama, S. Furukawa
58. **Amplitude-modulation tuning in the auditory midbrain provides a robust mechanism for vowel coding,** *L.H. Carney,* T. Li, J. McDonough
59. **Dynamics of synaptic circuits in the mouse auditory cortex,** K. Moczulska, D. Aschauer, Y. Loewenstein, *S. Rumpel*
60. **Spectral and spatial tuning of onset and offset responses in the auditory cortex of awake macaque monkeys,** *D.L. Ramamurthy*, C.W. Ng, D.T. Gray, J.A. Overton, G.H. Recanzone
61. **Reversible inactivation of primary auditory cortex by cooling in the awake, behaving ferret: effect on sound localisation ability,** *K. Wood*, S. Town, H. Atilgan, J. Bizley
62. **Visual modulation of neurons in voice-sensitive auditory cortex and the superior-temporal sulcus,** *C. Perrodin,* C. Kayser, N.K. Logothetis, C.I. Petkov
63. **Corticostriatal synaptic weights encode arbitrary associations between stimuli and motor responses during auditory discrimination,** *Q. Xiong,* P. Znamenskiy, A.M. Zador
64. **Dopamine modulates auditory responses in the inferior colliculus in a heterogeneous manner,** *C. Portfors,* J. Gittelman, D. Perkel
65. **Epigenetic regulation of remembering what: an account of neuroplasticity in auditory cortex that links histone-deacetylase regulation of gene expression to sound-specific behavior,** *K. Bieszczad,* K. Bechay, E. Gregor, J.R. Rusche, N.M. Weinberger, J.L. McGaugh, M.A. Wood
66. **Noise correlations and invariance to basic acoustic transformations of vocalizations in the auditory cortex,** *I.M. Carruthers,* R.G. Natan, D. Jaegle, L. Mwilambwe-Tshilobo, D.A. Laplagne, M.N. Geffen

67. **Effects of noise exposure on sound processing in the mouse primary auditory cortex,** *O. Zelenka,* O. Novak, T. Hromadka, J. Syka
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69. **Whole field spatial receptive fields measured with spatially dense acoustic stimuli in marmoset auditory cortex,** *E. Remington,* X. Wang
70. **Timbre discrimination in ferrets: exploring the neural basis of perceptual constancy,** *S. Town,* K.C. Wood, J.K. Bizley
71. **Encoding of sound frequency and location in human subcortical structures: preliminary results using functional MRI at 7T,** *M. Moerel,* F. De Martino, R. Santoro, E. Yacoub, E. Formisano
72. **Decoding working memory for pitch of pure tones in auditory cortex,** *S. Joseph,* S. Kumar, A. Halpern, M. Husain, T.D. Griffiths
73. **The phase of low-frequency cortical activity is involved in the detection, discrimination, feature encoding, and behavioral dissimilarity of natural sounds,** *B.L. Giordano,* R.A.A. Ince, A. de Cheveigné, J. Gross, P. Belin, S. Panzeri
74. **Oxytocin-based neuromodulation of mammalian social behavior,** *B.J. Marlin,* R.C. Froemke
75. **Layer 6 corticothalamic projections actively maintain sound selectivity in the lemniscal subdivision of the medial geniculate body but provide gain control to a non-lemniscal subdivision,** *A.R. Clause,* D.B. Polley
76. **The role of ventral prefrontal cortex in auditory, visual and audiovisual working memory,** *B. Plakke,* J. Hwang, M.D. Diltz, L.M. Romanski
77. **Responses of prefrontal multisensory neurons to mismatching faces and vocalizations,** M.M. Diehl, M.D. Diltz, *L.M. Romanski*
78. **Differential encoding for species-specific vocalizations along the ventral auditory cortical stream,** *M. Fukushima,* R.C. Saunders, D.A. Leopold, M. Mishkin, B.B. Averbeck
79. **Population receptive field analysis of auditory frequency tuning in early blind individuals,** *E. Huber,* J.M. Thomas, I. Fine
80. **(De-)Constructing the ERP: Phasic excitability changes measured by psychophysics,** *C. Daube,* M.J. Henry, J. Obleser
81. **Functional connectivity within and across structures in the barn owl midbrain in response to auditory and visual stimulation,** *D. Totten,* W. DeBello
82. **Hearing the light: a behavioral and neurophysiological comparison of two optogenetic strategies for direct excitation of the central auditory pathways,** *W. Guo,* J.X. Chen, N. Klapoetke, B. Shinn-Cunningham, E. Boyden, D.J. Lee, D.B. Polley
83. **Auditory cortical GAD65 regulates gap detection behavior in mice,** *A. Miyakawa,* S. Yang, S.-J. Cho, S. Bao
84. **Eye position influences on auditory processes measured from within the external ear canal,** *K.G. Gruters,* C.A. Shera, J.M. Groh
85. **Discriminating an auditory "figure" from "ground": an MEG study,** *S. Teki,* C. Payne, T.D. Griffiths, M. Chait
86. **Socially induced increases in the inferior colliculus of male mice correlate with the behavior of female partners,** *S. Keesom,* L.M. Hurley
87. **The functional organization of human non-primary auditory cortex,** *S. Norman-Haignere,* J. McDermott, N. Kanwisher
88. **The effects of distortion in auditory fMRI research: measurements and solutions,** *S. Norman-Haignere,* N. Kanwisher, J.H. McDermott
89. **Changes in mutual information, redundancy, and stimulus selectivity of simultaneously recorded neurons in the developing auditory cortex,** *B.F. Albanna,* M.N. Insanally, S. Bao, M.R. DeWeese
90. **Macaque brain areas related to auditory-motor circuits show increased activity in response to sounds with a regular versus an irregular beat,** *S. Baumann,* M. Grube, T.D. Griffiths
91. **Measurement of pitch discrimination thresholds in the common marmoset (*Callithrix jacchus*),** *X. Song,* M.S. Osmanski, X. Wang
92. **Local field potentials reveal novel multisensory interactions in cat cortex,** *J. Krueger Fister,* L.R. Kurela, A.R. Nidiffer, W.H. Lee, T.A. Kackett, M.T. Wallace
93. **Smooth-pursuit eye movements of auditory targets suggest motion-specific processing,** C. Cloninger, E. Clark, P. Allen, W. O'Neill, *G. Paige*
94. **Spatiotemporal cortical representation of phonological units in continuous speech perception,** *R. Xu,* C. Song, B. Hong
95. **Dimensionality of neuronal response to complex sound in rat inferior colliculus,** W. Tang, R. Xu, *B. Hong*
96. **The effects of adult visual deprivation on multisensory integration in the cat superior colliculus,** *L.R. Kurela,* J. Krueger Fister, A.R. Nidiffer, M.T. Wallace
97. **Neural population decoding of sound source location in the face of changes in sound level,** *M.L. Day,* B. Delgutte

Title

Neural correlates of sensory memory in auditory cortex

Authors

S. Akram[1, 2], B. Englitz [1, 2], C. Chambers [3], D. Pressnitzer [3] , J. Z. Simon[2]. A. Shamma [1, 2]

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Abstract

The perception of an auditory stimulus can be strongly influenced by its immediate context in a variety of ways.An effective way to study contextual effects is to vary them while holding fixed an ambiguous stimulus. A compelling example of such an ambiguous stimulus is a sequence of two octave-spaced tone-complexes (Shepard tones) that are spectrally shifted relative to each other by half an octave. This two-tone sequence can be perceived as ascending or descending in pitch depending on preceding sounds that act as a "biasing context". Specifically, previous psychoacoustic experiments have shown that a preceding sequence of appropriately shifted tones leads to stable and compelling shifts in pitch direction depending on the details of the biasing tones.

Here, we investigate the neural mechanisms underlying this phenomenon using Magnetoencephalography (MEG) recordings in humans. We show diagnostic probe sequences inserted between the biasing sequence and the ambiguous Shepard tone-pair, collocated in frequency bands activated by the biasing sequence reveals a strong suppression of their response compared to frequency regions, not preceded by the biasing sequence. Moreover, this suppression lasts over multiple seconds and its relative strength is correlated with the behavioral performance of the listeners.

These results suggest that the short-term contextual effects produced by the biasing sequence are neurally encoded as a sustained depression (rather than an enhancement of sensitivity) in specific frequency channels of the auditory cortex, and that this suppression in turn strongly influences the decision of the listeners regarding the perceived pitch-shift direction of the Shepard tones

Changes in mutual information, redundancy, and stimulus selectivity of simultaneously recorded neurons in the developing auditory cortex.

Badr F. Albanna[1,2], Michele N. Insanally[4,5], Shaowen Bao[3], Michael R. DeWeese[1,2,3]

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Recent studies have used information theoretic tools in mammalian animal models to examine the mutual information between auditory stimuli and neural responses, the redundancy of different neural responses to the same stimuli, and the information theoretic stimulus selectivity of neural responses (Chechik et al. 2006, Montgomery & Wehr 2010). In this study, we expand upon previous investigations by tracking these quantities over the course of development using simultaneously recorded multiunit activity to directly evaluate information measures for a population of neurons across auditory cortex. We employ a novel application of the Agglomerative Information Bottleneck method to group stimuli in a way that preserves as much of the mutual information between the stimulus and response (Slonim & Tishby 1999). Using this method, we find that each of the information measures is extremely dynamic. Mutual information peaks during the third week of postnatal development. Although we find most cortical sites encode independent information throughout development, there is a marked increase in the redundancy of multiunit sites at the beginning of the third week which persists in a diminished form even as the mutual information decreases. Throughout development, neurons separated by a greater distance exhibit less redundancy on average than those closer together, however during the third postnatal week, we observe a higher level of redundancy for sites separated by more than one octave. Taken together, these results indicate that the third week of postnatal development is crucial in the evolving relationship between neural activity and acoustic stimuli commensurate with previously reported changes in receptive field properties during this window (Insanally et al. 2009, Dorrn et al. 2010). Perhaps surprisingly, none of the observed measures exhibit a simple monotonic relationship over development suggesting that the stimulus representation changes from early life into adulthood only after a period of heightened cortical interdependence and sensitivity to external stimulus features.

Independent or integrated processing of interaural time and level differences in human auditory cortex?

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Terada, Satoshi (b)
Kashino, Makio (c)
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Fukuyama, Hidenao (a)
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Sound localization in the horizontal plane (left/right) is mainly determined by two cues: interaural time differences (ITD), i.e., the difference in sound arrival times caused by a difference in distance from the two ears to the sound source; and interaural level differences (ILD), the difference in sound intensity caused by the head shadowing the sound at the far ear.
Both cues result in an estimate of sound source lateralization and in real-life situations these two cues are usually congruent, i.e., not contradictory. When stimulating listeners with head phones it is possible to counterbalance the two cues, so called ITD/ILD trading. This phenomenon speaks for integrated ITD/ILD processing at the behavioral level. However, it is unclear at what stages of the auditory processing stream these ITD and ILD cues are integrated to provide a unified percept of sound lateralization.
Therefore, we set out to test for integrated versus independent ITD/ILD processing with human electroencephalography (EEG) by measuring the mismatch negativity (MMN) to changes in sound lateralization. The MMN is a negative deflection of the evoked potential obtained at fronto-central electrodes about 100-250 ms after a deviant in a series of stimulus repetitions, proposed to be generated within bilateral superior temporal lobes. We presented a series of diotic standards (perceived at a midline position) that were interrupted by deviants that entailed either a change in a) ITD only, b) ILD only, c) congruent ITD and ILD, or d) counterbalanced ITD/ILD (ITD/ILD trading). The sound stimuli were either i) pure tones with a frequency of 500 Hz, or ii) amplitude modulated tones with a carrier frequency of 4000 Hz and a modulation frequency of 125 Hz. The traded ITD/ILD stimuli were determined individually for each subject in a psychophysical experiment before the EEG study. During the EEG study, subjects were presented with the sound stimuli while watching a silent movie with sub-titles.
We observed significant MMNs for the ITD/ILD traded deviants. Thus, even though behaviorally these stimuli were perceived as originating from a midline position, and therefore should not have constituted a spatial deviant, the observed MMN suggests that these stimuli activated change-detectors in auditory cortex. This speaks for at least partial independent processing of ITD and ILD at the level of the MMN within auditory cortex.

Behavioral and neural effects of silencing the auditory cortex in adult ferrets using optogenetics

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Massachusetts Institute of Technology, Depts. of Biological Engineering and Brain and Cognitive Sciences (Boyden)

The role of the primary auditory cortex (A1) in accurate sound localization has been demonstrated by lesions and reversible inactivation lasting minutes to days depending on the cooling or pharmacological techniques employed. We aimed to silence cortical neurons in A1 of adult ferrets with high temporal precision using the light-sensitive proton pump archaerhodopsin (Arch), in order to examine the effects of light-induced inactivation on performance in a sound localization task.

Arch was expressed in cortical neurons in ferret A1 (n=5) after viral vector injections whose placement was guided by neural recordings. The vectors used were a lentiviral vector and an AAV vector tagged with GFP. Arch expression was validated by GFP immunocytochemistry (n=3). GFP-positive cell bodies were found in A1 at the injection sites, and profuse labeled axons and terminals were observed in auditory cortical projection targets, including the medial geniculate body at the level of the thalamus and the inferior colliculus at the level of the midbrain. Both constructs produced similar labeling, although GFP expression was more abundant using the AAV vector.
Effectiveness of neural inactivation was confirmed in an acute experiment in which A1 activity driven by acoustic stimulation (broadband noise and pure tone bursts) was suppressed or reduced by illumination with green laser light (200 micrometer multimode optic fiber coupled to a lambda=532 nm DPSS laser, 5 mW intensity measured at the tip of the fiber).

In two ferrets trained by positive conditioning to localize sound in the horizontal plane in a 12-choice 360º task, a fiber optic was chronically implanted in the high frequency region of A1 previously injected with the viral vectors. We observed the effects of cortical inactivation by randomly coupling laser illumination with stimulus presentation on half of the trials (broadband or high-frequency narrowband stimuli of 40-2,000 ms duration). The proportion of correct responses was reduced and mean errors were larger at shorter sound durations (40, 100 and 200 ms) when light inactivation was coupled with narrowband noise stimuli centered on 16 kHz, but not when broadband noise was used.

These results suggest that silencing neurons in the auditory cortex impairs the ability of ferrets to localize sound in a selective, temporally-specific and reversible manner. Our study lays the groundwork for the use of optogenetic manipulation of neural activity as a means of investigating auditory function in the ferret.

The Wellcome Trust & Action on Hearing Loss
Key words: ferret; behaviour; sound localization; optogenetics, Arch

Characterizing Central Auditory Neurons in *Drosophila*

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Drosophila use acoustic communication signals during courtship, but little is known about the representation of sound in central auditory pathways. We have identified novel central auditory neurons whose processes overlap with the axon terminals of primary auditory neurons. We are investigating the synaptic inputs and receptive field properties of these neurons using *in vivo* whole-cell patch clamp recordings, a combination of acoustic and piezoelectric stimuli, and genetic inactivation of afferent auditory neurons. Our preliminary findings indicate that these central auditory neurons encode low-frequency amplitude modulations and that the preferred modulation frequency varies across the population. Pharmacological experiments suggest that GABAergic inhibition plays a key role in shaping these diverse responses. Based on these neurons' receptive field properties, we hypothesize that they receive convergent inputs from a functionally heterogeneous set of primary auditory neurons. These findings shed light on how auditory neurons in any system extract the relevant features of acoustic stimuli.

Macaque brain areas related to auditory-motor circuits show increased activity in response to sounds with a regular versus an irregular beat

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Data in humans suggest that activities requiring the interaction of auditory and motor systems in speech and music activate an auditory-motor network of cortical areas including the premotor cortex, posterior auditory cortex and basal ganglia. The processing of rhythmic auditory stimuli seems to be a particularly strong driver of this auditory-motor network. Whether the same brain structures play a similar auditory-motor role in non-human primates that lack the ability of speech and music production is controversial. As a first step, we investigated whether the passive presentation of regular, rhythmic sounds is sufficient to activate areas in macaques that are homologue to the human auditory-motor network. We measured the blood oxygen level dependent (BOLD) signal across the brain with fMRI during the presentation of regular sound beats and compared it to the presentation of irregular beats as a control. The regular beats consisted of noise bursts presented at a regular frequency of 2 Hz while the irregular beats were based on the same stimuli but the regularity was abolished by applying a random jitter between 0-30 %. During the presentation of the sound stimuli, the animal was involved in an unrelated visual fixation task.

Both auditory conditions compared to silence showed robust BOLD responses in the auditory system with additional activity being observed in extra-auditory brain structures including motor related areas. A comparison of regular versus irregular sound bursts showed increased responses in the premotor cortex and the posterior auditory cortex (area Tpt). The results suggest that in monkeys regular sound bursts have the ability to drive responses in brain areas that also show increased activity in rhythm processing and general auditory-motor tasks in humans. These findings support the idea basic auditory-motor processes have a common neuronal basis in primates even in absence of speech.

In a next step we want to test the influence of an active involvement of the animals in rhythmic tasks on the auditory-motor network.

Distinct Roles of Anterolateral and Posteromedial Heschl's Gyrus in Coding Human Voice Fundamental Frequency

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The human core auditory cortex within posteromedial Heschl's gyrus (HG) was previously shown to code repetitive transients by phase-locking to periodic stimuli such as click trains. The phase-locking capacity of the core was characterized by looking at the frequency following responses (FFRs) in average evoked potentials (AEPs) and event-related band power (ERBP) recorded using hybrid depth electrodes (low and high-impedance) chronically implanted in gray matter of HG in human patients undergoing surgical evaluation for medically intractable epilepsy. The FFR responses were shown to be strongest at click rates below 50 Hz but reliably detectable at click rates as high as 200 Hz in the posteriomedial HG. However, recording from the anterolateral HG showed no evidence of FFR responses even to click rates as low as 25 Hz. In the present study, we used the same electrode implantation setup to simultaneously record from the posteromedial and anterolateral HG while 6 human patients actively produced a steady vowel vocalization (/a/) and passively listened to the playback of their own self-generated sounds. The mean voice fundamental frequency (F0) in these subjects ranged from 90 to 140 Hz. The FFR responses to voice F0 (F0FFR) were calculated by averaging the extracted narrow-band (bandwidth: 10 Hz) spectral power of the ERBPs at voice F0 across each individual trial. Analysis of the data for passive listening condition yielded nearly similar results to that of click train stimuli, meaning that the high-magnitude F0FFRs were present at core auditory cortex within posteromedial HG and declined or were absent in anterolateral HG. During active vocal production, the F0FFR responses in posteromedial HG had relatively similar magnitudes to those during passive listening. However, limited regions within anterolateral HG showed significantly stronger F0FFR responses during active vocalization compared with passive listening. This finding indicates that the functional capacity of the auditory cortex within anterolateral HG for phase-locking to repetitive transients in human voice can be modulated during active production of vocalization or speech. The underlying mechanisms of such modulatory effects are unknown but they suggest the importance of coding the behavioral aspects of voice F0 for effective vocal communication in humans. The enhanced F0FFR response in anterolateral HG can possibly contribute to better vocal controlling mechanisms that use auditory feedback information to produce a stable vocal output during speech production.

Neural correlates of hearing in noise in macaque auditory cortex

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The perception of sound in a noisy environment is a critical function of the auditory system. Previously, we trained monkeys to report the presence of a tone embedded in co-modulated noise masker. The monkeys were trained to participate in two tasks: the 'target-in-noise' and the 'noise-only' task. In the target-in-noise task, a target tone was presented in a background of masking noise. Monkeys indicated hearing the target by releasing a lever after target offset. We varied the relative difficulty of this task by varying the target-tone level between 60 dB SPL and 85 dB SPL in intervals of 5 dB SPL, whereas the level of the masking noise was kept constant at 60 dB SPL. Trials of the noise-only task were catch trials and only the masking noise was presented; monkeys were instructed to maintain their hold on the lever during these trials. We found that the monkeys' performance varied as a function of target level (relative to masker level) as quantified with a psychophysical curve and a d' analysis.

Here, we describe results from our study into the link between neural activity in the auditory cortex and the hearing-in-noise tasks described above. We recorded neural activity from single neurons in the core auditory cortex (i.e., A1) while monkeys were participating in these tasks. Neural recordings were conducted with tetrodes, and the frequency of the target matched the best frequency of the recorded auditory neuron. We found that the relative intensity of the target tone in the presence of the noise masker significantly modulated the response of A1 neurons. In contrast, the presentation of the target sound alone did not elicit a significant response from A1 neurons. This suggests a task-relevant contextual modulation of A1 responses during hearing in noise. Additionally we found no correlation between the monkey's behavioral choices - as assessed by their responses on choice trials - and A1 activity. Our results suggest that the encoding of a sound of interest in the presence of a noise masker is an active process, providing new insights into the neural basis for hearing in noise in the auditory system.

Epigenetic regulation of remembering *what*: An account of neuroplasticity in auditory cortex that links histone-deacetylase regulation of gene expression to sound-specific behavior.

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Epigenetic mechanisms have come to the forefront of neurobiological investigations in learning, memory and neural plasticity. Chromatin modifications, e.g., via histone acetylation by transferases (HATs) and deacetylases (HDACs), engage in the adult brain in an experience-dependent way to robustly modify neuronal function, and ultimately, animal behavior. For example, a histone deacetylase called HDAC3 is an essential determinant of long-term memory formation: it can transform what would otherwise have been forgotten into a robust memory that persists even beyond the point at which normal long-term memory fails. However, despite significant advances to identify the genes critical for memory formation that are regulated by HDAC3, vastly unknown is the form of neural plasticity that actually links HDAC3-regulated gene expression to long-lasting effects on behavior. While transcription is necessary for establishing stable changes in plasticity, neuronal plasticity is the substrate of memory that ultimately drives long-term changes in behavior. Here we show in primary auditory cortex (A1), the first report of a precise locus and form of HDAC3-mediated neuroplasticity. Rats were subjected to a pharmacological block of HDAC3 (RGFP966; 10 mg/kg) while learning to associate sound with reward (vs. a vehicle-treated group). Sound A was a signal to press a lever, which activated a delivery mechanism (Sound B) that produced reward. Thus, Sound A and B predict reward. Because inhibition of HDAC3 by RGFP966 increases acetylation, and increases transcription, it was expected to enhance memory for "*what acoustic frequency*" is associated with reward. Indeed, a frequency-specificity test after training to asymptotic levels of performance revealed behavioral responses that were enhanced to Sound A and B frequencies over other non-signal frequencies. Thus, RGFP966-treated rats had more specific memory for sounds associated with reward. Moreover, cortical remodeling of acoustic frequency-representation in A1 (measured electrophysiologically) linked to these changes in frequency-specific behavior (auditory memory). RGFP966 mediated highly specific representational plasticity in A1 by tonotopic expansion of Sound A & B *frequencies*, and unexpectedly, also their *intensities*. Combined with reports that A1 plasticity underlies formation of auditory-specific memory, these results support that HDAC3-inhibition mediates the formation of robust memory by engaging neural plasticity that better encodes multiplex features of transient experiences. This reveals a potential neural explanation for the formation of specific memory. Furthermore, it introduces epigenetic mechanisms in the regulation of A1 plasticity and cortical reorganization and A1 as a model for studying specific neural plasticity that links epigenetics to behavior.

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Keywords: epigenetics, auditory cortex, memory

Neural correlates of proactive interference in primate A1 during auditory short-term memory

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Within the past several decades, the known functions of the auditory cortex have expanded to include learning and memory (Poremba & Bigelow, 2013; Weinberger, 2010). This includes the observation that the activity of some auditory cortical neurons is correlated with retention and recognition phases of auditory short-term memory (STM) tasks (Gottlieb et al., 1989; Sakurai, 1990, 1994). We recently conducted an experiment in which neurophysiological activity was recorded in the auditory cortex of two monkeys performing an auditory STM task. Each trial began with a sample sound, which was followed by a 5-s retention interval. A test sound was then presented, and the monkeys were trained to indicate whether it was identical to ("match") or different from ("nonmatch") the sample. Consistent with previous results, we observed correlates of auditory recognition at the neuronal population level: evoked firing rates during the latter cue presentation and cue offset periods were relatively enhanced when the test sound matched the sample. In several behavioral studies (Bigelow & Poremba, 2013), we have observed that monkeys are more likely to make an incorrect "match" response on a nonmatch trial if the test stimulus had also occurred on the prior trial. This phenomenon, known as proactive interference (PI), has been observed in a variety of STM tasks in humans and animals (Wright et al., 1986). However, to our knowledge, there have been no investigations of the effects of PI at the neurophysiological level in animals. In the current study, we investigated the possibility that PI would affect multi-unit activity (MUA) recorded from the auditory cortex of two monkeys performing an auditory STM task. One of 12 stimulus sets containing 10 sounds each was used for each session. Each stimulus set included two pulsed white-noise stimuli plus one exemplar from each of the following sound types: conspecific vocalizations, human vocalizations, animal vocalizations, environmental sounds, pure tones, synthetic sounds, music clips, and band-passed noise. As each session consisted of 200 trials, the 10 sounds occurred on multiple trials throughout the task. Consistent with previous results, accuracy fell significantly on nonmatch trials when the test stimulus had also occurred on the previous trial. On these trials, there was a small but significant increase in the MUA beginning near the end of the test stimulus period, similar to that observed on match trials. These results extend the evidence that the auditory cortex is part of the cortical network involved in auditory STM, and reveal that it is susceptible to the influence of PI from previous cues, which are irrelevant to the current trial.

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Key words: awake, monkey, multi-unit, neuronal recordings, primary auditory cortex, rhesus macaque

Nonauditory task-related modulations of neuronal activity in auditory thalamus and cortex in freely moving rat

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Sensory cortices and their associated thalamic nuclei are traditionally thought to be primarily concerned with modality-specific stimulus representation. Here we present evidence that auditory thalamus and cortex can also encode a variety of signals relating to behavioral events. We recorded single units in auditory thalamus and cortex of freely moving rats as they performed an auditory cue-driven task. Rats were trained to move toward one of two reward ports depending on the identity of simple sounds. The relation between stimulus and reward port was periodically switched, forcing the rats to alter their sound-action associations and hence providing a model of behavioral flexibility. In addition to representing auditory stimuli, the activity of many cortical neurons showed modulations that correlated with task-related events such as trial initiation, behavioral choice, reward, and trial history. Surprisingly, such task-related activity was also prevalent in the thalamus. We speculate that these modulations arise from frontal areas involved in cognition and/or motor preparation, and may serve to integrate sensory information with behavioral output. Our data support a conceptual shift away from the view of auditory thalamus and cortex as merely sensory way-stations along a feedforward pathway, and instead suggest that they may be inextricably involved in non-sensory aspects of decision making.

Amplitude-modulation tuning in the auditory midbrain provides a robust mechanism for vowel coding

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Models for neural coding of speech sounds tend to focus on the representation of the spectrum in discharge patterns of the auditory periphery or lower levels of the ascending pathway. Here we show that at the level of the midbrain, rate-based tuning for amplitude-modulation plays a role not only in the representation of temporal envelopes, but also in robust coding of voiced speech sounds. Amplitude-modulation (AM) frequency tuning first appears in ascending auditory pathway at the level of the auditory midbrain (inferior colliculus, IC). Approximately 50% of IC neurons have band-pass modulation transfer functions (MTFs), and the other 50% have low-pass, band-reject or high-pass MTFs. A computational model derived from the same-frequency inhibitory-excitatory model (Nelson and Carney, JASA 2004, 116:2173) is able to explain all of these MTF types. Bandpass AM tuning in the original model is derived from the dynamics of excitatory and inhibitory inputs to IC neurons, with excitation arising from the auditory brainstem (i.e. cochlear nucleus or superior olive) and similar inhibitory inputs relayed by interneurons. In the extended model presented here, the other MTF types are created by combining the brainstem excitatory inputs and inhibition from the bandpass MTFs. The best modulation frequency of the bandpass inhibition determines the shape of the other MTFs. A population model based on these model neurons provides robust representations of a wide range of vowels across a large range of sound levels and in background noise.

Noise Correlations and Invariance to Basic Acoustic Transformations of Vocalizations in the Auditory Cortex

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Many behaviorally important acoustic signals, such as USVs or speech, undergo acoustic transformations when presented in varying environments or produced by different speakers. In order to create a representation of a complex acoustic signal, the auditory system needs to exhibit invariance to acoustic transformations that do not change the object identity. Mixed evidence exists on whether the primary auditory cortex (A1), a key auditory processing area, exhibits invariance to basic temporal and spectral transformations of con-specific vocalizations. Here, we test whether populations of neurons in A1, recorded in awake rats, exhibit invariance to transformations in the basic acoustical features of rat ultra-sonic vocalizations (USVs). We find that, while not demonstrating invariant representation directly, the population code in A1 contains enough information for a circuit just one synapse up to construct an invariant representation. Furthermore, we show that population activity, including noise correlations between neurons, improves discrimination of USVs.

In order to evaluate how the population code of primary auditory cortex facilitates invariant representations of similar stimuli, we recorded simultaneous neuronal activity from ensembles of 5-20 units in A1 in response to a set of USV, presented both in the original and in transformed versions, in which the amplitude- and frequency-modulation rates had been increased or decreased. We compared the classification accuracy of support vector machines (SVMs), which were fit and tested on each stimulus condition. We found, as expected, that the classification accuracy was significantly higher when the SVM was tested on the same stimulus condition on which it was trained. We also found that the performance of the SVM, when trained to and tested on different conditions, was significantly above chance. Thus, neural representation of USVs allows neurons as little as a single synapse higher in the auditory hierarchy to be invariant to temporal transformations in USVs.

In order to evaluate how noise-correlations in neural responses may facilitate decoding, we presented a series of 350 USVs. After training to distinguish between 1-s long segments of the USV series based on the neural data, the classification performance of SVMs was significantly decreased with the elimination of the noise-correlations. Therefore, noise-correlations improve the accuracy of potential classification neurons higher in the processing hierarchy.

Our data demonstrate the importance of population neuronal codes in creating invariant representations of complex sounds within and beyond the auditory cortex.

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Microstimulation of Frontal Eye Field in concert with saccades to visual or auditory targets

We localize events in the world by integrating signals from multiple sensory modalities. Visual and auditory targets alone can both effectively direct our gaze, yet auditory signals in the Frontal Eye Field are weaker than visual signals and occur in a smaller subpopulation of neurons. They are also less well aligned to an eye-centered reference frame than visual signals (Caruso, Pages, Groh, SfN 2011).

This poses an interesting problem for the read out of FEF by downstream brain areas specifying the final movement vector of a saccade. Is there a modality-specific gain modulation that allows the weak auditory activity to effectively guide saccades similar in metrics and kinematics to visual ones, or does the readout normalize away modality differences in target-evoked activity via a weighted averaging/center of mass extraction schema? And in the latter case, when and where is the normalization for level of activity performed?

Probing the readout of the FEF with microstimulation in concert with visual and auditory targets can shed light on these questions. We previously showed that supra-threshold micro-stimulation paired with visual and auditory targets gave rise to "combined" saccades akin to a weighted averaging of the saccades evoked by either the target or stimulation alone, but the contribution of the auditory target was much weaker than that of the visual target in comparison to the stimulation. These data are consistent with a center of mass extraction but do not rule out the possibility that the activity read out from FEF is homogeneously enhanced during auditory saccades (Caruso, Pages, Groh, SfN 2012).

Here we microstimulated in the subthreshold-to-threshold range, again pairing with visual or auditory targets, to test for the presence of a modality-specific gain acting on the whole FEF. Such gain would enhance the effect of the low intensity stimulation when paired with auditory (but not visual) targets, thus shortening the saccade reaction time of the "combined" saccades in the presence of an auditory (but not visual) target.

We observed no effect on saccade reaction times due to the low intensity stimulation in either condition. The low intensity stimulation gave no contribution to the combined saccade in the presence of a visual target but interacted with an auditory target in a way consistent with weighted averaging.

These results are most consistent with a read-out mechanism for the FEF that does not rescale the activity, but weights all its components including the activity due to subthreshold stimulation according to the vigor of that activity.

AMPLIFIED CORTICAL, BUT NOT THALAMIC, SOMATOSENSORY AND VISUAL PROJECTIONS TO THE ANTERIOR AUDITORY FIELD FOLLOWING EARLY- OR LATE-ONSET DEAFNESS

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Investigations of the cortical consequences of deafness show that secondary auditory cortical areas cross-modally reorganize to exhibit visual or somatosensory responsiveness. This reorganization may be related to the onset of deafness. However, recent studies have found that this plasticity is not restricted to secondary cortical regions, but can also be identified in core auditory areas. Specifically, in early-deaf cats, tactile and visual stimuli evoke activity in the anterior auditory field (AAF). The purpose of this investigation was to examine possible alterations in thalamic and cortical projections to AAF that may underlie the crossmodal plasticity identified following early-onset deafness. To accomplish this, we deposited a retrograde tracer (biotinylated dextran amine) in AAF of early-, late-deaf, and hearing cats (*n*=5 per group). We found that 1) compared to late-deafness, early-deafness results in a greater amplification of cortical somatosensory and visual projections to AAF, 2) following deafness, there is a greater amplification of somatosensory, than visual, projections to AAF, 3) the anterior ectosylvian visual area is the only visual area with amplified projections to AAF following deafness, 4) projections to AAF from primary auditory cortex and the dorsal zone decrease following both early- and late-onset deafness, and 5) thalamocortical projections to AAF were similar in both hearing and deaf subjects. In total, the results show that the deafness primarily alters cortical, but not thalamic, projections emerging from somatosensory and visual regions.

Recovery of central auditory function in mice following profound peripheral deafferentation: a combined behavioral and neurophysiological study

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Adult brains show a remarkable ability to reorganize in response to peripheral nerve injury. This adaptive plasticity may allow for a partial restoration of sensation over the course of recovery. In the auditory system, deafferentation due to spiral ganglion neuron (SGN) degeneration occurs as a natural consequence of aging, in cases of acoustic trauma, and in auditory neuropathy spectrum disorder (ANSD). In a subset of patients with severe ANSD, the profound hearing loss suggested from brainstem-mediated proxies of hearing, such as the auditory brainstem response (ABR) and acoustic reflexes, is at odds with their relatively normal pure tone hearing thresholds. Our preliminary studies compared recovery in the auditory periphery and CNS in an adult mouse model of unilateral SGN degeneration. Ouabain, a Na/K ATPase inhibitor, was applied onto the round window at dosages sufficient to eliminate >90% of SGN synapses onto inner hair cells. Despite the near-complete and non-recovering elimination of the ABR and acoustic startle reflex, responses in the inferior colliculus (IC), an auditory midbrain structure, revealed partial recovery of pure tone thresholds and tonotopy at one month, but not one week, after ouabain treatment. Temporal encoding of amplitude modulations was greatly reduced and did not recover at one month, consistent with the severely impaired speech perception observed in human ANSD. Interestingly, by measuring tone detection thresholds with an operant auditory behavior rather than a brainstem-based auditory reflex, we observed a more rapid and complete recovery than that seen in IC responses, motivating the study of higher levels of the CNS more intimately linked to auditory perception. Ongoing experiments address this need by simultaneously recording activity in the IC and primary auditory cortex of awake mice with chronically implanted multichannel probes. Pure tone responsiveness and selectivity, as well as synchronization to amplitude modulations, are tested before and after unilateral ouabain treatment. Single-unit tuning to a combination of acoustic features is also tested with a neural feedback-guided search procedure, effective at eliciting high-rate, sustained responses in both brain areas in normal mice. Finally, cochlear histopathology is performed to correlate perceptual and physiological recovery with the degree of deafferentation along the cochlear frequency axis. Collectively, these findings highlight a compensatory plasticity that allows higher levels of the adult CNS to rebuild the neural substrates for sensory perception following a massive loss of peripheral input.

Auditory streaming in rhesus macaques

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Abstract:
The environment is filled with acoustic stimuli that our brains transform from low-level sensory representations into perceptual representations that can guide behavior. These perceptual representations are the computational result of the auditory system's ability to detect, extract, segregate, and group the spectrotemporal regularities in the acoustic environment into perceptual units. Behavioral tasks that test auditory streaming are used extensively to study the principles and mechanisms that underlie a listener's ability to group and segregate auditory stimuli into perceptual units. In one such task, two alternating sequences of tone bursts are presented, while a listener reports whether the tone-burst sequences sound like one "auditory stream" (i.e., "galloping" tones) or two auditory streams. Human listeners report one stream when the frequency separation between tones is small, whereas they report two streams when the frequency separation is large. Interestingly, at intermediate frequency separations, a listener's reports become less reliable: on alternating trials, they report hearing one or two streams. In addition to manipulations of frequency separation, systematic changes to listening duration and temporal overlap of the tones alter a listener's reports. Although behavioral performance on this task is well described in humans, no other species has been trained to perform the task. As a consequence, there remain fundamental questions regarding whether humans and non-human animals perceive the auditory scene in a comparable fashion. Here, we trained rhesus macaques to perform a one-interval, two-alternative forced-choice version of the task. As with humans, longer listening durations and greater frequency separations biased the monkeys' behavioral reports toward two streams; whereas temporal overlap of the sequences biased reports toward one stream. Moreover, like humans, intermediate frequency separations result in reports of one or two streams that vary on a trial-by-trial basis. These results set the stage to investigate the neural correlates of auditory streaming because the responses at the intermediate frequency separations allow differentiation between neural activity that is modulated by the stimulus parameters versus that modulated by the monkey's behavioral report.

Layer 6 corticothalamic projections actively maintain sound selectivity in the lemniscal subdivision of the medial geniculate body but provide gain control to a non-lemniscal subdivision

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Corticothalamic (CT) projections originating from layers 5 and 6 of the cortex (L5 and L6, respectively) make up the largest component of the auditory corticofugal system and provide a massive, specifically patterned input to the lemniscal and non-lemniscal subdivisions of the medial geniculate body (MGB). L5 and L6 CT projections have distinct innervation patterns, axon morphology, and functional properties. However, conventional approaches for neuronal silencing affect both L5 and L6 rather than isolating each laminar component. Accordingly, the effects of AC silencing on sound representations in the MGB have been mixed and difficult to interpret.

We have taken a chemical-genetic approach to selectively and reversibly inactivate L6 neurons in the mouse auditory cortex (AC) while simultaneously recording sound-evoked activity in the medial, dorsal, and ventral subdivisions of the MGB. The AC of both hemispheres was infected with a cre-dependent adeno-associated viral vector that drove expression of a mutant acetycholine receptor only in L6 pyramidal neurons. When activated by the systemic injection of its otherwise inert synthetic ligand, this receptor elicits robust membrane hyperpolarization. Unlike optogenetics-based inactivation, this approach, known as DREADDs, provides long-lasting neuronal inhibition (4 hrs in vivo) throughout a large, irregularly shaped expression area without the risk of tissue toxicity.

By chronically implanting multi-channel silicon probes mounted on a lightweight microdrive, we were able to record from neurons throughout the different subdivisions of the MGB in freely moving mice before, during, and after L6 inactivation. We presented a large battery of sound stimuli to examine the influence of L6 feedback on a various aspects of sound-encoding, such as pure tone tuning, conspecific vocalization responses, and representations of signals in noise. Preliminary results demonstrate that the L6 inactivation was associated with increased sound-evoked firing rates in the medial, but not ventral, subdivision, while tuning quality decreased in the ventral, but not medial, subdivision. CT feedback has been implicated in a wide array of functions, ranging from the dynamic modification of sensory filters to the adaptive re-mapping of sound localization cues, and is likely to be differentially active based on ongoing cognitive demand. Accordingly, current efforts are focused on comparing the effects of L6 inactivation when mice are in three listening conditions: anesthetized, awake and passively listening, and awake and actively monitoring sound cues to avoid an aversive stimulus.
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(De-)Constructing the ERP: Phasic excitability changes measured by psychophysics

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The auditory event-related potential (ERP) is characterized by fluctuating negative- and positive-polarity states. Often unrelated, scientific attention has also been devoted to neural oscillations that reflect alternation between periods of relative excitation and inhibition. In particular, behavioral detection performance has been shown to be better for events that occur in the excitatory portion of the oscillatory cycle. In the current study, we aimed to link these findings directly back to the auditory ERP by densely probing behavioral detection performance over the ERP window (40–400 ms). Human listeners monitored 30-s white noise stimuli for the presence of supra-threshold gaps, which were followed by shorter, near-threshold gaps that occurred after variable delay periods. Listeners indicated whether they detected a second gap. We predicted that the time series of perceptual sensitivity (as indexed by d') would resemble the ERP elicited by the first gap. This hypothesis was supported by a first psychophysical investigation employing 10 participants. In a second step, we showed high within-listener stability of the time course of sensitivity in a single participant over 8 sessions. Finally, EEG data were acquired from 6 participants, who completed the same gap-detection task. Optimal sensitivity coincided with a positive peak in the ERP occurring approximately 200 ms after the onset of the supra-threshold gap. Moreover, filtering the ERP in the delta band best explained the behavioral sensitivity time series variance, compared to other frequency bands. These results suggest a synchronous fluctuation of perceptual sensitivity and auditory EEG polarity, specifically in the time window of the auditory ERP.

Nonlinear spectro-temporal and spatio-temporal integration of natural stimuli in primary auditory cortex

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Hearing requires the integration of spectral information from different locations on the cochlea and spatial information between the two ears. Classical receptive field models for auditory neurons treat this integration as a linear weighted sum of the spectral and spatial information streams. Numerous studies have identified nonlinear interactions between streams, but data limitations have prevented the validation of general receptive field models that reliably account for these nonlinearities.

We developed a vocalization-modulated noise stimulus that could be described in a low-dimensional space, thus permitting the testing of new nonlinear receptive field models. The stimulus was similar to noise-vocoded speech, generated by multiplying a temporal envelope from natural vocalizations with simple bandpass noise. Multi-channel stimuli consisted of independent vocalization envelopes applied to spectrally and spatially distinct noise bands. We presented these stimuli to awake, passively listening ferrets while recording single-neuron activity from primary auditory cortex (A1).

Vocalization-modulated noise was effective at driving activity in many A1 units. A receptive field model that accounted for second-order multiplicative interactions between stimulus channels revealed nonlinear interactions between both spectral and spatial stimulus channels. The magnitude of this interaction tended to be greater between spatial channels, suggesting a greater role for this nonlinearity in spatial integration. A model that accounted for nonlinear synaptic depression revealed that responses to spectrally and spatially distinct stimulus channels tended to show the same degree of depression-like behavior within neurons, suggesting that a single neuron applies the same nonlinear temporal transformation to the different input channels. These findings point to new general receptive field models that can account for the neural representation of natural vocalizations and other stimuli.

Neural population decoding of sound source location in the face of changes in sound level

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The ability of neural representations to code stimulus properties invariantly to the magnitude of the stimulus is a general issue across sensory modalities. For instance, organisms must be able to visually identify the same object under bright and dim conditions, and to localize a sound source whether it is loud or soft. We tested several neural population decoding strategies for sound localization that attempt to compensate for changes in sound level. Decoders operated on the spike counts of a sample of neurons collected from the inferior colliculus (IC) of awake rabbits in response to broadband noise bursts presented at 13 different azimuthal locations and three different sound levels (35, 50 and 65 dB SPL). Decoders were trained on data from the highest sound level and tested on data from lower levels. The "two-channel difference" decoding model posits that source location is determined from the difference of summed firing rates on the left and right sides of the brain. The difference operation is intended to cancel out additive neural activity introduced on both sides through increases in sound level. However, this decoder failed to localize accurately across sound levels because changes in sound level tended to produce a multiplicative scaling of the dependence of summed firing rate on azimuth instead of an additive shift. Therefore, an alternative decoder that determined azimuth from the ratio of the summed firing rates from each side determined source azimuth with improved accuracy in the face of changes in sound level.
Unilateral lesion studies show that sound source location only requires the IC contralateral to the source, challenging any "two-channel" model. We tested the level-invariance of a "single-channel" model based on the summed firing rate from only one side. As expected, this decoder failed to localize contralateral sources accurately. We tested an alternative decoder operating on the pattern of activity across IC neurons on one side. The pattern decoder accurately estimated source azimuth when both trained and tested on all combinations of source azimuth and level, indicating that the pattern of IC activity for a particular azimuth and level combination is statistically distinct from all other combinations tested. The pattern decoder localized with reasonable accuracy when trained on 65-dB data and tested on 50-dB data, but localized poorly when tested on 35-dB data, even if a level-dependent scaling factor was introduced. Therefore the pattern of neural activity across the IC specific to sound source location is not invariant to changes in sound level.

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Neural discrimination of sequences of sounds during acute coma

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Auditory evoked potentials (AEPs) are informative of intact neural functions of comatose patients. One marker is provided by the differerential AEPs responses to standard and rare sounds in a standard mismatch negativity (MMN) paradigm. A rich literature interprets this effect as a preattentive and unconscious processing of the incoming stimuli. By contrast, an MMN-like effect induced by the identical repetition of groups of sounds has been typically reported when subjects were aware of the sound regularity. Here we tested this hypothesis in twentyfour postanoxic comatose patients who underwent therapeutic hypotermia (TH). We recorded AEPs during TH and after rewarming to normal temperature (NT) while delivering sequences of five sounds. Stimuli were either groups of five sounds in which four were identical and one different in duration, or five identical sounds. Each of these types of stimuli was used either as standard or as deviant stimulus in a way that we could test an MMN-like effect induced by the repetition of groups of five sounds. We carried out a multivariate topographic analysis which decodes single trial AEPs in response to sound types. Results show that eight patients could track the sound regularity largely independently of their final outcome. The progression of the decoding performance from TH to NT was highly informative of their chance of awakening, providing 89% positive predictive power. These results suggest that maintenance of perceptual representation does not require consciousness and that the progression over time of the neural auditory discrimination predicts chance of awakening.

Electrophysiological correlates of intra-categorical discrimination training

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Recognition of environmental sounds involves predominantly cortical regions on the temporal convexity. We investigated how cortical representations of environmental sounds, here birdsongs, are modulated by training to recognise individual items. EEG and behavioural data were recorded from 13 normal subjects who completed: 1) a pre-training session requiring local vs. exotic birdsong discrimination; 2) an auditory-visual training session requiring recognition of a subset of items (hereafter learned items); and 3) a post-training discrimination session identical to 1 and yielding learned and control items. Local and exotic birdsongs were equated for discrimination difficulty. Behavioural data were analysed with a two-way repeated measures ANOVA with factors of session (pre vs. post) and item (learned vs. control). Discrimination accuracy exhibited main effects of session ($p = 0.044$) and item ($p = 0.02$) as well as a significant interaction ($p < 0.001$). EEG data were analysed on the correct responses only with a paired t-test comparing the difference between pre- and post-training sessions for learned vs. control items. Statistical analysis of distributed inverse solutions averaged over significant time windows implicated the left superior temporal gyrus at 206-232 ms, left middle frontal gyrus at 246-291 ms, left superior parietal lobule at 289-313 ms, left middle temporal gyrus and bilateral cingulate cortex at 512-545 ms. In conclusion, brief recognition training improved discrimination performance and modulated neural activity within a wide-spread left temporo-parieto-frontal network. In this study, we show for the first time that the categorization of an individually known sound object within a semantic category occurs as early as 200 ms.

Neural correlates of musical memory: an ECoG study on musical imagery

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Musical memory refers to the ability to remember musically relevant information, such as melodic content, progression of pitch and timing of notes. How musical memory is stored and replayed in the brain remains largely unknown. While previous studies have suggested that musical memory is associated with the activation of specific human brain areas such as inferior frontal lobe, supplementary motor area, superior temporal gyrus, hippocampus and supra-marginal areas, how neural activation patterns are related to the imagery of musically relevant information is not clear. We have used electrocorticography (ECoG) obtained from subdural electrode array implanted in Chinese-speaking epilepsy patients to explore the cerebral activity associated with musical imagery and compare neural activation patterns between musical imagery and listening in various brain areas. Subjects were asked to first listen to the initial segment of a familiar music piece that was stopped at 2 or 5 seconds before the end, and then to complete the rest of the piece by imagery. Subjects indicated the completion of the imagery by pressing a response button. The duration of the imagery was found positively correlated with the length of the absent segment of the music piece. We observed significant sustained high gamma band (60~140Hz) activity throughout the imagined segment in the right supra-marginal gyrus (SMG) and the left motor cortex (M1). Significant sustained beta band (13~30Hz) activity was observed in the right anterior superior temporal gyrus (STG) and middle temporal gyrus (MTG). In addition, sustained suppression in the beta band was observed in the left inferior somatosensory cortex and inferior SMG. Interestingly, the envelope of the beta band activity (suppressed by music imagery) was found significantly correlated with the intensity envelope of the segment of the music piece that a subject imagined. In all these brain areas, listening to and imagery of the same segment of music piece evoked significantly different ECoG activities. In summary, our experiments indicated that high gamma band activation in the right SMG and left motor cortex, beta band activation in the right STG and MTG, and beta band suppression in the left SMG and inferior somatosensory cortex are related to the imagery of familiar music piece. Further studies will investigate the relationships between high gamma and beta band activations and beta band suppression patterns, and the dynamic neural activation among these brain areas relevant to the time course of musical imagery. [This research was supported by NSFC grants 61071003]

Task Engagement Selectively Modulates Noise Correlations in Primary Auditory Cortex

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Mitchell Sutter, UC Davis

Changes in an animal's behavioral state affect the responses of sensory neurons in multiple ways. We have recently shown that when rhesus macaques engage in an auditory detection task, single neurons in primary auditory cortex (A1) increase their sensitivity to the target feature. Behavioral state can also affect sensory sensitivity by modulating interactions between neurons. For instance, visual attention reduces correlations in trial-to-trial variance between neurons in extra-striate visual cortex. Decreases in such correlations, sometimes called noise correlation, can have large-scale effects on the sensitivity of a population of neurons even if individual neurons show only modest modulation. We therefore asked whether task engagement affects the noise correlation between simultaneously recorded A1 neurons. Animals were trained to detect amplitude modulated (AM) sounds and to indicate AM detection with the release of a lever in a Go-No Go task. The animals were also presented with the same sounds in an awake, passive condition. Extracellular recordings were made from A1 during both conditions and single units were sorted offline with principal components analysis. We find that task engagement selectively modulates noise correlations, depending on both the sign of the passive noise correlation and the tuning similarity (signal correlation) between the neurons. Rather than a general effect of reduction in noise correlations, we find that task engagement selectively modulates the noise correlation to increase the separability between the joint distributions for target and non-target stimuli. Our findings provide evidence that auditory cortex can adapt to behavioral demands not only via changes in single neuron activity but also by selectively modulating network interactions to enhance population encoding.

Neural correlates of consciously-perceived, unattended sounds

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The extent to which sensory stimuli require attention in order to transcend subconscious processing and enter awareness is a fundamental question in neuroscience. We examined this question in the context of audition utilizing M/EEG and a dual-task informational-masking paradigm with trial-by-trial perceptual reports. Listeners performed a demanding primary task in the right ear and, in the left ear, retrospectively reported whether brief, unattended target streams – four isochronous, identical tones – “popped out” from the random tone clouds in which they were embedded. All targets, irrespective of the percept they evoked, elicited early, bilateral activity in auditory cortex. In contrast, a later, N1-like response was strongly contralateralized, and significantly larger for targets that were detected. Interestingly, while detected and undetected targets both elicited significant contralateral activity, only late detected targets elicited activity ipsilaterally; early detected targets, like undetected targets, elicited virtually no response. Detected target streams also elicited P3b and slow-wave responses. The results indicate (i) a severe contralateral processing bias under load, (ii) a specific role for left auditory cortex in conscious audition, and (iii) the potential for certain, non-salient sounds to reach awareness even when selective attention is strongly focused elsewhere.

SPECTRO-TEMPORAL RECEPTIVE FIELD MODELS OF INFERIOR COLLICULUS NEURONS

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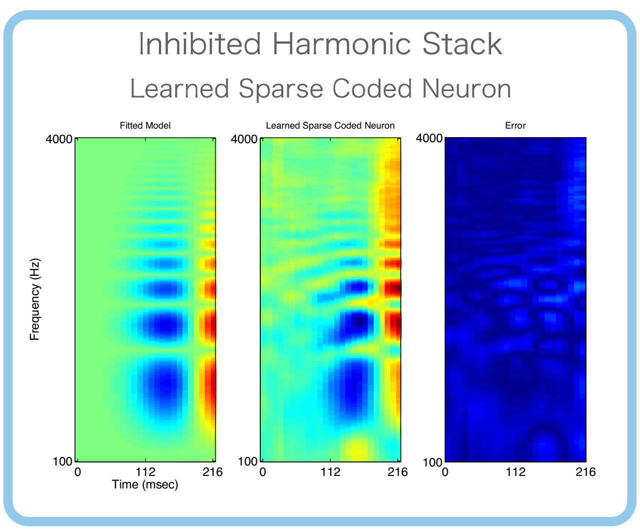
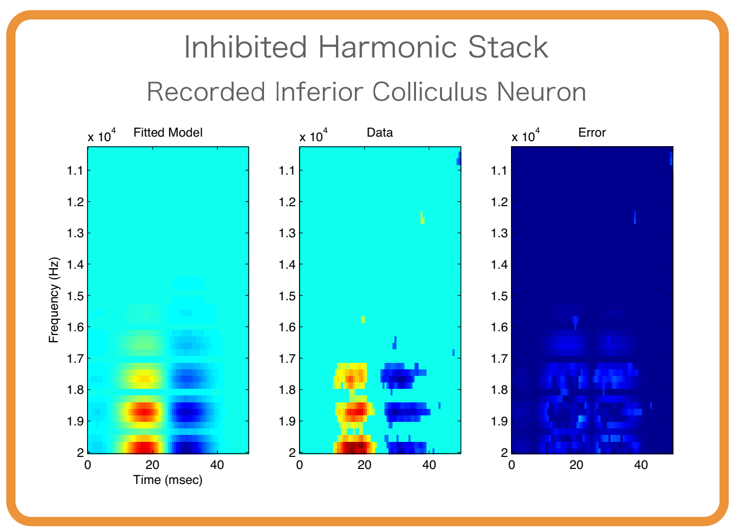
1. Introduction

We propose parametric model classes for the spectro-temporal receptive fields (STRF) of auditory neurons. A STRF represents the intensity of a neuron's response to different values of frequency and time. To determine STRF model classes we constructed models for the learned STRFs of a sparse coded neural network trained on speech-spectrograms. Our models were then fit to the learned STRFs using non-linear least squares methods. The learned STRFs from this neural network were also found to qualitatively match the STRFs of neurons recorded from the Inferior Colliculus (ICC) of anesthetized animals [1]. In order to better quantitatively analyze these comparisons we compared the best-fit parameters of our model classes for the learned STRFs and the best-fit parameters of our models when fit to STRFs generated from recordings from ICC neurons of anesthetized cats [2]. We then analyzed both data sets in this parameter space. Our classes (Checkerboards, Harmonic Stacks, Inhibited Harmonic Stacks and Phase Variant Checkerboards) accurately model the STRFs of the sparse coded neurons and the experimentally recorded ICC neurons. Furthermore, in parameter space we are able to show that the learned STRFs match properties of neurons recorded from the ICC. These include similarities in modulation of the neuron's response along frequency and the temporal time-span of STRF features. In order to determine the quality of our models we examined various goodness-of-fit measures and to determine similarities between the learned and experimentally recorded neurons we made statistical comparisons of the best-fit parameters for each data set. Additionally, our new models are able to find good fits for STRFs using approximately 10 parameters that previously had models that were characterized using 1000s of parameters [2].





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Title:
Learning the Stimulus Space Geometry from Auditory Neural Population Responses

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Abstract:
When decoding neural responses it is typically assumed that the topology and the geometry of the stimulus space are known. However, this kind of knowledge is neither available to the brain a priori, nor trivially discoverable from the neural responses. In this study, we try to answer the question how the geometry of the stimulus space (which implicitly includes the topology) can be reconstructed from neural recordings, using almost no assumptions. We then apply these algorithms to neural responses from the auditory cortex of the ferret for different stimulus sets.

Typical decoding algorithms, which are based on dimensionality reduction, fail to reconstruct the proper geometry of the stimulus space, since they underestimate the absolute distances between non-adjacent stimuli. Usually this leads to a folded representation of the stimulus space, e.g. a linear stimulus space may attain a convoluted shape. Under certain limiting assumptions a linear stimulus space may even be closed, i.e. topologically incorrect.

This failure is not a weakness of dimensionality reduction per se, but accurately reflects the distances in the high dimensional space, spanned by neurons, which are locally tuned, e.g. two tones separated by 2 or 4 octaves will appear to have a similar distance, if the responses of two narrowly tuned (and hence uncorrelated) neurons are considered.

We address this problem by computing distances between stimuli within the neural response manifold created by presenting the entire stimulus set. Neighborhoods in the manifold are constructed by stochastic exploration of the correlation based similarity matrix between neural responses. I this manor a path length between two stimuli is established as the shortest path between the responses in the neural response manifold i.e. the internal distances of the manifold are used rather than the distances of the ambient space.

Using this method we accurately reconstruct the geometry of the linear frequency axis, the circular Shepard tone space and 2 dimensional frequency level stimuli for both simulated and actual neuronal responses. While these examples demonstrate a successful algorithm for reconstructing well known stimulus geometries, this method will be of greatest interest to understand the mapping/projections of more complex stimulus spaces into the space of neural responses, and can thus help to identify the scope and shape of the internal representation of the outside world in a neural population.

Title: Spectral templates for encoding harmonic structure in marmoset auditory cortex

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Abstract:

Many natural and man-made sounds, such as animal vocalizations, human speech, and music contain rich harmonic structures. Although the peripheral auditory system decomposes these sounds into separate frequency channels, harmonically related frequency components must be grouped together in order to form a single auditory percept. A central neural process is required to accomplish this perceptual grouping and to compute spectral properties, such as pitch and timber, which are not explicitly encoded in the auditory periphery. In auditory cortex, single neurons have been found to encode low-frequency pitch (<1kHz) of harmonic complex tones in their firing rates. It is still largely unknown, however, whether auditory cortex processes harmonic complex tones over a broader frequency range outside the tentative pitch-region. In the present study, we systematically tested neurons in the primary auditory cortex (A1) with harmonic and inharmonic complex tones, varying fundamental frequency (f0) and harmonic composition. We found harmonic template neurons with emergent sensitivity to harmonicity. These neurons were strongly driven by the combination of certain harmonics of a preferred f0 and can encode information of both f0 and harmonic numbers. They usually weakly responded to individual harmonics alone or did not respond to pure tones at all. They also exhibited a reduced firing rate in response to inharmonic complex tones. Harmonic template neurons were distributed across the frequency range of marmoset A1 (2-35 kHz) outside low-frequency pitch region, with preferred f0s ranging from 400Hz to 12kHz. They were organized tonotopically by their best frequencies (BFs). The preferred f0 was usually equal to the BF or its subharmonics (BF/2, BF/3, ···). The integrative representation of harmonic complex tones by harmonic template neurons in A1 represents an important stage for robust feature recognition and sound source identification. (This research was supported by NIH grant DC 03180)

Title: Differential neuronal responses in ferret frontal cortex during performance of positive and negative reward versions of an auditory long-term memory task.

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Abstract:
An earlier study in ferret frontal cortex (FC) revealed persistent changes in neuronal responses to novel auditory target stimuli over a time course of minutes to hours following performance of auditory discrimination tasks (Fritz et al 2010). In order to explore the role of the FC in auditory memory, we developed a new auditory task that depends on information retrieval from an auditory long-term memory (LTM) store. Ferrets were trained to classify single tone-bursts into three frequency ranges (Low, Middle and High). Three animals were trained on a positive reinforcement (PR) task version, in which they learned to approach a waterspout for reward (Go-response) when the tone-burst fell in the Middle frequency range, and to avoid a time-out by not licking the waterspout after tone-bursts in either the Low or High frequency range (No-Go response). Five additional ferrets were trained on a conditioned avoidance (CA) version of the task, in which they received a mild shock if they licked to tones with frequency in the Middle range, but could lick freely through the tones in both Low and High range. Each trial thus consisted of the presentation of a single tone-burst that occurred randomly within one of the frequency zones, and the animal's response to this tone. After learning the frequency range classification LTM task, 4 ferrets (2 in PR and 2 in CA) also learned a similar 3-zone classification for different rates of amplitude modulation (AMR) of white noise. Each daily session consisted of 100-200 trials on

one or both tasks. After animals were trained, they were implanted with head-posts to secure head position during task performance. We recorded chronically from the FC of head-fixed ferrets, using a multiple electrode system (Alpha Omega). Preliminary neurophysiological results from the PR pitch LTM task indicate the presence of two major neuronal response types in FC that were strongly activated during performance and selectively preferred tonal frequencies that corresponded to behavioral choices rather than acoustic zones. FC neurons responded to either (a) the Middle range “Go” stimuli or (b) both Low and High range “No-go” tone-burst stimuli (Yin et al 2012). In contrast, during the CA pitch LTM task we only observed FC neuronal responses to the Middle range “No-go” tone bursts, even though the animal was performing the same pitch discrimination task. A similar response pattern was found during the AMR task in the same neuron population. These preliminary results provide insights into how the FC encodes, represents, classifies and retrieves the associative meaning of sensory stimuli during performance of auditory LTM pitch or AMR tasks under different reward conditions.

Differential encoding for species-specific vocalizations along the ventral auditory cortical stream

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Abstract:

The auditory cortex underlies our effortless ability to discriminate complex sounds. Vocalizations are an important class of natural sounds that are critical for conspecific communication in a wide range of animals, including macaque monkeys. The auditory cortex in the macaque monkey consists of several interconnected subdivisions on the supratemporal plane (STP) of the lateral sulcus. Here we investigated the nature and emergence of specialization for vocalizations by measuring auditory evoked field potentials to species-specific vocalizations from primary and higher-level auditory cortex of macaques. This approach exploited three high-density micro-electrocorticographic arrays (totaling 96 channels) chronically implanted on the STP in each of three macaque monkeys. Examination of characteristic frequency maps, derived from high-gamma band responses to pure tone stimuli, revealed tonotopic maps that reversed frequency direction at putative areal boundaries. These boundaries divided the STP into four sectors. To assess the differential encoding of vocalization stimuli across these sectors, we used evoked broadband waveforms within each sector to predict stimulus identity. Classification analysis was performed using a multivariate regularized classifier to estimate the classifier with these high-dimensional data sets. We found that neural discrimination performance among vocalizations, compared to matched control stimuli in which only the frequency spectra or temporal content was preserved, was highest in the most rostral sector, while this difference was minimal in the caudally-located primary auditory area. The most rostral sector had greater representation for stimuli in particular vocalization categories, consistent with this sector's functional specialization for vocalizations. Moreover, while the discrimination in the primary areas was based on broadband frequency components, discrimination in the rostral areas was driven fundamentally by the low, theta-band frequency components of the measured neural signals. These findings directly illustrate the progression in differential coding of conspecific vocalizations along the ventral auditory pathway.

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

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Abstract:
We extended the work of Griffiths et al. (2010) exploring pitch-related activity in human auditory cortex. Mechanisms for human pitch analysis were investigated by recording evoked and induced local field potential activity along Heschl's gyrus (HG) and lateral superior temporal gyrus (STG) in response to regular interval noise (RIN) presented at rates below and above the lower limit of perceived pitch (8, 16, 32, 64, 128, 256Hz). Data were recorded from HG depth electrodes with fourteen high-impedance contacts and 96-channel subdural grids over perisylvian cortex in each of six participants during presurgical epilepsy monitoring. Stimuli were randomly presented as part of a sound complex of 1s broadband noise and 1.5s RIN, followed by 1.5s of silence.
Evoked responses from the noise to RIN transition emerged as the pitch salience increased and reached its maximum for the 256Hz rate. Similarly, induced responses in the gamma range (60 - 200Hz) emerged as the rate crossed the lower limit of pitch and were most robust for the 128 and 256Hz rates, with typical onset latencies of approximately 70ms. RIN induced responses were sustained for a longer duration than to noise, and in some electrodes for the duration of the stimulus. Location of pitch-associated gamma responses in HG was found to vary across subjects, but were more pronounced at medial and central HG electrodes.
These data are consistent with previous work (Griffiths et al, 2010) and also provide information about the variability across subjects that exist in pitch-evoked response properties and location along HG.

Neural mechanisms underlying the coding of time-varying stimuli in primary auditory cortex of awake marmoset studied by intracellular recording

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Extracellular recording studies have shown that neural responses in auditory cortex of awake animals often differ from those observed in anesthetized animals, especially in temporal firing patterns in response to time-varying stimuli. However, cellular mechanisms underlying such differences remain largely unknown. Although intracellular recordings are the most widely used techniques in studying synaptic and intrinsic properties of neurons, few studies have been conducted in auditory cortex of awake animals due to technical challenges. In the present study, we developed a method to record intracellularly from the primary auditory cortex (A1) of awake marmosets using sharp electrodes. We replaced the traditional borosilicate glass pipette with a quartz glass (ID=0.5 mm, OD=1.0 mm) to improve the mechanic property of recording electrodes in order to penetrate through intact dura. In addition, we used a co-axial guide tube made of borosilicate glass pipette (ID=1.1 mm, OD=1.5 mm) outside the recording electrode, which was bonded to the recording electrode using a custom-made holder to provide protection of electrode tip during the tissue penetration. Once the desirable recording depth is reached, the binding between the recording electrode and the guide tube is released, allowing the recording electrode to be moved freely. With these improvements, we were able to perform intracellular recording reliably in awake marmoset, a non-human primate model that is increasingly used for studying auditory neurophysiology. The recording time varied from a few minutes to more than an hour. Using this method, we observed sustained depolarization superposed by sustained spiking activity from neurons in A1 when a neuron's preferred stimulus was played and transient depolarization evoked by non-preferred stimuli. The sustained depolarization can last from hundreds of milliseconds to several seconds. When stimulated with sinusoidal amplitude modulated tones (sAM), subthrehold response patterns of A1 neurons changed dynamically. Subthreshold depolarization exhibited entrainment to sAM stimuli at higher modulation frequency than spiking activity, suggesting a temporal-to-rate transformation of thalamic inputs in A1. At high modulation frequency when spiking activity showed non-synchronized firing, subthreshold activity of many neurons displayed sustained instead of transient depolarization. These observations shed light on neural mechanisms underlying the coding of time-varying stimuli in auditory cortex in awake conditions.
[This research is supported by NIH grant DC-03180.]

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Abstract title: The phase of low-frequency cortical activity is involved in the detection, discrimination, feature encoding, and behavioral dissimilarity of natural sounds.

Abstract text: Complex auditory stimuli such as speech are known to be discriminated by the phase of low temporal frequencies of evoked cortical activity. To date, several aspects of this discrimination process are largely unclear. In this study, we used information-theoretic methods to analyze the spectrotemporal decomposition of MEG data evoked by largely diverse natural sounds. We sought to further characterize this discriminatory process by: [1] comparing it with sound detection (i.e., discrimination against the null silence stimulus); [2] ascertaining the role played by the encoding of time-varying low-level features (e.g., loudness; spectral centroid); [3] assessing the extent to which it accounts for the behavioral dissimilarity of sound stimuli. [1] Both sound detection and discrimination relied predominantly on the phase of low-frequency components (< 6 Hz). More specifically, detection information peaked in the delta-low band (0.2-2 Hz), and was mainly characterized by transient onset and offset responses (sound-edge encoding). Discrimination information instead peaked in the delta-high band (2-4 Hz), and was characterized by a transient onset response, followed by sustained information throughout the entire sound. [2] Low-frequency phase contained significant information about sound features throughout the entire sound. However, time-varying feature information appeared to follow an oscillating pattern, supporting a multiple looks rather than continuous-tracking process. [3] Consistently with an attention-capturing effect of onset phase reset, behavioral dissimilarity matrices were significantly associated with onset-related information-theoretic sound-discrimination matrices derived for the phase of theta-low components (4-6 Hz). Together, these results provide a comprehensive empirical framework for understanding the role played by low-frequency cortical activity in the encoding of complex natural sounds.

Spatial hearing capabilities of the adult guinea pig (Cavia porcellus)

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Despite the common use of guinea pigs in investigations of the neural mechanisms of binaural and spatial hearing, their behavioral capabilities in spatial hearing tasks have surprisingly not been thoroughly investigated. To begin to fill this void, we tested the spatial hearing of adult, male guinea pigs using a paradigm based on the pre-pulse inhibition (PPI) of the acoustic startle response. We conducted two experiments aimed at quantifying 1) the minimum audible angle and 2) the spatial release from masking; the physiological correlates of both of these tasks have been intensively investigated in the guinea pig. Animals were placed in an acoustically transparent wire cage, with their head facing towards or 45° to the right of the midline of a 1m radius hemispheric ring of loudspeakers mounted every 7.5°, inside of a double walled sound attenuating chamber lined with acoustical foam. The startle response was captured via a cage-mounted accelerometer, and quantified as the PPI of the startle (1 minus the ratio of RMS amplitude of response to control), such that a positive PPI indicates stimulus discrimination. In the first experiment, continuous noise was presented from one speaker for at least 15s, and then immediately swapped to another speaker a short time interval (5-300ms) before a loud (~120 dB SPL) startle eliciting stimulus was presented overhead. For all stimulus conditions, PPI was greatest for a 180° swap, and was systematically lower for smaller angular separations. These data reveal that guinea pigs can discriminate changes in source location across the midline of at least 30° for broadband and high-pass noise (4 kHz cutoff), 45° for low-pass (2 kHz cutoff), and 30° for broadband noise sources centered 45° offset from the midline. The second experiment was similar, except a continuous broadband noise was played from the midline (0°) and a variable intensity, 200ms duration broadband chirp train (the pre-pulse in this condition) was played from a more lateral position (7.5-90° separation) immediately before the startle eliciting noise burst. PPI was weakest for chirps presented at a low intensity, from a nearby (7.5° separation) speaker, and increased with chirp intensity and angular separation. The results indicate that guinea pigs can: 1) discriminate changes in source location within a hemifield as well as across the midline, 2) discriminate sources of low- and high-pass sounds, demonstrating that they can effectively utilize both low-frequency interaural time and high-frequency level difference sound localization cues, and 3) utilize differences in source locations to increase detection of a sound signal. Supported by NIDCD R01-DC011555.

Eye position influences on auditory processes measured from within the external ear canal

Kurtis G Gruters, Christopher A Shera, Jennifer M Groh

Coordination between vision and hearing in the spatial domain requires that both the visual eye-centered and auditory head-centered reference frames share information about eye position with respect to the head. Previous research has found that the position of the eyes in their orbits can modulate the firing rates and response patterns of auditory cells in the inferior colliculus (e.g. Groh et al. 2001, Zwiers et al. 2004), primary auditory cortex (Werner-Reiss et al., 2003; Fu et al. 2004), lateral/medial banks of the intraparietal sulcus (e.g. Mullette-Gillman et al., 2005, 2009), and superior colliculus (e.g. Jay and Sparks, 1984, Lee & Groh, 2012). However, it is not clear at what level of the system eye position begins to influence auditory processes. We sought to test this question by determining whether eye position affects the collection of gain control mechanisms that act on auditory signals within the ear itself.

We measured sound pressure level in response to brief clicks in the external ear canal of monkeys (n=2) and humans (n=2) as they fixated various locations along the horizontal azimuth. Sound pressure measured in this fashion reflects both oto-acoustic emissions generated by outer hair cells and the action of middle ear muscular reflexes. Both monkeys and one of two humans exhibited statistically significant effects of eye position on the sound pressure level recorded in at least one of their ear canals during a period of time after the stimulus (ANOVA, $p<0.05$) . The time course of the effect varied across subjects.

These preliminary results indicate that eye position influences auditory activity even at the very periphery of the auditory system. Regardless of where eye position signals first "enter" the auditory pathway in a neuroanatomical sense, their presence at this early stage of processing suggests that they then have the potential to ramify throughout the system from the periphery and support a variety of interactions between vision and audition.

Hearing the light: a behavioral and neurophysiological comparison of two optogenetic strategies for direct excitation of the central auditory pathways

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Optogenetic technologies provide a means to manipulate specific neural circuits with high temporal precision. Neurons in the central auditory pathway encode temporal modulation of acoustic signals with submillisecond precision as high as hundreds - or even thousands - of Hertz. Thus, to faithfully reconstruct auditory representations in the CNS, optogenetic stimulation must provide excitation that is both precise and fast. In this study, we used viral mediated gene transfer to infect neurons in the mouse central nucleus of the inferior colliculus (ICc) with two types of blue-light drivable channelrhodopsins: standard channelrhodopsin (ChR2) or Chronos, a recently isolated opsin that has been shown in recent acute brain slice experiments to have enhanced photosensitivity and faster channel activation kinetics. Extracellular *in vivo* recordings from infected ICc neurons confirmed these observations. By delivering optical or acoustic pulse trains at rates ranging from 0 – 200 Hz, we observed highly synchronized responses with ChR2 as high as 40 Hz, but only rapidly adapting onset-like responses at higher rates. By contrast, neurons infected with Chronos accurately entrained their spike trains to optical stimulation as high as 140 Hz, which approximated the synchronization limit for natural acoustic stimulation in the same neurons. Stimulation at higher rates evoked non-adapting responses as high as 200 Hz, though spikes were no longer synchronized to the optical pulse train. Ongoing experiments seek to implant the ICc with chronic optical fibers to determine whether the enhanced temporal coding range with Chronos translates to an enhanced ability to behaviorally discriminate optogenetic excitation at high rates. These studies expand the framework for using the ever-growing toolkit of optogenetic stimulation strategies in auditory experiments.

Enhanced cognitive flexibility in reversal learning induced by removal of the extracellular matrix in auditory cortex

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Keywords: auditory cortex, cognitive flexibility, extracellular matrix, reversal learning, synaptic plasticity

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Abstract

During brain maturation, the occurrence of the extracellular matrix (ECM) terminates juvenile plasticity by mediating structural stability. Interestingly, enzymatic removal of the ECM restores juvenile forms of plasticity, as for instance demonstrated by topographical re-connectivity in sensory pathways. Complementary, synaptic plasticity is fundamental for learning and memory formation in the adult. Henceforth, to which degree the mature ECM is a compromise between stability and flexibility for adult neuronal circuits and might thereby impact new learning and higher cognitive functions is virtually unknown.

In this study, we removed the ECM in primary auditory cortex (ACx) of adult Mongolian gerbils during specific phases of cortex-dependent auditory relearning, which was induced by the contingency reversal of a frequency modulated (FM) tone discrimination, a task requiring high behavioral flexibility. We found that ECM removal promoted a significant increase in relearning performance, without erasing already established learning capacities when continuing discrimination training. The cognitive flexibility required for reversal learning of previously acquired behavioral habits was enhanced by ECM removal within sensory cortex. Our findings further suggest experimental modulation of the cortical ECM as a tool to open short-term windows of enhanced activity-dependent reorganization allowing for guided neuroplasticity.

Pre-stimulus phase affects auditory perception during continuous-mode processing

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Low-frequency oscillations are assumed to reflect fluctuations between periods of low and high excitability, and near-threshold auditory stimulus detection is enhanced when stimuli coincide with high-excitability phases of the oscillation. However, studies on the behavioral effects of low-frequency neural phase typically make use of rhythmic stimulation and thus involve entrainment of low-frequency neural oscillations. From a theoretical point of view, however, a distinction has been made between "rhythmic-mode" processing, which takes place in the context of temporally-structured stimulation, and "continuous-mode" processing, which takes place during vigilance-style monitoring of temporally-unstructured stimuli. In the current study, we were interested in characterizing the effects of pre-stimulus neural phase during continuous-mode processing. Listeners monitored 15-s narrowband noise stimuli for the presence of near-threshold gaps while EEG was recorded. Critically, stimuli lacked any temporal structure by which low-frequency oscillations could be entrained. Spectral analyses over the full-stimulus epoch confirmed that neural oscillations were not phase-locked across trials. Analysis of pre-stimulus neural phase suggested that detection performance was predictable from theta-phase (5–9 Hz) in a time window centered approximately 200 ms prior to gap occurrence, and by delta phase (~1 Hz) over a more extended time window lasting from 400 ms prior to gap occurrence until target onset. For both the delta and theta bands, we observed an oscillation of accuracy with pre-stimulus phase, indicating a trading relation between hits and misses. Interestingly, we also observed that optimal delta phase was consistent across listeners, but optimal theta phase was not, suggesting a dissociation between the delta and theta bands' roles in continuous-mode stimulus processing.

Neural oscillatory dynamics reveal distinct mechanisms underlying auditory perception of time

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Abstract
Perception of time and of temporal rate change is a core human cognitive faculty. Behavioral data provide support for oscillator models of time perception, and neural oscillations and oscillatory entrainment are good candidate neural instantiations of such models. Thus far, however, the underlying neural mechanisms of time perception have mainly been investigated via hemodynamics in functional imaging, but not directly in terms of neural oscillatory dynamics. Furthermore, although time perception has been shown to be susceptible to illusions induced by, for example, pitch, the nature of such context-induced illusory percepts with respect to coding by neural oscillations has thus far been unaddressed. Hence, the current study investigated the neural oscillatory responses that underlie veridical and illusory percepts of time. Magnetoencephalography (MEG) data were recorded while human participants (N=18) listened to frequency-modulated sounds (~4 Hz) that varied over time in both modulation rate and pitch. Participants judged the direction of the velocity change (rate decrease vs. increase) while ignoring pitch changes. Participants' modulation rate judgments were strongly biased by changes in pitch, such that participants perceived the rate to slow down when pitch decreased and to speed up when pitch increased (rate change illusion). For the MEG recordings, modulation rate changes directly influenced the exact frequency of the neural oscillation. However, pitch-induced illusory rate changes were unrelated to the exact frequency of the neural responses. The rate change illusion was instead linked to changes in neural phase patterns. That is, illusory under– or overestimations of perceived rate change were tightly coupled to increased phase coherence and changes in cerebro-acoustic phase lag. The results provide insight on how illusory percepts of time are coded for by neural oscillatory dynamics.

Regional tuning to interaural time and level difference in human auditory cortex

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Interaural time (ITD) and level differences (ILD) provide the primary means for sound localization in the horizontal dimension. Encoding of these cues is evident throughout the auditory system from the point of binaural integration in the auditory brainstem up through the cortex. Despite this pervasive representation, the cortical organization and role of these cues in is still poorly understood, particularly in human auditory cortex (hAC). In this study, using functional magnetic resonance imaging (fMRI) we examine the BOLD response to a wide range of ILD and ITD cues across and within multiple regions of hAC.

Image acquisition employed a continuous event-related design (TR=2s, 42 slices, 2.75 x 2.75 x 3mm resolution, 3T) that parametrically modulated ILD or ITD cues carried by click trains. Participants were tasked with identifying a pitch modulated target presented orthogonal to the experimental manipulation.

An increase in the BOLD signal in response to contralateral ILDs was observed across the full extent of Heschl's gyrus (HG) in both left and right hemispheres, and a strong ipsilateral response was also observed in HG of the right hemisphere. This lateralized response pattern was also observed in the superior temporal gyrus of both hemispheres, especially in regions of lateral STG adjacent to HG. The BOLD response pattern to ITD cues was similar across the STG in that a strong contralateral bias was observed, particularly around the border with HG. Interestingly, ITD sensitivity was present but fairly uniform across ITD space in medial HG, but more contralaterally tuned in lateral HG, consistent with past results showing lateral HG to be sensitive to low frequency and periodic stimuli (Patterson et al. 2002, Kumar and Schonwiesner 2012).

The results presented all support a neural encoding strategy that utilizes opponent populations to represent location in horizontal space based on ILD and ITD cues. Hemispherical asymmetry similar to that shown by Krumbholz et al. (2005) was observed in that the right hemisphere responded strongly to contralateral and ipsilateral ITD and ILD cues whereas the left hemisphere response was dominated by contralateral stimuli. The clearer overall responsiveness of the cortex to ILD compared to ITD suggests a larger proportion of cortical neurons sensitive to ILD (presumably in high-frequency areas), whereas only low frequency tuned areas may be sensitive to ITD as evidenced by the greater contralateral ITD response in lateral HG.

Dimensionality of neuronal response to complex sound in rat inferior colliculus

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Where the nonlinear processing of complex spectrotemporal patterns emerges in the ascending auditory system has yet to be elucidated. The encoding mechanism underlying nonlinear processing is more complex than linear summation of responses to simple acoustic features. In the linear-nonlinear (LN) model, the linear component of neural response is well captured by a single STRF dimension, while the nonlinearity is accounted for by the interactions between multiple STRFs. It has been suggested that the STRFs of neurons in A1 are best characterized by at least two STRF dimensions (Atencio et al. 2008, 2009), whereas single-STRF model is an adequate description for neurons in the central nucleus inferior colliculus (CNIC) (Atencio et al. 2012), which implies that the neural encoding mechanism of spectrotemporal patterns in CNIC is linear. However, other evidence supports that the CNIC neuron may exhibit a high level of nonlinearity (Nelken et al. 2003). To investigate the role of the CNIC in processing spectrotemporal patterns of complex sound, neural responses to the dynamic moving ripples (DMRs) were recorded from well-isolated single -units in the anesthetized rats. Under the general framework of the LN model, we applied maximally informative dimensions (MIDs) analysis (Sharpee 2004, Atencio et al. 2008) to reconstruct the STRF dimensions of neurons. In contrast to previous results (Atencio et al. 2012), we found a substantial portion of neurons (24%) in CNIC showed nonlinearity in processing spectrotemporal patterns, with two STRF dimensions according to MIDs analysis. Further examination revealed that the second STRF of these neurons had clear excitatory and inhibitory subregions, and exhibited either temporal (55%) or spectral (45%) shifts related to their first STRF, which imply that the CNIC neurons might show some invariance in processing spectrotemporal patterns. To examine whether the two-STRF model was necessary to characterize the neuronal responses, we presented 20~40 repetitions of a novel DMR segment and computed a correlation coefficient (CC) between the predicted and the actual firing rate. The CC of two-STRF model is significantly higher than single-STRF model ($p<0.01$), indicating that the two-STRF model was a better description of these neurons. Our findings suggest that CNIC neurons not only bear selectivity to high dimensional spectrotemporal patterns, but also show tolerance of temporal or spectral shifts, implying a critical role of the CNIC in processing complex sound.

Auditory-tactile integration in temporal frequency discrimination

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Previous studies have demonstrated auditory-tactile integration in the perception of musical meter and temporal sequence order, which has a temporal frequency range of ~0.2-5 Hz. Auditory-tactile integration has also been shown in speech perception, in which the dominant temporal modulation frequency range is ~2-33 Hz. The present study investigated the temporal frequency range within which auditory and tactile information are effectively integrated to form an integrated perception, using periodic and aperiodic click trains delivered through auditory or tactile channel alone or in combination. Subjects were given two click trains and were asked to indicate which click train contained the higher frequency under four testing conditions: (1) unimodal (auditory or tactile alone) (2) cross modal; (3) unimodal/bimodal; and (4) bimodal/bimodal. Results show that human subjects can integrate click train stimuli from auditory and tactile modality to form an integrated perception of temporal frequency in low frequency range below ~100 Hz. The performance began to deteriorate at higher temporal frequency ~60-100 Hz. We also showed that human subjects can discriminate the repetition rate of click train between auditory and tactile channels, regardless whether the click trains are periodic or aperiodic, over the same frequency range (15-100 Hz) where the auditory and tactile information could be effectively integrated. The performance in unimodal temporal frequency perception tasks was better for auditory than tactile stimuli. The performance for cross modal tasks, comparing temporal frequency between auditory and tactile channels, is similar to the performance in auditory unimodal tasks. In summary, like meter perception, low frequency tactile and auditory click trains are integrated to produce a single cross-modal percept. These results suggest that the perception of temporal frequency in auditory and tactile systems operates on similar neural mechanisms in low frequency range. Since neurons in both audition and touch show phase locked responses to vibratory and auditory stimuli, temporal codes may play a role in vibratory frequency perception in both sensory systems.

Population receptive field analysis of auditory frequency tuning in early blind individuals

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Early onset blindness has been linked to enhanced auditory abilities and altered BOLD responses in both auditory and occipital cortex in humans. In auditory cortex, changes in both the magnitude and extent of responses have been noted (Elbert et al. 2002; Stevens and Weaver, 2009). In occipital cortex, early blind subjects show cross-modal responses to a wide range of auditory stimuli across multiple visual areas (e.g., Poirier et al., 2006; Roder et al., 2002; Voss et al., 2008). Here, we measured tonotopic organization in early blind and sighted subjects to assess group differences in tonotopy and characterize the tuning properties of cross-modal responses in early blind subjects. Stimuli were pure tones ranging from 88 to 8000 Hz, presented in randomized sequences during six separate runs in a single scanning session. Our analysis, adapted from Dumoulin and Wandell (2008), treats the aggregate receptive field underlying each voxel's response as a one-dimensional Gaussian function of frequency, whose center and standard deviation reflect preferred frequency and population tuning bandwidth, respectively. We obtained consistent and reliable tonotopic maps within auditory cortex for both subject groups. We also observed cross-modal responses to pure tones in early blind, but not sighted, subjects. Frequency selective population receptive field estimates in occipital cortex of blind subjects were as robust as estimates in auditory cortex. The majority of these occipital voxels were narrowly tuned to frequencies within a 1000-1500 Hz range. The greater representation of these middle frequencies may provide a basis for superior auditory task performance.

Plasticity in hierarchical auditory cortical processing of behaviorally relevant vocalizations revealed by Arc/Arg 3.1 mRNA expression

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The nature of the transformation in the representation of sounds between “core” and “noncore” areas of the auditory cortex is not well understood. One emerging hypothesis is that neural activity is refined by hierarchical processing so that a stimulus’ behavioral relevance begins to more strongly modulate activity in higher-order areas. This would predict that as the behavioral relevance of a sound is acquired, neural activity elicited by such a sound should propagate more strongly to noncore areas of the auditory cortex. We explored this idea in a natural model of acoustic communication wherein mouse mothers acquire the behavioral relevance of ultrasonic vocalizations (USV) from pups. We have previously investigated this system using both electrophysiological and immediate early gene (IEG) expression methods. Here we focus on results using the effector IEG, Arc/Arg 3.1, which can be a proxy for activity in neurons likely to undergo plasticity after stimulation. Arc/Arg 3.1 is involved in synaptic plasticity and memory consolidation, and we have previously demonstrated sound-evoked Arc mRNA (Arc) expression in mouse core auditory cortex. In the core, total Arc expression remains the same after a sound becomes more familiar to an animal, in agreement with prior literature. However, a molecular trace of familiar sounds can be revealed in the core through a cell compartmental analysis of Arc expression (Ivanova et al, 2011). In the current study, we examined Arc expression in response to playback of pup USVs in mothers compared to pup-naïve virgin females, for whom the calls are behaviorally irrelevant. Animals were sacrificed 30 minutes after a 5 minute period of sound stimulation. We compared compartmental expression between a core (Au1) and noncore (AuV) field, focusing on cortical layers III-VI. While total Arc expression reached 55-65% of core neurons for both mothers and virgins, noncore total Arc expression reached ~50% only in mothers, with virgins showing only half as much expression. Moreover, extending our previous study on the effects of sound familiarity, a compartmental analysis revealed that there was a molecular trace of prior USV exposure in mothers in both core and noncore fields, but not in virgins. Therefore, our analysis of USV-elicited Arc expression discovered that when communication vocalizations gain behavioral relevance, their representation can propagate more strongly to higher order auditory cortical areas.

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Title : Tonotopic organization in monkey and human auditory cortex using phase-encoded functional MRI.

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Abstract :
Tonotopic organization is the main topographic feature of the primary auditory cortex. Importantly, tonotopy allows to define borders of cortical areas as reversals of the frequency gradient (i.e the spatial derivative of the preferred frequency map). Very different tonotopic organisations have been described with respect to Heschl's gyrus in humans. Furthermore, human tonotopy remains difficult to relate to the organization in nonhuman primates and a comparison would require the same measurement, design and analysis in both species. Here, we measured blood oxygen level-dependent signal with functional MRI (fMRI) in humans and monkeys. We applied phase-encoded designs ('travelling wave') and performed surface-based analyses using high-resolution individual anatomical MRIs. Thirteen humans and three rhesus monkeys were scanned during passive listening. Monkeys were scanned at 4.7 Tesla and humans were scanned at 3T and 7T. Two run types with either low-to-high or high-to-low progression of tone bursts were alternated. Cross-correlation between time-series from both run types were computed and time delay between the two signals revealed the preferred frequency. In monkeys, we found a tonotopic pattern with a postero-anterior axis of high-low-high preference located at the coordinates of A1-R according to monkey atlas. In humans, we also observed a tonotopic pattern of high-low-high preference along an overall postero-anterior axis, running across Heschl's gyrus. Our findings suggest that the precise 3D representation of the individual cortical surface is critical to better appreciate the organization in both species. This first comparative fMRI study of the tonotopy would contribute to the definition of a unified primate model of core and belt fields (Baumann et al., 2013).

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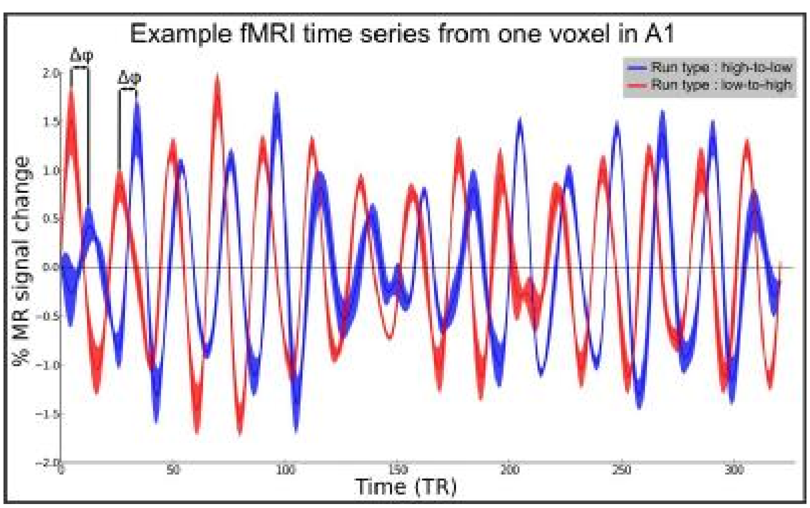

Title:
Oxytocin-based neuromodulation of mammalian social behavior

Status:
Graduate Student

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Abstract:
Social interactions are essential for normative development and lifelong physical and mental health. The neuromodulator oxytocin is believed to be important for some forms of social behavior, specifically parent-child bonding and maternal behavior. Here we investigate a fundamental form of rodent social behavior that depends on both social cues and modification of neural substrates: pup retrieval.

To initiate pup retrieval behavior, mouse pups produce ultrasonic vocalizations (USVs) when separated from the nest. Dams and other experienced caregivers use these acoustic signals to locate and retrieve isolated pups. Importantly, virgin female mice can also learn a variety of maternal behaviors, including pup retrieval. We hypothesize that oxytocin plays a major role in this form of learned social behavior (Pedersen et al., Science 1982). However, it is unclear how oxytocin impacts the activity of the cortex, leading to the robust increase in maternal behavior.

We have confirmed that virgins can also learn to retrieve pups. Furthermore, learning is accelerated after either systemic or cortical application of oxytocin. Virgins were first tested for initial retrieval abilities. Virgins were then co-housed with a dam and her pups for up to three days, with some animals receiving oxytocin and other animals receiving saline. After 12 hours of co-housing, 16/31 (~50%) animals injected with oxytocin learned to retrieve pups, but only 6/24 (25%) control saline-injected virgins retrieved pups. Similarly, 7/9 animals receiving oxytocin infusion into left auditory cortex via cannula retrieved pups within 12 hours, but 0/4 cannulated virgins receiving saline infusion retrieved pups. Finally, infusing the GABA-A receptor agonist muscimol into left auditory cortex, to inactivate local circuitry, reduced or fully prevented pup retrieval in 6/9 experienced animals. Infusion into right auditory cortex did not seem to significantly affect retrieval. This demonstrates that left auditory cortex is required for USVs to engage pup retrieval. Furthermore, these data suggest that oxytocin-based neuromodulation, paired with acoustic stimuli, can modify auditory cortex to enable or improve learned social behavior.

APAN 2013 abstract

Session: auditory memory and cognition

Decoding working memory for pitch of pure tones in auditory cortex

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It is widely believed that early sensory cortices, including auditory cortex, are primarily involved in the perception of low-level stimulus features. Additionally, it has been shown that visual cortex is also involved in the maintenance of such basic stimulus features in working memory (WM), e.g. orientation (Harrison & Tong, 2009) and contrast (Xing et al., 2013). Here, we ask whether auditory cortex is sensitive to the memory of one basic feature. We asked whether the pitch of pure tones held in auditory working memory (WM) for a lengthy period can be decoded from activity patterns in auditory cortex.

Participants had to actively hold either a low or a high tone in mind for 16 seconds. Using functional magnetic resonance imaging (fMRI) with multivariate pattern analysis (MVPA), we found that activity patterns in auditory areas, such as Heschel Gyrus (HG) and planum temporale (PT), could successfully predict which tone had been held in WM. However, when extending our region of interest to include not only early auditory areas but the whole of superior temporal gyrus, classifier performance dropped, indicating that early auditory regions are especially involved in pitch maintenance. As a control, we scrambled the data obtained for HG resulting in at chance level classification. Similar results were obtained for other sensory cortices, such as primary somatosensory cortex as well as primary visual cortex.

Our results demonstrate that early auditory cortex (HG and PT) can retain specific auditory information about basic auditory features (pitch of pure tones) held in WM, over periods of many seconds in the absence of an external stimulus.

Socially induced increases in the inferior colliculus of male mice correlate with the behavior of female partners

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Neurochemical signaling pathways can mediate the effects of social context on auditory processing, by responding to social cues and subsequently altering the responses of auditory neurons to vocal signals. Previous studies have shown that the neuromodulator serotonin increases in the inferior colliculus (IC) in male mice paired with male social partners, and in female mice paired with male partners. Here, we voltammetrically measured serotonin in the IC of male mice interacting with females, and the correspondence between serotonin levels and behaviors displayed by the males and their female partners. Serotonin increased as the social interaction progressed, reaching average levels significantly different from baseline levels, and from controls of solo males, at 12 minutes after males and females were initially paired. Analysis of the magnitude of serotonergic increase across individual males showed that serotonin was not correlated with behaviors shown by males, including investigation of females or production of vocalizations, or with male characteristics such as age or weight. In contrast, serotonin in the male IC was significantly correlated with the number of broadband 'rejection' calls produced by females, as well as a behavioral index combining female rejection behaviors. This correlation was negative, such that increased numbers of female calls corresponded to decreased amplitude of the serotonergic signal. These findings suggest that the amplitude of the serotonergic signal, and potentially the modulation of auditory responses, within the auditory midbrain of male mice are influenced by their female social partners.

Cortical oscillations and spiking activity associated with Artificial Grammar Learning in the monkey auditory cortex

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Abstract
Artificial Grammars (AG) can be designed to emulate certain aspects of language, such as the structural relationship between words in a sentence. Towards developing a primate model system to study potential language precursors at the neuronal level, we obtained evidence that monkeys can learn relationships in sequences of nonsense words generated from an auditory AG and used functional MRI (fMRI) to study the brain regions engaged (Wilson et al., SFN, 2011). Here, we ask how monkey auditory neurons evaluate the within-word acoustics and/or between-word sequencing relationships, and whether these aspects engage theta and gamma oscillations, which are critical for speech processing in human auditory cortex (e.g., Giraud & Poeppel, *Nat. Nsci.* 2012). We recorded local-field potentials (LFPs) and single-unit activity (SUA) from 4 fMRI localised auditory core (A1 & R) and lateral belt (ML & AL) subfields in two Rhesus macaques (124 sites). During each recording session, the monkeys were first habituated to exemplary sequences generated by the AG. We then recorded neuronal activity in response to identical nonsense words, either in the context of a sequence that followed the AG structure ('correct') or one that violated its structure ('violation'). In response to nonsense words, the LFP power significantly increased in a broad range of frequency bands (4-100 Hz), including at theta (4-10Hz) and low (30-50Hz) and high (50-100Hz) gamma frequencies. We also observed a consistent increase in the inter-trial phase coherence, in particular in the theta band, and theta phase was associated with gamma power modulations in response to the nonsense words, in the correct or violation sequences, respectively, 42% vs. 39% of sites. Moreover, a substantial proportion of the LFP sites showed differential responses to the nonsense words depending on whether the word was in the context of a 'correct' or 'violation' sequence in theta (35/124 sites), low gamma (37/124) and high-gamma (25/124) bands. Lastly, the proportion of such sequence-context sensitive sites increased from core to lateral belt auditory fields (LFP: 18% vs. 82%; SUA: 39% vs. 61%). We provide evidence that monkey auditory neuronal responses, including theta and gamma oscillations, are associated with both the processing of nonsense words and the relationship between the words, as governed by an Artificial Grammar. These nonhuman primate results likely reflect domain general, evolutionarily conserved neuronal processes, rather than those that are language specific in humans.

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Title: Local field potentials reveal novel multisensory interactions in cat cortex

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Keywords: multisensory, multielectrode, cortex

Multisensory interactions have been well described at the spiking level in both cortical and subcortical structures, and generally entail changes in firing rate that differ significantly from those predicted by knowledge of unisensory firing patterns. Much less is known about the synaptic processes that likely give rise to these differences in spiking. In the current study, we focused on two cortical areas in the cat that are watershed sites for multisensory convergence, the cortex of the anterior ectosylvian sulcus (AES) and the insula, and employed local field potentials (LFPs) to begin to detail multisensory interactions beyond those that are visible in spiking patterns. A 16-channel multilaminar electrode was introduced into cortex and multiunit activity (MUA) and LFPs were recorded. The spatiotemporal structure of the receptive fields and response profiles were investigated by delivering unisensory (i.e., visual alone, auditory alone) and multisensory (i.e., visual-auditory) stimuli that varied in spatial location and in temporal relationship (stimulus onset asynchrony or SOA). Both MUA and LFP analyses revealed the presence of multisensory interactions throughout both the AES and insula. Often, these interactions were most visible in the LFP traces, in which the recorded LFP signals under multisensory conditions frequently exceeded the addition of the unisensory voltage signals (or the maximum unisensory voltage signals), suggesting the presence of substantial multisensory processing at the synaptic level. Furthermore, the nature of these interactions was strongly shaped by the spatial and temporal relationships of the paired stimuli, and showed a complex spatiotemporal architecture to cortical multisensory processing. In addition, the patterns of interaction varied greatly depending on presumed supra- versus infragranular recording location, and will be further explored in current source density (CSD) analyses. Collectively, these results demonstrate the presence of widespread multisensory interactions in both the AES and insula, and highlight the utility of the LFP in elucidating both the extent and spatiotemporal structure of cortical multisensory interactions.

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The effects of adult visual deprivation on multisensory integration in the cat superior colliculus

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Combining information from different sensory modalities is a prerequisite to navigate the world around us. The superior colliculus (SC) is a critical hub for multisensory processing, and has been shown to play an integral role in orientation behaviors. Previous research has revealed that over half of the neurons in the intermediate and deep layers of the cat SC receive convergent information from two or more sensory modalities, and that many of these transform these different inputs. Developmental studies have shown that multisensory SC neurons mature gradually during early postnatal life, and that this maturation is critically dependent upon sensory experience. For example, complete elimination of visual experience via dark-rearing results in the inability of SC cells to integrate their multisensory input. Restoration of visual experience in adulthood had relatively minimal effects on multisensory processing, with most neurons still lacking integrative capacity and suggesting the presence of a critical or sensitive period for multisensory experience. If such is the case, then changes in sensory experience in adulthood should have little effect on multisensory processing. To examine this question, cats were reared under normal lighted conditions until adulthood. At 6 months of age they were transferred to a visually deprived environment and remained there for an additional 6 months. Extracellular recordings of local field potentials (LFP) and multi-unit activity (MUA) recorded from the intermediate and deep layers of SC were then performed. These experiments revealed that although multisensory integration remains in many neurons following adult visual deprivation, the response characteristics of these neurons were altered from normally-reared animals. Most apparent in this regard were changes in the temporal dynamics of the unisensory (visual, auditory) and multisensory responses. Collectively, these findings not only provide support for the concept of a critical period for multisensory development, but also show that adult experience is important for the preservation of normal response properties in these neurons.

Monkeys can localize more than one simultaneous sound, but how they do it is mysterious: behavior and neural activity in the inferior colliculus

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Knowledge of sound location is critical for survival. In humans and primates, sound location appears to be encoded using a monotonic or rate code in which neural activity is proportional to sound eccentricity (Groh JM et al., 2003; Porter and Groh, 2006; Werner-Reiss U and Groh JM, 2008; Salminen NH et al., 2012). This lies in marked contrast to the auditory spatial maps observed in barn owls (Knudsen EI, 1982; Knudsen EI et al., 19987) and other species (cat: Middlebrooks JC and Knudsen EI, 1984; ferret: King AJ & Hutchings ME, 1987). The key problem in encoding sound location using firing rates is that it is unclear how such code can represent *multiple* sound locations: neurons cannot have more than one firing rate at a time.

In current study, we tested whether rhesus monkeys (N=2) can segregate two sounds and how neurons in the inferior colliculus (IC) mediate this perception. Monkeys were initially trained with dual sounds presented sequentially (narrow bandpass noise centered on different frequencies), and rewarded for making eye movements to the locations of sounds. Gradually, the temporal overlap between the dual sounds was increased until these sounds were simultaneous with each other. Monkeys continued to successfully localize each individual component sound. That is, they made two saccades, first to one and then to the other sound location. Performance was better the greater the frequency separation between the two sounds.

We assessed the auditory responses of 230 IC neurons while the monkeys performed this task. We found that neural responses to dual sounds were best described as averaging. That is, the response when two sounds were presented was intermediate between the responses evoked when those same two sounds were presented separately. The average-like neural response in the IC is quite surprising since the monkeys do not make saccades to the average location between the two sounds, and raises questions about how the monkeys are able to accomplish this perceptual challenge. We explore possible computational solutions to this conundrum, including inter- and intra-trial switching between the two responses.

Acknowledgements

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Physiological but not anatomical abnormalities in the auditory thalamus of ectopic BXSB/MpJ-Yaa mice

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In the BXSB/MpJ-Yaa inbred mouse strain, approximately half the animals spontaneously develop nests of displaced neurons in cortical layer I, called ectopias. Neocortical ectopias have also been reported to occur in humans with developmental disorders such as dyslexia. Interestingly, although the ectopias occur outside the auditory cortex, both human studies of spontaneously occurring ectopias and studies of rats with induced cortical malformations have observed an association with anatomical abnormalities within the auditory thalamus. Previously, we have shown that ectopic BXSB/MpJ-Yaa mice have a physiological deficit in auditory thalamic processing, despite apparently normal hearing sensitivity. The aim of this current study was to determine whether the animals also have anatomical abnormalities in the auditory thalamus.

Following in vivo electrophysiological recordings, brain tissue was processed for histology. Alternate coronal brain sections were stained for cytochrome oxidase to differentiate thalamic subdivisions, and Nissl substance to reveal cortical ectopias and thalamic cell density. Volumes of cortical ectopias and auditory thalamic subdivisions were calculated using area estimates obtained by drawing borders on images of stained sections. Cell packing densities were estimated with a pixel-based density index, calculated from the distributions of pixel intensities across different image sections for the same subdivision and animal. All ectopic animals had at least one ectopia located in the motor cortex. Anatomical analysis showed no significant differences in thalamic volume or cell packing density between ectopic and non-ectopic mice, for either the whole auditory thalamus or any individual subdivision, even though positive controls for detection of differences between subdivisions were highly significant. These results suggest that previously observed physiological deficits in the auditory thalamus of ectopic BXSB/MpJ-Yaa mice might arise outside the auditory thalamus, or from causes with no anatomical correlate.

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Modulation of spontaneous and sensory-evoked synaptic dynamics in A1 during auditory discrimination tasks in mice

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Sensory cortex is capable of remarkable plasticity in the coding of stimuli, particularly during complex behaviors. The dynamics of sensory coding and its plasticity have been extensively studied with extracellular single unit recordings and lower resolution measures of population activity (e.g. EEG, LFP, and fMRI). However, whole-cell recordings of the membrane potential dynamics of cortical neurons have largely been restricted to anesthetized or passively awake and unengaged animals, yielding diverse and apparently conflicting results. For example, membrane potentials in some cortical areas of awake cats and mice are depolarized in a persistent UP state (Steriade, Timofeev, and Gernier, J Neurophysiol 85:1969-85, 2001; Haider, Hausser, and Carandini, Nature 493:97-100, 2013).However, other areas of the mouse cortex show different patterns of activity. Membrane potentials in auditory cortex of awake mice are hyperpolarized in a persistent DOWN state (Hromadka, Zador, and DeWeese, J Neurophysiol 109: 1989-95, 2013) and in barrel cortex of quietly awake mice they exhibit slow-oscillations reminiscent of sleep (Crochet and Petersen, Nat Neurosci 9:608-10, 2006). Task related plasticity in the membrane potential dynamics of cortical neurons has not been demonstrated. Here, we perform whole-cell recordings in the primary auditory cortex of mice engaged in two auditory discrimination tasks of varying difficulty while head-fixed on a cylindrical treadmill. In the simpler task, mice are trained to distinguish complex noise stimuli (temporally orthogonal ripple combinations; TORCs) from a pure tone. Sounds are presented in trial blocks with 1-6 TORCs followed by a tone. The pitch of the tone is fixed during each training session but is varied randomly day-to-day. In the more difficult task the tone is embedded in a TORC with variable signal-to-noise ratio between trials. These tasks result in rapid changes in gain and shape of receptive fields for extracellular recordings in ferrets (Atiani, Elhilali, David, et al., Neuron 61:467-80, 2009). Mice were able to learn both tasks and perform them reliably for up to 1000 trials with sigmoidal psychometric curves and during whole-cell recordings. We find that membrane potentials are stable and frequently depolarized when animals are engaged in the difficult task, whereas they undergo slow fluctuations or sustained hyperpolarization when unengaged or unchallenged. Investigation of the effects of task performance on receptive fields is ongoing.

Phonetic feature representation in human superior temporal gyrus

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Speech perception is the process by which we hear and interpret the sounds of language. The superior temporal gyrus (STG) has been implicated in the auditory processing of speech, but how this brain region encodes phonetic information has not yet been determined. Here, we used multi-electrode cortical surface recordings in human subjects while listening to natural continuous speech to demonstrate the STG representation of English speech sounds. At single electrodes, we found evidence for response selectivity to phonetic feature categories (e.g. plosives, fricatives, vowels, and nasals), which was related to tuning for specific spectrotemporal acoustic cues. Selectivity for manner of articulation was stronger than for place of articulation (lips, tongue tip, tongue body). A more continuous encoding for secondary acoustic features (e.g. spectral peak, formants, pitch) was mediated by a distributed representation across electrodes as well as tuning for non-linear complex acoustic parameters. These findings reveal a specialized multi-dimensional representation of the acoustic-to-phonetic transformation in human STG that underlies our ability to perceive speech.

Cortical Neurons Segregate Competing Sound Sequences With High Spatial Acuity

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Spatial hearing aids a listener in disentangling competing sequences of sounds. In a recent psychophysical study, human listeners discriminated sequences of noise bursts that differed only in rhythm. Discrimination was disrupted by interleaved masker sequences from a co-located source, but a spatial separation of as little as 8° between signal and masker permitted listeners to hear two segregated streams and thereby to identify the signal rhythm. We explored cortical mechanisms that might underlie such spatial stream segregation. We studied 205 single- and 710 multiple-unit responses in cortical area A1 of anesthetized cats. Interleaved sequences of broad-band noise bursts alternated between two source locations. Neural responses tended to synchronize preferentially to one or the other source, thereby segregating the sequences. Spatial acuity for competing sources was substantially sharper than previous accounts of sensitivity to single source locations, with many neurons showing significant segregation of competing sources separated by as little as 10°. Stream segregation was greatest among neurons with characteristic frequencies ≥4 kHz. The majority of neurons favored the more contralateral of two sources, but a sizeable minority favored the more ipsilateral source. Neurons favoring one or the other source tended to occupy discrete cortical modules. A parameter-free model could predict the responses of neurons to interleaved sound sequences based on spatial tuning to single sources and a measured forward suppression term. The results support a view in which perceptually segregated streams correspond to activity in discrete cortical modules. "Selection of auditory objects" could correspond to top-down "selection of cortical modules".

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Oxytocin receptor expression in the rodent central nervous system

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Oxytocin is an important and evolutionarily conserved neuropeptide that regulates social behaviors such as maternal care and parent-infant bonding (Insel, TR., Young, LJ, 2001). Oxytocin is synthesized in the paraventricular nucleus and supraoptic nucleus of the hypothalamus and is released both peripherally and centrally. Peripheral release into the systemic circulation is responsible for its classical physiological functions of milk ejection and initiation of parturition, whereas central release seems to modulate of social cognition in animals, and has been implicated in maternal behavior, aggression, anxiety, fear, interpersonal trust, autism spectrum disorders, schizophrenia, and depression. In particular, it is believed that the forebrain distribution of oxytocin receptors is crucial for social behaviors and cognition; however, the precise expression pattern of oxytocin receptors and the downstream effects of oxytocin receptor signaling both remain unclear.

Work in the Froemke lab has determined that parental experience interacts with oxytocin-based neuromodulation to affect the response of neural circuits of the adult mouse auditory cortex to neonatal vocalizations. Here we examine the distribution of oxytocin receptors and mechanisms of action in rodent brain and in auditory cortex particularly. To follow the distribution of the oxytocin receptor, we have designed an oxytocin receptor antibody, which is useful for Western blot, immunofluorescence, and immunohistochemistry. In addition, an oxytocin receptor-GFP mouse is being used as an alternative approach to verify the distribution of oxytocin receptors in the rodent central nervous system. We are studying how developmental age and breeding status modulate receptor expression, and aim to identify which cell types specifically express oxytocin receptors.

AUDITORY CORTICAL GAD65 REGULATES GAP DETECTION BEHAVIOR IN MICE

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We tested two strains of mice, C57BL/6 and FVB, on a gap detection task—a test of temporal processing and a putative measure of tinnitus in the rodent model—following unilateral noise-induced hearing loss (NIHL). Though the degree of peripheral hearing damage and post-NIHL cortical tonotopic disruption was similar across strains, only C57BL/6 showed significant impairment in gap detection task 14 days after NIHL. This behavioral change was accompanied by a 40% reduction of GAD65 mRNA in the auditory cortex contralateral to the lesioned ear. FVB mice showed neither gap detection impairment nor cortical GAD65 reduction following the same NIHL protocol.

Following the identification of the behavioral impairment resistant strain, FVB, we artificially knocked-down GAD65 in the auditory cortex using a post-transcriptional mRNA silencer (GAD65 shRNA lentiviral particles) to examine whether cortical reduction of GAD65 was sufficient to impair gap detection. FVB developed a significant impairment following GAD65 knockdown, despite preserving normal hearing threshold and normal (AI) tonotopy. This result highlights that downregulation of GAD65 is particularly detrimental to gap detection behavior. Taken together, we have identified a biochemical pathway that mediates strain differences in mice, and may also underlie individual differences in human susceptibility to auditory pathology.

Encoding of sound frequency and location in human subcortical structures: Preliminary results using functional MRI at 7T

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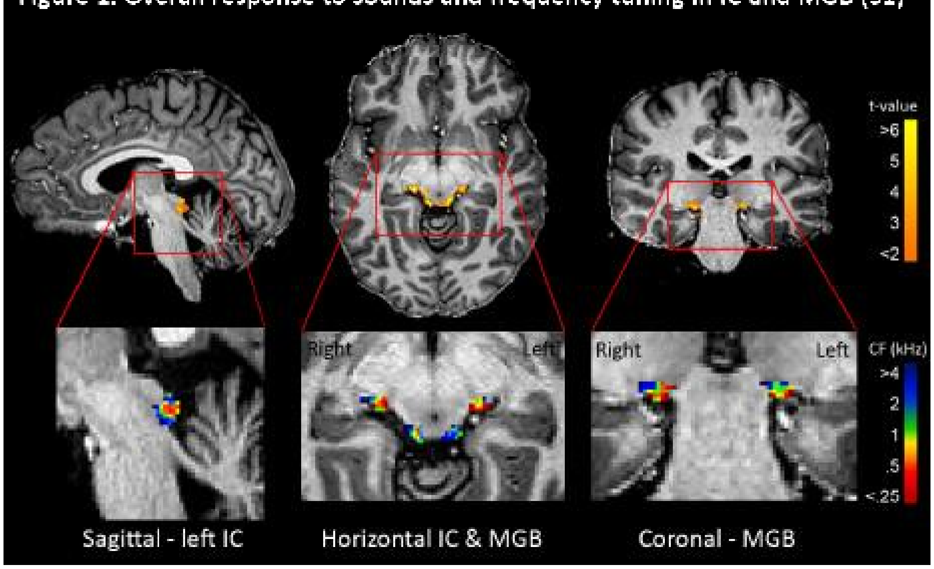
We investigated how human inferior colliculus (IC) and medial geniculate body (MGB) represent the frequencies and location of natural sounds. We measured subcortical responses to natural sounds with high field fMRI (7T), and compared the performance of four different models in representing these responses.

We acquired high-resolution fMRI data (1.1 mm isotropic), while subjects (n = 3) listened to individual binaural recordings of 84 sounds (e.g. speech, music; 56/28 training/testing sounds), presented at one of seven frontal locations (-90 to +90 degrees). The response in the IC and MGB was modeled as a linear combination of the sounds' features, representing the frequency content only, location only, or both frequency and location. For the combined representation of frequency and location, we compared a separable coding of the sound features to an inseparable coding. The models were evaluated by their prediction accuracy (their ability to identify a sound among the 28 testing sounds). Maps were obtained by color-coding each voxel according to the frequency and location to which it responded best.

We observed significant responses in IC and MGB (Figure 1). Only the inseparable model significantly predicted responses to testing sounds (average prediction accuracy = 0.60; chance = 0.50; $p < 0.05$ in each subject). In accordance with previous findings, a tonotopic gradient was observed in the IC. Also in the MGB, tuning to sound frequency was observed (Figure 1).

Our results suggest that subcortical responses to binaural sounds are best represented as the combined preference for frequency and location of neuronal populations. We will explore the distribution of location preference across regions and the relation between neuronal population frequency and location tuning.

Figure 1. Overall response to sounds and frequency tuning in IC and MGB (S1)



Neural signature of inattentional deafness

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Perceptual processing has limited capacity and when attention is engaged in tasks involving a high perceptual load (with many stimuli or demanding perceptual requirements , e.g. Lavie, 2010), perceptual resources are depleted. In the extreme, this can mean that perfectly visible stimuli are missed entirely when unattended (e.g. "inattentional blindness", Simmons & Chabris, 1999). Recent research has extended the effects of perceptual load across vision and hearing showing that high visual perceptual load can cause "inattentional deafness" with the majority of people failing to notice a clearly audible tone (MacDonald & Lavie, 2011). Here we used magnetoencephalography (MEG) to establish the neural signatures of this inattentional deafness.

Participants performed a visual search task involving either low perceptual load (the target would pop out from dissimilar distractors) or high load (the target required search among similar items) on briefly presented (100 ms) displays. On 50% of the trials the visual display was accompanied by a pure tone. Participants were told that the tones were part of the scanning procedure and irrelevant to their task. The evoked potentials in visual cortex showed significantly greater activation in high compared to low load from 97 to 160ms after onset. The peak occurred at ~150ms, indicating that the perceptual load effect was maximised at this point. Auditory evoked potentials were significantly reduced in the high compared to the low load condition in the interval 147 -172 ms after tone onset, during the latter portion of the M100 response. Source analysis showed that the auditory responses originated in secondary auditory cortex. Our results indicate that early sound-evoked responses in auditory cortex are suppressed under high visual load, accounting for inattentional deafness.

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Keywords: Selective attention. Perception. Magnetoencephalography.

The critical period of recovery for me-IPSC inhibitory transmission within the auditory cortex closes prior to postnatal day 23.

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During development, primary sensory cortices go through brief epochs of increased plasticity known as critical periods (CP). Sensory deprivation that lasts throughout these critical periods of plasticity leads to functional deficits in adults. The current study investigated whether inhibitory synaptic transmission recovers following hearing loss reversal after the closure of the critical period.

We previously found that the critical period for hearing loss-induced deficits to auditory cortex inhibitory synaptic transmission and membrane properties closes at ~P18 (Mowery, Kotak and Sanes, submitted). Therefore, we induced mild hearing loss with bilateral earplugs throughout the critical period of plasticity (P11 to P23), followed by earplug removal. We then obtained whole-cell voltage-clamp recordings from gerbil L2/3 pyramidal neurons in a thalamocortical slice preparations.

When earplugs were removed after the closure of the critical period (P23), and animals were permitted normal hearing for 12 days, synaptic and membrane properties remained impaired. Compared to age-matched control neurons, spontaneous IPSC amplitudes were smaller (mean ± SEM; sIPSC Amp, pA; Ctrl, -32.4 ± 3.0 vs. EP11-23, -23.6 ± 2.0, $p = .09$), membrane time constants were slower (mean ± SEM sIPSC tau, ms: Ctrl,13.7 ± 1.3 vs. EP11-23, 17.4 ± .9, $p = .08$), and minimum evoked (me) IPSCs amplitudes were significantly smaller (mean mV ± SEM; Ctrl, -9.6 ± 1.3 vs. EP11-17, -7.8 ± 0.3, $p < .05$).

Even 2 months of normal hearing did not lead to full recovery of cellular properties. Compared to age-matched controls, the me-IPSC amplitudes remained smaller when recorded at P86 (Ctrl, -12.8 ± 0.5 vs. EP11-23, -7.6 ± 1.7, $p < .001$). However, sIPSC amplitude and decay time recovered to control values.

These results suggest that the critical period of recovery for some inhibitory synaptic properties may close permanently prior to P23, while other properties can recover albeit over a long time course.

Cellular and laminar specificity of stimulus-specific adaptation in the primary auditory cortex

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Neurons exhibit stimulus-specific adaptation (SSA), a property in which responses to frequently occurring stimuli are suppressed, and those to rare stimuli are enhanced. SSA is thought to underlie a range of auditory processing mechanisms, such as novelty detection and adaptation to background sounds. While functional aspects of SSA have been extensively characterized in the primary auditory cortex (A1), little is known about the neuronal mechanisms that control its generation and propagation. Here, we examined the changes in SSA across A1 lamina, as well as across neuronal sub-types.

We recorded neuronal spiking activity across all cortical layers in A1 of lightly anesthetized head-fixed mice, using linearly arranged multi-site electrodes. Mice were exposed to two sequences of tone pips at two frequencies, selected to fall within the receptive field of the neurons. In one sequence, one of the tones was presented as a deviant (10%) and the other as the standard (90%). In the second sequence, the tone presentation probabilities were switched. We characterized the index of SSA for each neuron as the mean relative change in the number of spikes evoked by a tone, when it was presented as a deviant or as a standard (Fig. 1A). Almost all recorded units exhibited positive SSA indices.

To investigate how SSA propagates within A1, we compared the mean SSA index in granular, supra- and infra-granular layers. We found that SSA was significantly weaker in the supra-granular than either in the granular or infra-granular layers (Fig. 1B). This finding sheds light on recent studies, which found weak SSA in the auditory non-lemniscal thalamus. We show that SSA is attenuated within the cortex, between the granular and infra-granular layers, possibly prior to propagation to the thalamus.

We further found that putative inhibitory (fast-spiking) neurons exhibited significantly stronger SSA than the putative excitatory (regular-spiking) neurons (Fig. 1C). This result establishes an important role for inhibitory interneurons in maintaining SSA within the cortical circuit.

Neural Correlates of auditory discriminations in the auditory cortex of behaving macaque monkeys

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The mammalian auditory cortex simultaneously encodes the spectral, temporal and spatial characteristics of auditory stimuli. The current study examines how the response properties of single auditory cortical neurons are influenced in an auditory discrimination task that is dependent on whether the monkey must attend to the spatial or temporal aspects of an acoustic stimulus. We recorded the responses of single neurons in the auditory cortex of two adult macaque monkeys to 100% amplitude modulated (AM) noise (500 ms duration) presented from one of five speaker locations. Monkeys were trained to initiate a trial by depressing a lever. Two S1 stimuli (18 or 30 Hz AM rate) were presented (250 ms ISI) and then a third stimulus (S2) was presented that was either different from or the same as the S1 stimuli. The monkey was rewarded with a drop of juice for lifting the lever if the S2 was different from the S1, or keeping the lever depressed if it was the same (catch trials). Within a block of trials, the S2 stimulus could either change in AM rate but not location (AM task) or change in location but not AM rate (spatial task), but never both. Alternating blocks were presented to each neuron, and the monkey was cued to the type of change at the start of each block. Preliminary findings revealed that auditory cortical neurons showed a significant change in firing rate between the second S1 and the S2 when the monkey correctly detected a change in the target sound attribute (i.e. AM rate or spatial location) compared to when there was no change in the S2 stimulus (catch trials). However, across the population changes in spiking activity were poorly correlated with performance levels on the auditory discrimination task. These differences were greater for change trials than catch trials regardless of the monkey's response. Additionally, the majority of the neurons in this study were recorded from caudal auditory cortical areas, and exhibited greater differences in activity during the spatial task compared to the AM task. These findings are consistent with previous studies showing greater spatial sensitivity in the caudal auditory cortex. Our findings further suggest that changes in activity across the population of auditory cortical neurons can be influenced by behavioral engagement in an auditory discrimination task, but not necessarily with perception. This suggests that higher-order auditory regions are also necessary for processing complex acoustic information during this perceptual discrimination task.

Keywords: attention, encoding, discrimination, amplitude-modulated

Spatial processing of cortical neurons in the primary auditory cortex after cholinergic basal forebrain lesion in ferrets

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Cortical acetylcholine release has been implicated in different cognitive functions including sensory plasticity. Furthermore, we have recently shown that cortical cholinergic innervation is also necessary for a normal auditory perception (Leach et al. 2013, J Neurosci. 33: 6659-71). To explore whether behavioural sound localisation deficits observed in ferrets with reduced cortical cholinergic inputs were due to changes in spatial sensitivity of cortical neurons, we recorded neural activity in the primary auditory cortex (A1) from 3 animal in which nucleus basalis was previously lesioned bilaterally.

Neural activity was recorded from 146 penetrations on the left and right A1 under anaesthetia (medetomidine/ketamine) using silicon neuronexus probes (single shank, 16 recording sites). Diminished cholinergic innervation was achieved by prior bilateral injections of the enzyme saponin (ME20.4-SAP) in the nucleus basalis. Histological analysis after the recording sessions confirmed a mean loss of cholinergic cells in the nucleus basalis of 89.3±7.1% when compared to control animals. This resulted in a significant reduction of cholinergic fibres across all auditory cortex and especially on the middle ectosylvian gyrus where A1 is located.

Photographic documentation of the location of the penetrations at the time of the recordings and the electrophysiological characterization of the recordings that typically exhibited a mean latency ≤20ms, frequency tuning and onset response with an occasional weaker offset responses allowed us to assign the recordings to primary auditory cortex (A1). Frequency tuning was used to ensure an even sampling across the tonotopic axis of A1. Spatial tuning was determined using virtual acoustic space (VAS) techniques using 200ms broadband noise presented at three different intensities (56,70 and 84 dB SPL) from 12 locations separated 30° in azimuth and interaural elevation. Onset response spikes counts (40ms time window) were used to build response plots and calculate the overall spatial preference as the vectorial sum of responses to all spatial positions. Most of the units responded to all the spatial locations and showed a broad spatial tuning. Overall direction vectors indicated a contralateral preference for most units with much less incidence of ipsilateral. The majority of the spatial preference vectors were oriented towards the front hemifield (±60°) regardless of lateral hemispheric preference. These spatial profiles are in consensus with a population coding of spatial location described in normal animals and their properties enough to support an accurate sound localisation.

The Wellcome Trust & Deafness Research UK

Key words: ferrets; sound localisation; achetylcholine

The Functional Organization of Human Non-Primary Auditory Cortex

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Compared with visual cortex, the organization of auditory cortex remains poorly understood, particularly outside the primary auditory areas near Heschl's Gyrus. Here, we investigate whether non-primary auditory cortex is composed of functionally distinct brain regions like those found in the visual system, and if so, whether specific features and/or categories drive the response of each region. Using fMRI, we measured responses throughout auditory cortex to a diverse set of 8 natural sound categories that varied widely in their acoustic and semantic content. We then applied a data-driven clustering algorithm (Vul et al., 2012) to discover clusters of voxels in auditory cortex that have similar response profiles over the eight categories. The algorithm is not constrained by anatomy or by assumptions about which response profiles are more likely, and merely tries to account for the observed responses with a small number of canonical response profiles. This analysis revealed four response profiles that collectively accounted for 87% of all sound responsive voxels in auditory cortex, and that corresponded to distinct anatomical regions: 1) a primary auditory region near Heschl's Gyrus that responded similarly to all 8 sound categories 2) a region in the anterior superior temporal plane that responded mainly to sounds with strong pitch 3) a bilateral region of the superior temporal gyrus that responded primarily to speech and 4) a left-lateralized region of the superior temporal sulcus that responded exclusively to speech. These results suggest that pitch and speech may play a dominant role in the organization of non-primary auditory cortex, analogous to the importance of visual motion, faces, and places in the organization of non-primary visual cortex.

The Effects of Distortion in Auditory fMRI Research: Measurements and Solutions

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Nonlinearities in the cochlea can introduce frequency components not present in the original signal, known as distortion products (DPs). DPs can complicate the interpretation of auditory perception and neurophysiology experiments. Nonlinear sound presentation devices can also introduce distortion, a particular concern for fMRI research given that the Sensimetrics earphones in common use are substantially less linear than most high-end audio devices due to their design constraints. Here we describe the acoustic and neural effects of cochlear and earphone distortion in the context of pitch perception, and discuss how the effects of distortion can be minimized with appropriate stimuli. Cochlear and earphone DPs were measured for a large collection of harmonic complexes to assess the effect of level, frequency range, harmonic number, and waveform peak-factor on DP amplitudes. Cochlear DP amplitudes, measured using psychophysical beat-cancellation, depended primarily on DP frequency and were most prominent at frequencies below 300 Hz, consistent with prior findings (Pressnitzer and Patterson, 2001). Earphone DPs, measured with a sound meter and artificial ear, were, in contrast, highly sensitive to all of the acoustic parameters tested. For stimuli containing high-numbered 'unresolved' harmonics (widely used in pitch research), earphone DPs were often more prominent than cochlear DPs, with individual components reaching levels of 40 to 50 dB SPL for stimuli of moderate level (individual frequency components at 65 dB SPL). Using fMRI, we found that pitch-sensitive brain regions responded to both types of distortion, but that earphone distortion had a larger effect than cochlear distortion, consistent with our acoustic measurements. Based on these findings, we designed a set of pitch stimuli optimized for localizing pitch-sensitive brain regions. These stimuli robustly drive pitch-sensitive brain regions while producing minimal cochlear and earphone distortion, and will hopefully help fMRI researchers avoid distortion confounds in the future.

Sensitivity of macaque auditory cortical neurons to amplitude modulation as a function of modulation frequency and duration.

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The time –varying amplitude envelopes of natural sounds serve as important carriers of information. In order to understand how the nervous system codes for, and acts upon, this information we have recorded from macaque auditory cortical (ACx) neurons while the animals report the presence (or absence) of sine-amplitude modulation (AM) in a noise carrier target. Our recent work revealed differences in human and macaque AM sensitivity as a function of both AM frequency and duration (O'Connor et. al. 2011). To explore the neural basis of these differences, we examined the sensitivity of ACx neurons to AM depth across five intervals of AM noise (50-800 ms), and 10 AM frequencies (2.5-500 Hz), while the animals were actively engaged in detecting AM in 800-ms targets (Niwa et. al. 2012). Initial analysis showed that most neurons (132/175; two macaques, one female) increased their overall rate of response as a function of modulation depth. The AM sensitivity of these neurons was assessed using signal detection theory; receiver operating characteristics (ROCs) were computed based on the probability distributions of spike-counts elicited by each target depth and the unmodulated standard, and the area under the resulting curve was used as a measure of sensitivity. This was done for five durations (50, 100, 200, 400 and 800 ms) starting at the onset of each 800-ms stimulus. Neurometric functions were then computed by plotting ROC area against modulation depth and fitting a logistic function to the points, and threshold modulation levels (ROC area = 0.75) were determined from these functions. In general, neural thresholds were lower at intermediate AM frequencies and longer durations, mirroring behavioral thresholds, with shifts in peak sensitivity to lower frequencies with increasing duration. Interestingly, the subject with lower behavioral thresholds also tended to have lower neural thresholds. Thresholds of the most sensitive neurons also tended to be slightly lower than behavioral thresholds, suggesting that behavioral AM sensitivity arises from pooling across a neural population.

High-resolution fMRI phase-mapping of azimuth space in rhesus monkey auditory cortex.

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Sound localization is one of the most fundamental tasks performed by the auditory system. In mammals, the location of a sound source in azimuth is mainly determined by interaural time and intensity differences between sounds reaching the two ears. Although binaural sound processing in subcortical structures is well understood, much less is known about the representation of space at the cortical level. In humans, the left auditory cortex (AC) shows a predominant response to sounds in the right hemifield, while the right AC responds to sounds in both hemifields (Krumbholz et al., 2007), with contrast between the two hemifields revealing activation along the dorsal stream into parietal cortex. In the monkey, selectivity of neurons in primary AC for positions in contralateral space has been observed, albeit with broad spatial tuning (Middlebrooks et al., 1994). Spatial tuning sharpens significantly in the caudal belt regions (Tian et al., 2001; Recanzone & Beckerman, 2004), but it is not known whether the preferred azimuth positions form a map of auditory space. Here we attempt to bridge studies across human and nonhuman primates by obtaining a comprehensive overview of the cortical representation of azimuth space in the monkey for the first time using phase-mapping functional magnetic resonance imaging (fMRI).
Sounds were generated in virtual acoustic space and played back via headphones during fMRI. Stimuli consisted of broad-band noise bursts (0.2-16 kHz, 100 ms duration) moving through azimuth in steps of 30° at a rate of 5° per second. They were presented in a sparse-sampling design as a moving wave analogous to methods used in visual field mapping (Wandell & Winawer, 2011). We acquired high-resolution images oriented along the superior temporal plane in two anesthetized monkeys. We then analyzed the BOLD signal amplitude modulation at the frequency of stimulus presentation (12 cycles per scan) to determine voxel coherence and phase values corresponding to the stimulus cycle.
In accordance with prior single-unit studies, a robust contralateral response to azimuth position was observed. The left AC represented mainly the anterior contralateral quadrant, including straight-ahead positions, while the right AC represented both ipsilateral and contralateral space. This hemispheric bias supports previous neuroimaging studies in humans. In addition, it may elucidate the hierarchical processing of space from AC into posterior parietal cortex and the sound localization deficits observed in humans with damage to the right temporo-parietal cortex (Spierer et al., 2009, Rauschecker & Tian, 2000).

Defining harmonic resolvability in the common marmoset (Callithrix jacchus)

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Pitch is one of the most important percepts in audition. Computationally, pitch can be calculated using either spectral or temporal cues present in a sound. Whether a spectral or temporal mechanism is used to extract pitch is believed to be dependent on the harmonic resolvability of the stimulus. For example, the lower order (resolved) harmonics of a complex tone provide spectral cues for extracting pitch, while higher order (unresolved) harmonics provide only temporal cues. In humans, the boundary between resolved and unresolved harmonics has been estimated by using measurements from notched noise experiments. These experiments produce measures of auditory filter bandwidths, including the equivalent rectangular bandwidth (ERB), for different frequency channels. The ERB for a particular center frequency defines the highest fundamental frequency (f0) that a particular auditory channel can resolve, or the lowest f0 it cannot resolve, in the format f0 = alpha*ERB, where alpha is a constant. Depending on how subjects are asked to subjectively report resolvability, alpha has been defined across a range of values from 0.55 to 1.25. Recent work from our laboratory has shown that marmosets can extract pitch using either spectral or temporal cues, depending on the resolvability of the stimulus spectrum (harmonic templates [spectral] for resolved harmonics, and envelope extraction [temporal] for unresolved harmonics) (Osmanski et al., 2013). However, resolvability boundaries have not been quantitatively established for any nonhuman primate species besides humans. Here we propose a framework for defining harmonic resolvability for marmoset monkeys based on ERB estimation and compare our measured estimates to the tuning widths and frequency response properties of neurons in marmoset primary auditory cortex. (This research is supported by NIH grant DC-03180).

Smooth-Pursuit Eye Movements of Auditory Targets Suggest Motion-Specific Processing

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Two theories address how we perceive auditory motion. One proposes a dedicated motion-specific process within the CNS responsive to auditory target *velocity*. A second posits a ‘snapshot’ process that entails repeated sampling of target *position* as it moves through space. Eye movements (saccades and smooth pursuit) provide a useful and informative method of quantifying motion perception, as smooth pursuit (SP) eye movements require a moving target, primarily a visual one but not exclusively so. SP maintains foveal fixation on a moving visual target by matching eye to target *velocity*. In contrast, saccades ballistically shift foveal fixation from one *position* to another. Saccades are often employed during visual SP when the eyes fall behind and must catch-up to the now peripheral (non-foveal) target, and this can occur repeatedly. Previous studies have shown little, if any, SP of moving auditory targets, but most studies have used excessively high or low velocities that are not ecologically relevant to daily life. We presented auditory and visual moving targets over a range of realistic velocities (ramps of 10-40º/s) using a loudspeaker/LED target carried on a robotic arm. Eye movements of head-fixed subjects were recorded using EOG. Results reveal that at modest target velocities (10-30º/s) SP of auditory targets routinely occurs, but with gains ~half that for visual targets. This provides strong evidence for a motion-specific auditory processing mechanism, presumably feeding into the SP system, dominated by vision. Catch-up saccades are intermingled with pursuit, aiding to overcome the relatively low gain of auditory SP so as to best track sound objects overall. Thus, both position-dependent corrections (saccades) and co-existing true motion processing yielding SP, routinely occur in response to moving auditory targets. Further, periodic (triangular) target trajectories reveal evidence of prediction in auditory SP, as for visual SP. This provides additional evidence for a shared SP motion-tracking system in which vision is most robust but which is also accessed by moving auditory targets.

Visual modulation of neurons in voice-sensitive auditory cortex and the superior-temporal sulcus

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Effective social interactions can depend upon the receiver combining vocal and facial content to form a coherent audiovisual representation of communication signals. Neuroimaging studies have identified face- or voice-sensitive areas in the primate brain, some of which have been proposed as candidate regions for face-voice integration. However, it was unclear how audiovisual influences occur at the neuronal level within such regions and in comparison to classically defined multisensory regions in temporal association cortex.

Here, we characterize visual influences from facial content on neuronal responses to vocalizations from a voice-sensitive region in the anterior supratemporal plane (STP) and the anterior superior-temporal sulcus (STS).

Using dynamic face and voice stimuli, we recorded individual units from both regions in the right hemisphere of two awake Rhesus macaques. To test the specificity of visual influences to behaviorally relevant stimuli, we included a set of audiovisual control stimuli, in which a voice was paired with a mismatched visual facial context.

Within the STP, our results show auditory sensitivity to various vocal features, which was not evident in STS units. We newly identify a functionally distinct neuronal subpopulation in the STP that carries the area’s sensitivity to voice-identity related characteristics. Audio-visual interactions were prominent in both areas, with direct crossmodal convergence being more prevalent in the STS. Moreover, visual influences modulated the responses of STS neurons with greater specificity, such as being more often associated with congruent voice-face stimulus pairings than STP neurons.

Our results show that voice-sensitive cortex specializes in auditory analysis of vocal features while congruency-sensitive visual influences emerge to a greater extent in the STS. Together, our results highlight the transformation of audio-visual representations of communication signals across successive levels of the multisensory processing hierarchy in the primate temporal lobe.

The role of ventral prefrontal cortex in auditory, visual and audiovisual working memory.

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The ventral frontal lobe is well known for its role in language processing and social communication. Previous work has demonstrated that individual neurons within ventrolateral prefrontal cortex (VLPFC) process and integrate face and vocal information (Romanski et al., 2005; Sugihara et al., 2006). We have also recently shown that VLPFC neurons are active during audiovisual working memory (Hwang and Romanski, 2010). The effect of VLPFC lesions on tasks which assess learning or memory has been equivocal, with some studies demonstrating impairment on visual learning and memory, auditory discrimination, rule learning, and decision making, while other studies have failed to demonstrate any deficits during working memory tasks. In the current study we asked whether VLPFC was essential in an audiovisual non-match-to-sample (NMTS) task designed to assess auditory and visual working memory. During the task, rhesus macaques attended an audiovisual movie as the Sample and were required to press a button when a non-matching stimulus, i.e. one whose auditory or visual track differed from the Sample, occurred. Our subjects detected the Non-Match (NM) with a button press in order to receive a juice reward. We inactivated VLPFC while subjects performed the task by cooling the cortical surface of VLPFC below 20° C. During each testing session, 100 baseline trials were completed (WARM trials) and then the cortex was cooled below 20° C, and another 100 trials were completed (COLD trials). We assessed performance accuracy and reaction time in the auditory and visual non-match trials of the audiovisual NMTS task during WARM and COLD trials. Performance accuracy was significantly decreased during COLD trials compared to performance during WARM trials. Subjects also completed trial blocks where only auditory or visual stimulus changes occurred. There was no decrease in accuracy during visual-only Non-Match trials. In contrast, cooling of VLPFC during auditory-only trials resulted in a decrease in performance accuracy. The combined effects across all trial blocks suggests that VLPFC is necessary for crossmodal attention/ switching and auditory working memory but not for visual working memory.

Keywords: multisensory, monkey, vocalization

Dopamine modulates auditory responses in the inferior colliculus in a heterogeneous manner

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Perception of complex sounds such as speech is affected by a variety of factors, including attention, expectation of reward, physiological state and/or disorders, yet the mechanisms underlying this modulation are not well understood. Although dopamine is commonly studied for its role in reward-based learning and in disorders, multiple lines of evidence suggest that dopamine is also involved in modulating auditory processing. In this study, we examined the effects of dopamine application on neuronal response properties in the inferior colliculus (IC) of awake mice. Because the IC contains dopamine receptors and nerve terminals immunoreactive for tyrosine hydroxylase, we predicted that dopamine would modulate auditory responses in the IC. We recorded single unit responses before, during and after the iontophoretic application of dopamine using piggy-back electrodes. We examined the effects of dopamine on firing rate, timing and probability of bursting. We found that application of dopamine affected neural responses in a heterogeneous manner. In more than 80% of the neurons, dopamine either increased (32%) or decreased (50%) firing rate, and the effects were similar on spontaneous and sound-evoked activity. Dopamine also either increased or decreased first spike latency and jitter in almost half of the neurons. In 3/28 neurons (11%), dopamine significantly altered the probability of bursting. The heterogeneous effects of dopamine observed in the IC of awake mice were similar to effects observed in other brain areas. Our findings indicate that dopamine differentially modulates neural activity in the IC and thus may play an important role in auditory processing.

Neural representations of Background speakers at the Cocktail Party

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Selective listening gives a human subject the ability to robustly process speech despite the presence of interfering speakers. In a selective listening scenario with only one interfering speaker, the attended speech is foreground and the other is background, and previous work has demonstrated robust neural representations of each. It is not clear, however, whether the unattended speech has a distinct representation due to the fact that it is a different speech stream or due to the fact that it is background (i.e., everything that the listener is not attending to). This critical ambiguity is here investigated using three speech streams, of which only one is attended to. We observe whether the two background speech streams have distinct neural representations or a single unified neural representation.

Five human subjects were presented with three spatially co-located speech streams of perceptually equal loudness, but attended to only one of the three (ignoring the others), while their neural activity was recorded with magnetoencephalography (MEG). Neural MEG signals precisely follow the slow temporal modulations (< 10Hz) of speech. Analysis using the neural responses to reconstruct the stimulus envelopes demonstrates that the envelope of the entire background (as an inseparable mixture of the unattended speakers) can be reconstructed better than either of the envelopes of the individual background speech streams. This indicates that the experimentally measurable neural representation of the background is more consistent with a single unified neural representation than with two distinct neural representations (of the two background streams). Further analysis, modeling the neural representation as a temporal response function to be convolved with the stimulus envelope, demonstrates that the amplitude of first positive (M50-like) peak of the temporal response function is not modulated by attention, where as its latency is. In contrast, we find that the first negative (M100-like) peak is modulated in both amplitude and latency, indicating that the neural origin of the later peak is a strong candidate for representing the perceived (rather than physical) stimulus.

Spectral and spatial tuning of onset and offset responses in the auditory cortex of awake macaque monkeys

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Keywords: auditory cortex, electrophysiology, single unit

The mammalian auditory cortex processes spectral, temporal and spatial properties of acoustic stimuli. While many studies of the response properties of neurons in the auditory cortex have focused on the onset and sustained portions of the driven response, there have been far fewer studies on the relationship between onset and offset responses, particularly in the alert non-human primate. In the current study, we compared spectral and spatial tuning of onset and offset responses of neurons in the auditory cortex of awake macaque monkeys. Single unit activity was recorded in response to broadband noise stimuli from sixteen different locations spanning 360 degrees (in azimuth) around the animal, or tone stimuli ranging from 0.25 to 32 KHz. The onset period was defined as the first 100 ms from the start of stimulus presentation, while the offset period was defined as the first 100 ms following the end of stimulus presentation. Onset and offset frequency and spatial tuning data were interpolated with a cubic spline function. Peaks of the tuning functions were determined using an algorithm that detected local maxima at which the firing rate was at least 50% higher than the firing rate at the preceding local minimum. Best frequency and best location were defined, respectively, as the frequency and location that evoked the highest firing rate (highest peak of the tuning function). Using this method, almost all cells analyzed were found to have both onset and offset responses in the frequency domain (91 out of 93 units), as well as the spatial domain (93 out of 93 units). In most cases, best offset responses had lower peak amplitudes than best onset responses. The relationship between the best onset and the best offset responses was examined for both frequency and location. While best onset frequency and best offset frequency were found to be weakly correlated ($r = 0.169$, $p = 0.1099$), a significant correlation ($r = 0.327$, $p = 0.0014$) was found between best onset location and best offset location. These results suggest that the relationship between the tuning properties of onset and offset responses of neurons in the auditory cortex may vary based on which property of the stimulus is being encoded.

Whole field spatial receptive fields measured with spatially dense acoustic stimuli in marmoset auditory cortex

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In natural acoustic environments, the auditory system often has to identify a sound source's location among competing sounds from multiple locations. Auditory cortex is believed to be essential for behaviors involving sound localization in complex acoustic environments, but studies of spatial processing in auditory cortex have primarily relied on single source stimulus presentation. Here we employed a systems identification approach to estimate spatial receptive fields for single neurons in the auditory cortex of awake common marmosets (Callithrix jacchus), simultaneously presenting broad band sounds with randomized intensities from 24 speakers positioned on a 1 meter sphere surrounding the subject. In an analogous manner to comparing frequency receptive fields measured with narrow and broad band sounds, we compared spatial receptive fields measured from responses to 24-speaker stimuli to those measured using single-speaker stimuli. Using this approach, we observed that in some neurons, 24-speaker stimuli can unmask suppressive regions of space which are not apparent using single-speaker stimulus presentation. Moreover, we found that while some neurons showed little correlation between receptive fields measured with single-speaker stimuli and 24-speaker stimuli, there was agreement for others (30/74 units had $r > 0.4$ and tuning vector shift < 45 degrees). We hypothesize that neurons with high correlation between receptive fields measured with single- and 24-speaker stimuli are particularly well-suited for encoding sound source location in a spatially dense acoustic environment. For the remaining neurons, the low correlation between the two types of receptive fields suggests highly non-linear processing in integrating sounds from multiple spatial locations. The mechanisms of such non-linear processing remain to be investigated. [This research is supported by NIH grant DC-03180.]

Intracranial recordings reveal spatial and temporal differences in the processing and categorization of speech

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Abstract:
Speech perception requires listeners to map acoustic cues onto linguistic categories. There is active debate about the degree to which the brain represents fine-grained differences that do not distinguish categories. We test whether auditory cortical areas are differentially sensitive to within-category acoustic variation using single-trial classification of electrocorticographic (ECoG) signals recorded from human cortex.
Participants were neurosurgical patients (N = 3) undergoing chronic ECoG monitoring for diagnosis and treatment for medically intractable epilepsy. All subjects were left hemisphere language-dominant. Stimuli were synthetic consonant-vowel syllables that varied in the second formant to create a /ba/ to /da/ continuum. Stimuli were presented binaurally via insert earphones at a comfortable level in a two-alternative forced choice task. Each stimulus was presented for at least 50 trials; order was randomized within block. ECoG recordings were simultaneously obtained from Heschl's gyrus and perisylvian cortex of the right hemisphere using multicontact depth electrodes and subdural grid electrodes, respectively. Averaged evoked potentials and event related band power in the high gamma band (70-150 Hz) were measured at each electrode site. In all subjects, evoked and high gamma responses were localized to auditory and auditory-related areas, including the superior temporal plane, lateral superior temporal gyrus, and inferior frontal gyrus. For classification analysis, recording sites were grouped according to their anatomical location in each subject.
Support vector machine classification was used to determine the nature of the representations at each brain area over time by using single-trial activity to discriminate individual continuum steps. High gamma power and ECoG voltage, averaged over overlapping 100 ms windows with 50% overlap, were used as input features. Classifiers were trained with a 15-fold cross-validation procedure. Stimulus-specific (seven-way) classification accuracy exceeded 30% in all subjects (chance = 14%), and was above chance beginning at 50-100 ms and peaking at 200-300 ms after stimulus onset. The timing of classification accuracy varied by anatomical region. Confusion matrices were consistent with a linear, not categorical response to continuum step, suggesting a veridical encoding of the stimulus. Thus, despite categorical behavioral responses, we demonstrate differential temporal and spatial sensitivity to within-category information in the human auditory cortex, suggesting that early speech processing represents continuous detail in the signal.

Responses of prefrontal multisensory neurons to mismatching faces and vocalizations

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Evidence has suggested that the multisensory integration of social communication information enhances perception compared to the processing of unimodal stimuli. The ventral frontal lobes are one of several brain regions involved in processing social communication information including faces and vocalizations. We have previously demonstrated that single neurons in ventrolateral prefrontal cortex (VLPFC) respond to and integrate conspecific vocalizations and their accompanying facial gestures (Sugihara, et al, 2006; Diehl and Romanski, 2011). We were therefore interested in how VLPFC neurons responded differentially to matching (congruent) versus mismatching (incongruent) facial and vocal stimuli. We recorded VLPFC neurons during the presentation of movies with congruent or incongruent species-specific facial gestures and vocalizations as well as their unimodal components. Recordings showed that a subset of multisensory VLPFC neurons exhibited a significant change in neuronal activity during incongruent vocalization movies. Furthermore, the majority of these incongruent-responsive cells exhibited incongruent suppression during the early phase of the stimulus period, whereas other incongruent-responsive neurons exhibited incongruent enhancement in the late phase of the stimulus period when compared to the neuronal responses for congruent audiovisual stimuli. These results suggest that ventral prefrontal neurons are sensitive to differences between congruent and incongruent face-vocalization stimuli that may be important in identity processing or more generally, recognition, and confirms the role of VLPFC in the processing and integration of multisensory communication information.

Stimulus quality modulates primate auditory recognition memory and PFC activity

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Auditory matching-to-sample tasks have an additional temporal dimension that may be encoded, similar to the stimulus encoding that occurs in standard visual tasks. Experiment 1 sought to determine the stimulus length necessary to support recognition memory. Three rhesus monkeys (Macaca mulatta) were tested on an auditory delayed matching-to-sample (DMS) task which utilized both simple and complex stimuli. DMS task trials involves the presentation of a sample stimulus, a 5 s delay period, and then the presentation of a test stimulus. Trials must be identified via button press as to whether the sample and the test stimulus match. The sound stimuli presented in Experiment 1 were 500 ms, and truncated, i.e., degraded, versions of the 500 ms stimuli at 50 and 100 ms. Animals were first tested on each sound duration separately by testing session. Stimulus truncations incrementally affected DMS task performance, as accuracy was the highest for the 500ms stimuli, and lowest for the 50ms stimulus truncations (500ms: 81% correct, 100ms: 70%, 50ms: 64%). In Experiment 2, all three sound durations were presented in equal number within a given test session. For these sessions, performance accuracy was still highest for 500 ms, and lowest for 50 ms (500ms: 84% correct, 100ms: 75%, 50ms: 65%). These results demonstrate that although the animals can perform above chance with only 50 ms of data for the test stimulus, the full sample increases performance significantly. This suggests that the entire sound stimulus is encoded neuronally as opposed to only a portion of the stimulus (e.g. only the beginning or the end). This aforementioned encoding may be taking place at the level of the prefrontal cortex (PFC), as it has been cited that the encoding of temporal aspects of an auditory stimulus into working memory may occur at the level of the PFC (Pesaran, 2002). Experiment 3 sought to examine PFC involvement and neuronal recordings were obtained from the left dorsal lateral PFC of two awake rhesus monkeys performing an auditory DMS task. Sound stimuli were both simple and complex in nature, and the standard sound stimulus duration was 500 ms. However, at random intervals within the recording sessions, particular trial stimuli were truncated from the standard 500 ms stimulus duration. Multi-unit activity shows significant differences between standard and truncated sound lengths, on average at 300 ms after onset. Single and multi-unit data in addition to local field potentials will be assessed. Neurons within the PFC may be important for encoding sound duration, and representing auditory stimuli as cohesive objects (Griffiths & Warren, 2004; Romanski et al., 1999).

Keyword: duration; dorsal lateral prefrontal cortex; sensory processing; temporal; rhesus; novel; local field potential activity; multi-unit activity; delayed-matching-to-sample task

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Dynamics of synaptic circuits in the mouse auditory cortex

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The structure of neuronal circuits largely determines what patterns of activity can be elicited by sensory stimuli. However, the rules how the fine structure of synaptic circuits in the auditory cortex is established and how this structure is dynamically maintained or adapted upon learning are poorly understood. We performed repeated two-photon imaging of synaptic spines, the morphological correlates of excitatory synapses, through a small implanted glass window over the auditory cortex in transgenic mice that express GFP only in a small subset of neurons. We observed significant dynamics of spines under basal conditions: spines being formed and eliminated and persistent spines showing fluctuations in sizes, a morphological proxy for the strength of a synaptic connection. Using theoretical modeling, we show that the size fluctuations could be captured in an empirical model that predicts the emergence of a stationary log-normal distribution of synaptic strengths in the network, a fundamental property that is indeed observed in our structural data, as well in electrophysiological recordings. On top of the basal dynamics, we find that paired auditory conditioning and unpaired conditioning induce a transient increase in spine formation or spine elimination, respectively. A fraction of spines formed during paired conditioning persists and leaves a long-lasting trace in the network thus providing a potential synaptic mechanism for a fear memory trace. Conceptually, it will be interesting to determine the impact of basal synaptic remodeling and learning-induced plasticity on the stability of sound-evoked patterns in neuronal populations. We are currently establishing chronic calcium imaging approaches based on viral expression of genetically encoded calcium indicators that will allow measuring the stability of auditory representations in the future.

Representation of periodic sounds in the inferior colliculus of the gerbil - Periodotopy revisited

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Many natural sounds are periodic, and their periodicity is a key determinant of sound qualities such as rhythm, tremolo and pitch. The relationship between a sound's periodicity and its frequency content is not straight-forward. A number of previous studies have suggested that, just as frequency content appears to be represented across populations of central auditory neurons by means of systematic "tonotopic" variations in tuning, sound periodicity might equally be represented by means of a "periodotopic map", possibly oriented orthogonally to the tonotopic axis. Evidence that the central nucleus of the inferior colliculus (ICc) might be organized in this manner comes from microelectrode recordings by Schreiner & Langner (1988) in the cat, and, more recently, from fMRI data collected by Baumann et al (2011) in the macaque. However, due to limitations on sample sizes obtainable with single electrodes or limited temporal resolution of fMRI, these studies used only limited stimulus sets, consisting solely of sinusoidally amplitude modulated (SAM) tones or noises.
Using 64 channel, 8 x 8, 200µm spaced silicon array electrodes we have been able to make recordings in vivo from slices through the ICc of gerbils which simultaneously sample most of the anterior-posterior or medio-lateral extent of the nucleus, and thus reveal its tonotopic or periodotopic organization. We recorded responses to pure tones (to reveal frequency tuning) as well as three different types of periodic sound: SAM noises, click trains and iterated rippled noises (IRN).
Preliminary analysis of the data found strong evidence for tonotopy, but not for a consistent periodotopy. Responses at sites within the ICc showed clear frequency tuning and a tonotopic gradient running from ventro-lateral (low frequencies) to dorso-medial (high) positions. While at the same recording sites we always also found strong responses to all of the periodic stimuli, tuning to periodicity varied by stimulus type, being typically low- or bandpass for click trains, but relatively flat for SAM noise and completely flat for IRN. Phase locking to click trains was ubiquitous up to periods of a few 100 Hz, but there was no systematic relationship between phase locking characteristics and anatomical location. Phase locking was also frequently observed in response to SAM, but not in response to IRNs.

Activity of auditory cortical neurons in monkeys performing a short-term memory task

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Short-term memory (STM) for visual stimuli has been shown to engage both prefrontal cortex (PFC) and the modality-specific cortical areas that support visual perception. Although monkeys can perform auditory STM tasks, their ability is limited relative to that in vision, and appears to depend on retention of a stimulus trace in a passive form of STM. The neural underpinnings of this putative trace are unknown, but by analogy to sensory memory in vision and touch, they are likely to engage non-primary auditory cortex, e.g., the rostral superior temporal plane and gyrus, components of the ventral auditory processing stream that provide input to the PFC. We recorded single-unit activity across these regions while monkeys performed a serial delayed-match-to-sample (DMS) task. On each trial, the monkey grasped a bar to initiate the presentation of a sample sound (~300 ms duration), followed by 0-2 nonmatch sounds (delay interval ~1 s), before the sample was presented again as a match; the monkey released the bar to indicate a match. Among 280 sound-responsive neurons in 3 animals, we identified two phenomena potentially associated with mnemonic tasks. First, 35% of units exhibited a sustained change in firing rate (relative to the pre-trial baseline) during the delay interval (17% excitation, 18% suppression). Second, the auditory response was modulated by task context in 20% of units, with 7.5% showing match enhancement (relative to the sample presentation), and 12.5% showing match suppression. The prevalence of excitatory and suppressive effects differed between early and late phases of the trial: delay and match suppression were observed throughout the trial, but the proportion of units exhibiting delay or match excitation declined significantly after the presentation of the first nonmatch sound. The decline in excitatory response modulation following the first nonmatch sound coincides with a marked increase in behavioral error rate, suggesting that these signals may aid match detection. However, in the spiking activity there was no evidence of a stimulus-specific trace spanning the delay interval – analysis of firing rate in a sliding time window revealed that the variance explained by stimulus identity decayed to zero ~300 ms after stimulus offset for the population on average (whether during the task or during passive listening). The dynamics of spiking activity in the auditory ventral stream are consistent with characteristics of DMS performance, but additional sub-threshold mechanisms are likely to support the neural trace on which STM depends.

Rapid task-related plasticity of spectrotemporal receptive fields in the auditory midbrain

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Previous research has demonstrated that auditory cortical neurons can modify both their spatial and spectrotemporal receptive fields (STRFs) when animals engage in auditory discrimination tasks. In the mammalian auditory system, massive corticofugal projections send information from cortical neurons to subcortical nuclei, suggesting that neurons in the earlier stages of the auditory system may also undergo receptive field changes. We tested this hypothesis by recording neural activity in the inferior colliculus (IC) while ferrets engaged in an auditory discrimination task. Ferrets were trained using a go/no-go paradigm to withhold licking of a waterspout during a sequence of reference stimuli and to receive a reward for licking during a target stimulus. To study the effects of behavior, we compared STRFs measured from responses to the references during behavior and during a passive state before and after behavior.

Preliminary results suggest the following: 1. When the target was placed at the best frequency (BF) of the IC neuron, responses to reference stimuli were usually suppressed. These changes were usually accompanied by suppression of the BF component of the STRF. 2. When the target was placed more than one octave above or below BF, reference responses were usually enhanced, as was the BF component in the STRF. 3. Neurons in the central nucleus (ICC) showed changes primarily in the driven response and smaller or no change in spontaneous rate. 4. Effects on neurons in the external nucleus (ICX) were more variable, showing changes in both driven and spontaneous rates. Taken together, these results suggest that rapid behaviorally-driven STRF changes in the auditory midbrain are qualitatively similar to those described previously in the cortex and demonstrate significant behavioral modulation of the subcortical auditory pathway.

Neural representations of visual stimuli in human auditory cortex correlate with illusory auditory perceptions

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In most interpersonal communication, a listener can see as well as hear a speaker. Visual stimuli can subtly change a listener's auditory perception in quotidian speech comprehension. An example of this phenomenon is the McGurk illusion, in which perception of a phoneme's auditory identity is changed by a concurrent video of a mouth articulating a different phoneme. Studies have yet to link visual influences on the neural representation of language with subjective language perception. Using the McGurk effect to dissociate the subjective perception of phonemes from the actual auditory stimuli, we demonstrate that neural representations in human auditory cortex are more closely correlated with the visual stimuli of mouth articulation than the actual auditory stimuli. This representation occurs over all trials and on a trial-by-trial basis. Additionally, we quantify the extent to which information about visual and auditory stimuli transfers in temporal lobe speech perception networks. These results show how visual stimuli influence the neural representation in auditory cortex early in sensory processing and may override the subjective auditory perceptions normally generated by auditory stimuli. These findings depict a marked influence of vision on the neural processing of audition in tertiary auditory cortex and suggest a mechanistic underpinning for the McGurk effect.

Measurement of pitch discrimination thresholds in the common marmoset (Callithrix jacchus)

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Pitch, the perception of how high or low a sound is on a musical scale, is one of the most fundamental percepts in audition. In common marmosets, a fundamental frequency (f0) of 450Hz was reported as a transition point for the use of different pitch extraction mechanisms by cortical pitch neurons. Specifically, pitch neurons relied more on temporal envelope cues when f0<450 Hz and more on spectral cues when f0>450 (Bendor et al. 2012). More recent work from our laboratory has shown that whether a change in temporal envelope cues is used depends on the resolvability of the stimulus spectrum (using harmonic templates [spectral] for resolved harmonics, and envelope extraction [temporal] for unresolved harmonics) (Osmanski et al., 2013). Here we report on a further series of experiments designed to more closely align our studies of marmoset pitch perception with other studies from both human and nonhuman subjects. One of the most commonly used measures of pitch perception across species involves discriminating small changes in f0 between two successive tones. Such pitch discrimination thresholds, or f0 difference limens, are commonly assumed to measure the precision with which pitch is represented by the auditory system, and to be inversely related to pitch strength. We trained marmosets to report on changes in the pitch of both pure tones and harmonic complex tones differing in harmonic number, phase and spectral shift. Our results show that marmoset pitch discrimination thresholds at an f0 of 440 Hz (as A4 in musical scale) are substantially larger than those of similar f0 range measured in humans for single tones, although thresholds improve significantly with increasing harmonic number. This improvement is primarily due to the presence of multiple resolved components in the acoustic signal. These data suggest that pitch strength in marmosets, like humans, increases with the number of resolved harmonics in an acoustic stimulus and hint at a common mechanism of pitch perception shared by these species. (This research is supported by NIH grant DC-03180).

Streams of sound: a synfire sequence detector that performs auditory grouping.

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The grouping of sound components across frequency and time is crucial for auditory scene analysis. When presented with ABA_ pure tone sequences, subjects will report either hearing an integrated triplet pattern with a galloping rhythm, or report fission of the auditory sequence into two distinct isochronous streams. The strength of these perceptual organizations depends on the separation in frequency between tones as well as the presentation rate. These psychophysical effects are thought to reflect more general mechanisms for the brain to perform sequential streaming, for instance, grouping a series of footsteps together into one a representation of a single mover. We have developed a neuronal model which relates the strength of the cues for the integrated perceptual organization to the sensory coding of the stimulus itself. This model acts as a sequence detector, rapidly organizing incoming stimuli by recognizing underlying pattern regularities in the input. Our model uses the architecture of a synfire chain composed of Morris Lecar neuronal units with persistent activity, and captures the temporal coherence boundary stimulus parameters for which fission of the grouped auditory percept's triplet pattern occurs. Because of the persistent activity inherent in bursting-like Morris Lecar neuronal dynamics, this model is resistant to the silent interval and gaps between tones, recognizing not just short-term dependencies between subsequent auditory events but rather the global structure of the integrated tone pattern. We propose that such sequence detectors rapidly form and compete with one another in the case of ambiguous auditory inputs. The present work relates to previously reported psychophysics, human physiology eg mismatch negativity, and our own models for the case of perceptual bistability and buildup (Steele, Rinzel, Tranchina, 2012). Together, our computational models provide an account for the neuronal computations underlying the perceptual phenomenology of auditory scene analysis.

Organization of human auditory cortex: Modulation of response patterns on the posterior lateral superior temporal gyrus during a target detection task.

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Selective attention leads to the enhancement of cortical activity representing an attended sound stream in the posterior-lateral superior temporal gyrus (PLST) (Mesgarani & Chang, Nature, 2012, 485:233-6). Concurrently, there is a dampening of responses associated with the unattended stream. It is unclear, however, what mechanisms are associated with a target detection task that necessitates attention to all sounds in a stimulus set. In this study, we compared responses elicited by sounds when they were targets and non-targets, and when they were presented in a passive paradigm that did not require an overt behavioral response.

Subjects were neurosurgical patients undergoing chronic invasive monitoring for medically refractory epilepsy. All research protocols were approved by the NIH and The University of Iowa IRB, and subjects who consented to the research could rescind consent at any time without detriment to their medical evaluation. Event-related band power in the high gamma frequency range (75-150 Hz) was examined. Locations of recording sites were confirmed by co-registration of pre- and post-implantation structural imaging and aided by intraoperative photographs. Stimuli were complex tones or band-limited noise bursts. Subjects were instructed to press a button whenever they heard a target sound embedded in a stream of five other stimuli, or to passively listen to a set of six sounds.

Results indicate that there is no overall increase of high gamma activity during active versus passive listening, either in the response or pre-stimulus (baseline) period. However, responses to target sounds are increased when compared to responses elicited by the same sounds when they were not targets, and when they were presented in a passive paradigm. Increases in high gamma to target sounds are not necessarily larger during early response segments, and generally are larger during later response segments that preceded behavioral responses by about 500 ms. Regions of PLST where there are large early increases do not necessarily reflect locations of maximal increases when the sound is a target.

We conclude that task dependence modulates later activity in PLST when attention is directed at all sounds in an auditory environment. Differential modulation of locations on PLST by task dependence may further delineation of functional fields within this region of auditory cortex.
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Population responses for the simultaneous encoding of sound intensity and identity in primary auditory cortex

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A sound signal can contain many distinct pieces of information that must be simultaneously encoded by the auditory system and perceived by an organism for survival. At the level of individual neurons, these stimulus parameters are confounded because they all have potential to modulate neuronal response. Clearly, a neural population coding strategy must be utilized by the brain to resolve this confound. In this study, we investigated the simultaneous encoding of sound intensity and identity by applying data-driven approaches to analyze the neural population response patterns in primary auditory cortex of awake marmoset monkeys. Single neuron spike responses were collected for a variety of distinct wideband sound stimuli across a range of intensities, including random spectrum stimuli and marmoset vocalizations. Firing rate responses of individual neurons were then combined into vectors representing the collective population response in a high dimensional neural response space.The evolution of the population response in time forms a trajectory in this high dimensional space representing the dynamics of the population activity. Dimensionality reduction techniques, including principal component analysis and local linear embedding, were used to reveal trends in the neural data. Results show that the population response for the panel of random spectrum stimuli has a structure dominated by sound intensity, which accounts for most of the response variance. Sound intensity information can be easily recovered from the first two principal components of the population responses. Sound identity information was assessed by quantifying the distance between the response trajectories of different stimuli in principal component space. For intermediate sound intensities, population responses to stimuli of different intensities were more similar between those with the same identity than different identities. These findings suggest the presence of a systematic structure in the population responses of primary auditory cortex along the feature of sound intensity and a potential organization along the feature of sound identity for wideband sound stimuli. This work can readily be extended to explore the encoding of simultaneous sound mixtures with data-driven population coding techniques.

Discriminating an auditory “figure” from “ground”: an MEG study

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The natural acoustic environment comprises of a complex mixture of sounds. In order to isolate individual sounds of interest, the mixture needs to be parsed. This is a highly complex task whose underlying brain mechanisms are still not understood.

In order to model naturalistic acoustic scenes, we developed a stochastic figure-ground stimulus (SFG, Teki, Chait et al., 2011). The stimulus comprises a series of chords (25 ms long) containing random frequencies that vary from one chord to another. To study segregation, we introduced a figure by randomly selecting a certain number of frequencies ("coherence") and repeating them over a certain number of chords. This allowed us to control the salience of the figure, which can only be extracted by binding across time and frequency. We found that listeners are very sensitive to the emergence of these complex figures. We previously established a role for the intraparietal sulcus (IPS) in stimulus-driven segregation of these figures (Teki, Chait et al., 2011) and modeling work suggests a role for temporal coherence in mediating segregation (Shamma et al., 2011; Teki, Chait et al., 2013).

To understand the brain dynamics of segregation, we used MEG. Figures with different salience (coherence of 2, 4 or 8; 0.6s long) were presented after statistically similar background segments (0.6 s). Listeners were engaged in a visual task and were naive to the SFG stimulus. In another condition, we presented the same stimuli but interspersed with alternating white noise, as we previously found that this does not affect figure detection (Teki, Chait et al., 2013).

Analysis of time-locked activity in the auditory cortex shows that even in the absence of directed attention there is an initial onset response to the emergence of the figure, followed by a sustained response which follows the figure. The figure onset responses occur about 100 ms in the coherence=8 condition, and 150 ms for coherence values of 4 and 2. These latencies correspond to duration of 4 (or 6) chords and parallel behavioral performance (obtained separately). Latencies from the ‘noise’ condition reveal the same threshold, suggesting that the segregation mechanism was not affected by the interspersed noise bursts.

Source analysis based on fitting of equivalent current dipoles suggests that a model comprising four sources in bilateral planum temporale and IPS explains the post-transition responses to the figure, during both the early and sustained phases. Results from ongoing time-frequency analysis and beamforming will be presented.

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Stimulus expectancy influences auditory detection by selective cross-modal phase reset of different frequencies: evidence from EEG and behavior

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Recent research has shown that a unimodal stimulus of one modality can reset the phase of ongoing oscillations in unisensory cortices of another modality, as a means to enhance processing of subsequent events. But is this process affected by knowledge about how likely it is that such an event will occur? Using EEG, we investigated whether probability information regarding the occurrence of a sound influences to which frequency ongoing oscillations in auditory regions are reset by visual input, and thus whether processing of the sound will be enhanced or not. Visual stimuli had two different colors, which indicated a high (80%) or low (50%) probability that a sound would follow. The visual stimuli were followed by a low-intensity beep in the corresponding proportion of the trials, with stimulus onset asynchronies (SOA's) ranging from 0 to 450 ms. Participants indicated whether they detected a sound or not. The power of the Fast Fourier transform of the responses distribution for the two probability conditions separately showed that high probability sound elicited delta frequencies (2-4 Hz), while low probability conditions showed high power in theta band (8 Hz), suggesting that expectancy influences the period in time to which you attend. The EEG data showed higher power for low frequencies for the high probability trials. Inter trial coherence showed a similar pattern as the behavioral data: high and low probability trials were mostly associated with high coherence for delta and theta frequencies, respectively. Thus, the expectancy of sound seems to trigger a long high excitable period (caused by the lower frequency), optimizing auditory processing during a longer period close to the visual stimulus. These results indicate that the frequencies that are affected by cross-modal phase resetting are flexible and dependent on the expectancies about the occurrence of a sound.

Predicting benefits of multisensory memories

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Single encounters with multisensory auditory-visual pairings are sufficient to impact subsequent unisensory object recognition [Thelen et al., 2012]. Recognition accuracy for images that had been paired with a meaningless sound upon their initial encounter (V+) is generally impaired when compared with recognition accuracy of images encountered only visually (V-) during a continuous recognition task. This behavioral decrement correlates with differential neuronal activity at 270ms-310ms post-stimulus onset within middle temporal cortices. Moreover, activity within these areas appears to be linked to the episodic nature of the meaningless encounters and/or to behavioral outcome, rather than re-activation processes of initial encounter context as proposed by the 'redintegration' theory. In order to address this hypothesis directly, we divided subjects into groups according to whether recognition accuracy for images paired with a meaningless sound upon initial encounter (V+) was impaired (group1) or enhanced (group2) with respect to images encountered only visually (V-).
We computed sensitivity (d’) and response bias (c’) measures to investigate differences between groups in terms of perception and response strategy. Data were submitted to a 2x2 ANOVA with between-subject factor of group and within-subject factor of modality (V- and V+). A significant group x modality interaction for d’ and post-hoc paired t-tests revealed a significant decrease of d’ in group1 (mean ± s.e.m.: d’(V-)= 2.96 ± 0.28; d’(V+)= 2.27 ± 0.30; t=3.218; p=0.024). Analyses on relative criterion (c’) revealed a significant group x modality interaction, and post-hoc paired t-tests revealed a significant effect for c’ for group2 (mean±s.e.m.: c’(V-)= -0.23±0.03; c’(V+)= -0.18±0.03; t=-4.189; p=0.009). This pattern suggests the two groups use distinct strategies to perform the task, either relying on perception or adopting a lax response criterion. To examine the neural bases of these strategies, we analyzed event-related potentials (ERPs). In terms of initial multisensory presentations, we observed a significant group by condition interaction at 270-316ms post-stimulus for the GFP. Further, this group difference was also observed at the level of source estimations. A significant group by condition interaction within right temporal regions at 270-346ms post-stimulus was observed, suggestive of differential underlying multisensory processing that may explain the opposing behavioral outcome during unisensory repetition discrimination.

The Song in Your Head: Identifying Tonal Frequency Patterns in Auditory Cortex

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Purpose: Recent fMRI (Formisano et al. 2008) and EEG studies (Schaefer et al. 2011) have shown that it is possible to identify an auditory stimulus based on the spatial pattern of fMRI activity within the human auditory cortex (AC). We take this a step further by developing a decoding method based on quantitative receptive-field models to characterize the relationship between auditory stimuli and BOLD responses in AC (Kay et al. 2004). We first measured the population receptive fields (pRFs) of individual voxels (Dumoulin and Wandell 2008), then used the pRFs to predict the pattern of responses to novel stimuli. We were able not only to successfully classify novel stimuli, but also accurately estimate the frequencies presented in the stimulus over time. Our results suggest that, for simple pure tone stimuli, it is possible to reconstruct a reasonable representation of a person's auditory experience from measurements of brain activity.

Methods: Data were collected from 4 subjects (age: 26-45 years) on a 3T Philips Achieva using an 8-channel head coil. Pure tone stimuli were presented at an equal perceived volume (65-85 dB) as a random sequence of 240 unique frequency blocks (88-8000 Hz). Our pRF analysis assumes that the sensitivity of a voxel is a 1-dimensional Gaussian function of log frequency. PRF centers and widths were found that best-predicted the fMRI time-courses to this random stimulus. These pRFs were then used to estimate the frequencies presented over time from the time series generated by novel pure-tone sequences. This was done using a fitting algorithm that identified the series of frequencies for which the (previously estimated) pRFs generated a predicted time series that best matched the measured BOLD responses to the novel stimulus over time.

Results: Consistent with previous results, pRF centers were tonotopically arranged, forming two mirror-symmetric gradients running perpendicular to Heschl's gyrus, likely corresponding to hA1 and hR subdivisions of the primary auditory cortex (PAC) (Da Costa et al. 2011, Humphries et al. 2010, Striem-Amit et al. 2011). Performance classifying different tone sequences was near perfect. When identifying individual tones over time, the correlation for individual TRs between the actual frequency presented and the predicted frequency was .7632. Averaging across all trials (subjects, scans, and TRs) the correlation was .9631. Tone identification errors were limited to tones similar in frequency likely due to the relatively broad pRF bandwidths of most voxels, evoking similar levels of activation for nearby tones.

Conclusions: The pRF model can be used in auditory cortex to identify individual pure tones presented over time. A natural extension of these results will be to apply these methods to more natural stimuli including musical pieces (Schaefer et al. 2011) and behaviorally relevant stimuli such as speech (Formisano et al. 2008).

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Investigating auditory processing in conscious awake marmosets using fMRI

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Understanding the processing of sounds by the brain is a major goal in neuroscience. The common marmoset (Callithrix jacchus) is a New World primate that has gained increased popularity in experimental neurobiology. Like humans, marmosets are a social species that utilizes a vast array of vocalizations for communication. The use of non-invasive imaging techniques, such as fMRI, would allow the simultaneous investigation of the multiple brain areas involved in the perception, interpretation, and generation of sounds. Here, we propose to use fMRI to investigate auditory processing in common marmosets. Therefore, our goals are three-fold: 1) to develop a technique for auditory stimulation in marmosets, 2) to show significant activation of marmoset auditory cortex (AC), and 3) to investigate the tonotopy of different areas of AC. Adult marmosets (n= 2) were first acclimated to being restrained in an MRI-like scanning environment. Each subject's head was restrained with individual custom-made helmets designed to fit the contours of each subject. Subjects were placed in a 7T/30cm MRI where auditory stimulation was delivered directly to the ear canals. Two surface RF coils were placed above AC to acquire the MRI signal. In one experiment, a total of three different stimuli with a length of 4s each were presented: a burst of white noise, a phee call, and a frequency sweep ranging from 1kHz-20kHz. BOLD fMRI data were acquired using a gradient-echo echo-planar imaging sequence at the end of each stimulus according to a sparse-sampling paradigm. Other acquisition parameters were: FOV: 3.84 x 2.88 cm2, Matrix: 128 x 96, Slice thickness: 1 mm, 8 slices, and TE/TR=27ms/16s. In a second experiment, high, medium, and low tone sequences were presented and each stimulus consisted of three different frequencies with equal bandwidths (high = 11.5-12.5kHz, medium = 5.5-6.5kHz, low = 0.5-1.5kHz). Each stimulus was 36s. In a third experiment a total of six tones were presented ranging for 0.5kHz-16kHz separated by octaves. Each tone was 36s in duration. Acquisition parameters for the second and third experiments were: FOV: 2.88 x 2.88 cm2, Matrix: 96 x 96, Slice thickness: 1 mm, 4 slices, and TR=3.6s. The location of the auditory cortex was identified using the anatomical structure of lateral sulcus (LS). Our results show a robust bilateral activation of the primary auditory cortex during stimulation vs. silence in every experiment, $p<.001$. The time course of activation was also strongly correlated to the stimulations. Preliminary results show a differential activation between high and low frequencies in experiment 2.

Functional Connectivity Within and Across Structures in the Barn Owl Midbrain in Response to Auditory and Visual Stimulation

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We are using multielectrode arrays to measure correlations in firing between synaptically connected neurons in the barn owl auditory localization pathway. The targets are feedforward connections from ICCls to ICX and bidirectional connections between the ICX and dOT. To simultaneously measure paired responses, a 7-channel array (Thomas Recording) with tight concentric spacing was deployed in one structure and a single tungsten electrode in the other. Auditory and visual receptive fields were determined using, respectively, dichotic noise bursts and static, looming or moving dots presented via a DLP projector. The auditory and visual tuning of all sites within the array was similar, and electrode tract reconstruction confirmed sampling of nearby neurons. Functional connectivity was determined using cross-correlation analysis with shuffle. Preliminary results were obtained from 3 owls with sites located in ICX or dOT. Correlograms were diverse in profile, indicating heterogeneous connectivity patterns even among neighboring neurons. Tight peaks were found in a subset of pairs, suggesting neurons with common drivers and/or monosynaptic interconnections. This approach is now being applied to analysis of prism-adapted owls, to probe both the circuit mechanisms that guide learning and the functional consequences of the structural re-wiring that is known to occur. ICCls = lateral shell of the central nucleus of the inferior colliculus. ICX = external nucleus of the inferior colliculus. dOT = deep layers of the optic tectum.

Timbre discrimination in ferrets: Exploring the neural basis of perceptual constancy

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Perceptual constancy (or invariance) is the ability to recognize an object as the same despite variation in sensory input. For example when hearing a vowel (e.g. /u/), we can recognize a constant sound identity despite variation in pitch or voicing within or between speakers. Furthermore, we can maintain vowel identity in a variety of background noise conditions despite degradation in sensory input. We are interested in the neural mechanisms underlying perceptual constancy in hearing and specifically in vowel perception. Using the ferret as an experimental model, we have trained animals in a two-alternative forced choice task to discriminate between two artificial vowels (e.g. /u/ and /e/). Vowels were presented at a range of pitches (n = 7 ferrets), using a voiced or voiceless sound source (n = 4 ferrets) and also in varying noise conditions (n = 2 ferrets). We find that ferrets are able to accurately discriminate vowels despite task-irrelevant variation in sensory input due to vowel pitch, voicing or low level background noise (10 dB signal to noise ratio). In three ferrets trained in this task, we have implanted electrodes for chronic recording of neural activity in auditory cortex during vowel discrimination. We will discuss current work examining the responsiveness of auditory cortical neurons to vowels when discriminating across task-irrelevant parameters and the extent to which neuronal invariance exists within auditory cortex. To determine a causal a role for auditory cortex in maintaining perceptual invariance during vowel discrimination we are also performing reversible inactivation of auditory cortex via cooling.

Causal role of primate auditory cortex in auditory perceptual decision-making

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Auditory decision-making requires the conversion of an incoming auditory stimulus into a categorical perceptual judgment. Recent studies suggest that neural activity in the ventral auditory pathway, which begins in the medio- and antero-lateral belt regions (LB) of the auditory cortex and continues to the ventrolateral prefrontal cortex, plays a role in this conversion. For example, neurons in these brain regions can encode signals that are relevant to auditory perception. However, the causal relationship between neural activity in the ventral pathway and auditory perception has not been elucidated. To address this question, we recorded neural activity from the LB and then applied electrical microstimulation at the recording site while a monkey performed a novel auditory-discrimination task. For this task, the monkey reported whether a sequence of tone bursts contained more high-frequency tone bursts (>2 kHz) or low-frequency (<1.5 kHz) tone bursts; the monkey could report its choice at anytime during the presentation of tone bursts. The tone-burst frequencies were selected based on the best frequency of the currently recorded neuron. By systematically changing the proportion of high-frequency and low-frequency tone bursts, we manipulated the task difficulty: a trial that contained only high-frequency tone bursts was easy to judge as being a high-frequency sequence, whereas a trial with a mixture of high- and low-frequency tone bursts was relatively more difficult to judge. We found that, as the task difficulty increased, the monkey's accuracy decreased and reaction time increased. LB activity, on average (N = 47), was modulated by the stimulus parameters: LB activity increased as the proportion of tone bursts with frequencies matching the neuron's best frequency increased. Finally, microstimulation of the LB throughout stimulus presentation biased, on average (N = 42), the monkey's decisions toward the choice associated with the best frequency of the stimulated neurons. Together, these results suggest that LB neural activity represents the sensory evidence used to form a perceptual decision. Accordingly, microstimulation of LB sites alters this evidence and biases the decision process, a finding consistent with a causal role of LB neurons in auditory perception.

Direction selectivity mediated by adaptation in the owl's inferior colliculus

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Motion direction is crucial in natural scene analysis. It is thus not surprising that selectivity to motion direction is commonly observed in sensory systems. In the auditory system, the mechanisms that confer direction selectivity (DS) to neurons are not well understood. Neither is it known whether sound motion is independently encoded. Here we investigated these questions in neurons of the owl's external nucleus of the inferior colliculus (ICx), where auditory space is represented in a map. Using a high density speaker array we show that the preferred direction and the degree of DS can be predicted by adaptation, when sounds move over an asymmetric spatial receptive field (SRF). At the population level, we found an orderly distribution of DS overlapping the map of space, such that preference for sounds moving toward frontal space increased with eccentricity in spatial tuning. This trend was consistent with larger SRF asymmetry in neurons tuned to more peripheral auditory space. A model based on spatiotemporal summation predicted the observations. This study shows, for the first time, that response adaptation and receptive-field properties can explain DS to sound motion and an ordered distribution of preferred direction in the auditory system.

DURATION OF ACOUSTIC EXPERIENCE SHAPES DEVELOPMENT OF AUDITORY CORTEX CARTOGRAPHY

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Sensory input is essential for the functional development of the cerebrum. A lack of acoustic experience in deaf individuals impairs maturation of auditory circuits and structures. Auditory cortical areas are differentially affected in cats deafened shortly after birth versus cats deafened in adulthood. Interestingly, the total volume of auditory cortex is positively correlated to the age of deafness onset, such that auditory cortex is more diminished in cats deafened earlier in life. To further understand the relationship between acoustic experience and cortical development, auditory cortex of congenitally deaf cats (CDC) was examined. In CDCs, a genetic defect causes inner ear degeneration during development, preventing any hearing experience. Cerebral cytoarchitecture was revealed immunohistochemically using SMI-32, a monoclonal antibody used to distinguish auditory areas in many species. Auditory areas were delineated in coronal sections and their volumes measured. In CDCs, total auditory cortex volume was dramatically reduced in comparison to hearing animals. Total auditory cortex volumes were reduced, but to a lesser extent in early deafened and adult deafened cats, supporting the correlation between auditory cortex volume and hearing experience. While all ten auditory areas were significantly diminished in deaf animals, some regions appeared to be more affected than others. Within auditory cortex of CDCs, the fractional volume of primary auditory cortex was significantly reduced in comparison to hearing cats, while second auditory cortex was expanded. In early deafened or adult deafened cats, primary auditory cortex and second auditory cortex were similarly reduced or expanded, but to a lesser extent. Anterior limits of rostral auditory areas were shifted posteriorly, suggesting expanded somatosensory cortex. Additionally, posterior limits of caudal auditory areas were shifted anteriorly, suggesting expanded visual cortex. Furthermore, a novel area with uniquely light SMI-32 labeling was discernible from the strongly immunoreactive anterior auditory field and adjacent somatosensory cortex. This new area may reflect underlying crossmodal plasticity following congenital deafness. Overall, this study demonstrates the importance of sensory input during development to shape the overall cartography of the cerebrum.

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Reversible inactivation of primary auditory cortex by cooling in the awake, behaving ferret: effect on sound localisation ability

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Cooling of a brain area can be used to perform reversible inactivation of that brain area (Lomber et al. 1999). We sought to develop this technique for use in the awake, behaving ferret. Previous evidence of reversible inactivation in awake ferret, by $GABA_A$-subunit inhibitor, muscimol, and in cat, by cooling, suggests that inactivation of primary auditory cortex will cause a deficit in localisation of auditory cues in the hemisphere contralateral to the side of inactivation and in both hemispheres with bilateral inactivation (Malhotra et al. 2008, King et al. 2007). We cooled primary area A1 of ferret auditory cortex while the animal performed an approach-to-target auditory localisation task. Since cooling brain areas may be more sensitive than previous methods of inactivation (ablation and pharmacological) we tested a range of stimulus lengths from 2000-100 ms. Preliminary results, at stimulus length 500 ms, were compared to performance with cooling loop implants but without cooling and show reversible inactivation of A1 causes a significant deficit in the localisation ability of the ferret in the side contralateral to inactivation ($p<0.001$) but not to the ipsilateral side ($p>0.05$).

Title:

Corticostriatal synaptic weights encode arbitrary associations between stimuli and motor responses during auditory discrimination

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Abstract:

Corticostriatal plasticity plays a key role in reinforcement learning, but how associations between stimuli and motor responses are established remains unclear. Recent work from our group demonstrated a causal role of corticostriatal neurons in driving choices during an auditory discrimination task (inspired by the classic random dot motion task used by Newsome and colleagues in macaques), in which subjects were required to choose the left or the right response port depending on the perceived frequency of a sound. Here we test the hypothesis that changes in the strength of corticostriatal synapses underlie the association between sound and action required to perform this task. Our results indicate that changes in the strength of specific subset of corticostriatal synapses encode the arbitrary association between stimulus and motor response.

To study the synaptic changes underlying learning in this task, we developed a novel recording paradigm which enabled us to track corticostriatal synaptic strength *in vivo* across days. To assay corticostriatal connection strength *in vivo*, we injected a virus expressing Channelrhodpsin-2 into the auditory cortex, and implanted optic fibers with tetrodes into the striatal region receiving auditory cortical inputs. Pulses of blue light triggered presynaptic release from cortical axon terminals and elicited postsynaptic responses in striatal neurons. Because the striatum, like the CA1 region of the hippocampus, lacks recurrent excitatory connections, we could interpret the light-evoked local field potential (LFP) as a measure of evoked synaptic current. Using this approach, we monitored changes in corticostriatal synaptic connectivity during the course of training.

Acquisition of the task led to rapid and persistent potentiation of corticostriatal connections. Exploiting the spatial segregation of the striatal projections of auditory cortical neurons tuned to low or high frequencies, we characterized these changes as a function of the frequency preference of the recording site. We found that learning selectively potentiated light-evoked postsynaptic responses at only a specific subset of sites: those tuned to frequencies associated with contralateral choices. Since all sensory cortical areas send projections to the striatum, our findings suggest a general mechanism for the formation of arbitrary sensorimotor transformations.

Spatiotemporal cortical representation of phonological units in continuous speech perception

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Human speech is capable of conveying a huge amount of information by flexibly combing a finite set of phonological units. To perceive speech, one must extract and recognize these discrete units from continuous acoustic stimuli. Here, we used electrocorticography (ECoG) technique to explore the cortical representation of Chinese vowels in continuous speech perception. Subjects were presented with narrative stories read by Mandarin speakers. Based on the assumption that ECoG responses to continuous speech can be largely accounted for by the superimposition of cortical representation of phonological units, we applied Infomax algorithm (Lee et al. 1999) to millions of spatiotemporal patterns resampled from multi-channel ECoG signals (60~140 Hz), to obtain a set of filters for decomposing raw ECoG responses to spatiotemporally independent components. Interestingly, although no phonological information of stimuli was accessed in decomposing, many components were found significantly (p<0.01) associated with vowels. For example, peak responses of each component were more frequently observed within a ~300ms time window preceded by a unique subset of vowels, but were less frequently observed following a different subset of vowels. For most components, the characteristic spatiotemporal patterns were sparse in space, dominated by ECoG response within a single channel (mainly located in posterior superior temporal gyrus and supra-marginal gyrus), and the temporal courses resembled previous findings using separately presented stimuli (Chang et al. 2010). By combining the components, the neural distance among vowels was explored with hierarchical clustering and multidimensional scaling. The representational structure was in substantial concordance with phonological and perceptual similarity of Chinese vowels (Zhang et al. 1982). In summary, we demonstrated that cortical representation of discrete phonological units exists and is tractable during continuous speech perception, which is arguably a prerequisite for the full understanding of speech perception.

Keywords: speech perception, neural representation, vowels

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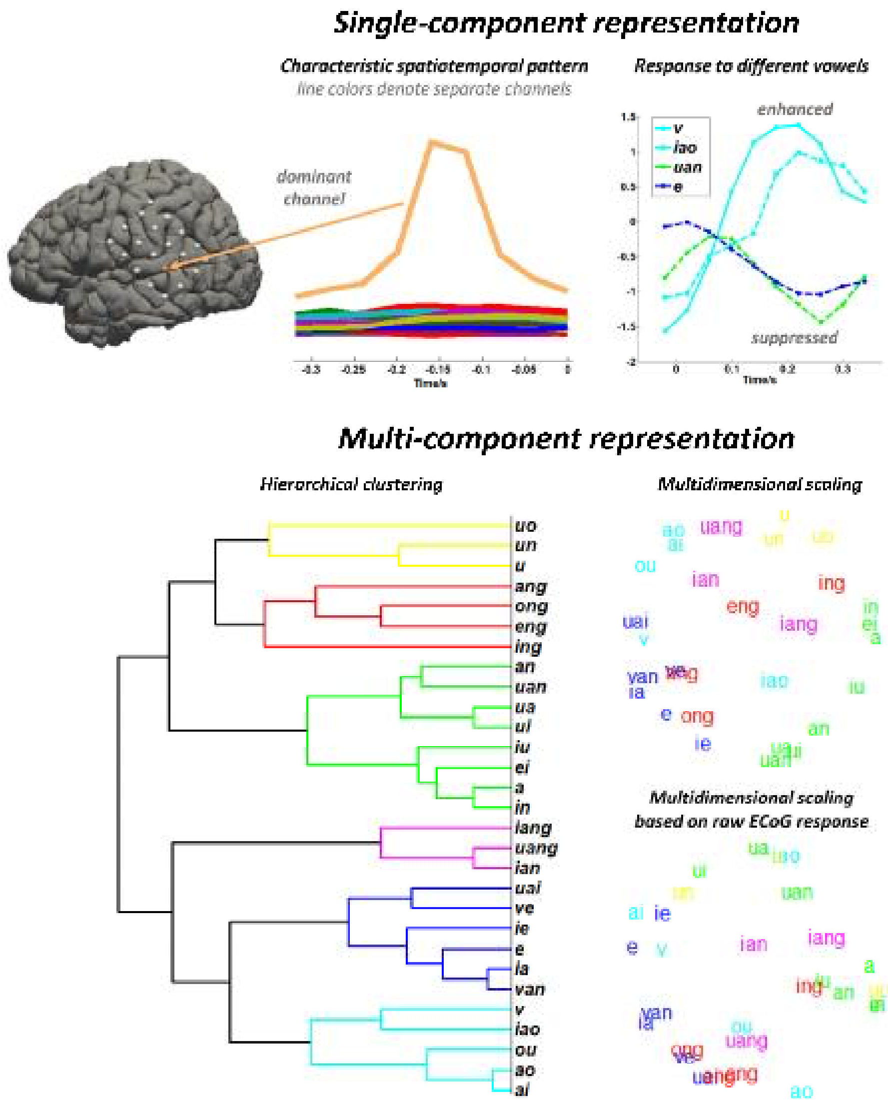
Single-component representation
Characteristic spatiotemporal pattern
line colors denote separate channels
dominant channel
Time/s
Response to different vowels
enhanced
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Time/s
Multi-component representation
Hierarchical clustering
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Multidimensional scaling
Multidimensional scaling based on raw ECoG response

Schizophrenia-associated microdeletion dynamically disrupts communication to the auditory cortex through microRNA-dependent mechanisms

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Auditory hallucinations are an enigmatic symptom of schizophrenia. Although hallucinations are alleviated by antipsychotic agents such as D2 dopamine receptor (DRD2) antagonists, the neural circuits responsible for auditory hallucinations and the mechanism of sensitivity of these circuits to antipsychotics are unknown. Here we show that murine models of 22q11 deletion syndrome, a genetic disorder associated with schizophrenia, have a specific synaptic transmission deficit at thalamocortical projections to the auditory cortex. Disrupted thalamocortical transmission is caused by aberrant elevation of Drd2 in thalamic relay neurons and rescued by antipsychotics. We also found that DRD2 is abnormally elevated in the thalamus of schizophrenic patients postmortem. Screening a panel of mutant mice revealed that haploinsufficiency of the microRNA-processing gene *Dgcr8* causes the *Drd2* elevation in the thalamus, thalamocortical deficiency, aberrant sensitivity of thalamocortical projections to antipsychotics, and abnormal auditory cortex processing. These data indicate that aberrant DRD2 elevation in the thalamus is a pathogenic event underlying the auditory symptoms associated with schizophrenia.

Effects of noise exposure on sound processing in the mouse primary auditory cortex

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Exposure to loud sounds damages the function of the inner ear and induces profound changes in the central parts of the auditory system. Acoustic trauma results in changes in the receptive fields of cortical neurons, which may contribute to the development of tinnitus. However, the role of different classes of cortical neurons in the development of various trauma-induced receptive field changes has not yet been resolved. Therefore, we evaluated the effects of acute acoustic trauma on the functional properties of neurons in the primary auditory cortex (A1) using single-unit extracellular recordings and two-photon calcium imaging *in vivo*.

We used C57Bl/6 mice aged 8-18 weeks, anaesthetized with ketamine and xylazine. Acoustic trauma was induced by 125 dB SPL white noise. Three 5-minute exposures to noise were followed by an additional 15-minute noise exposure. Before and after each successive noise exposure, the responses of neurons to two sets of acoustical stimuli (broad-band noise and pure tones) were recorded. Extracellular unit activity was recorded with a 16-channel multielectrode, and the two-photon imaging experiments were performed using the calcium indicator OGB-1. In addition, the auditory brainstem responses (ABR) were measured in separate experiments using the same noise exposure protocol to reveal the extent and character of peripheral damage.

ABRs showed a substantial threshold shift at higher frequencies, while the peripheral sensitivity in the area of lower frequencies remained rather unchanged. Similar trends were observed in the A1 using both extracellular recordings and in vivo calcium imaging. In the auditory cortex, neuronal response latency and threshold increased significantly after the first 5-minute exposure. In a subset of neurons with best frequencies (BFs) above 10 kHz, a shift of their BFs toward lower values was observed. Neurons with lower BFs mostly retained their frequency preference. The two subsequent noise exposures affected the response properties of A1 neurons to a lesser extent. After the final 15-minute exposure, enhanced stimulus-evoked responses were observed, characterized by a greater variability in the spike counts and spike timing as well as an increase in the rebound activity.

Evidence of voluntary vocal control by the common marmosets (Callithrix jacchus)

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Humans are capable of exquisite voluntary vocal control in such behaviors as speaking and singing. When presented with altered auditory feedback, human subjects quickly adjust parameters of vocal production to compensate for feedback perturbations. However, it has long been believed that non-human primates are incapable of voluntary vocal control. Instead their vocalizations are stereotyped and do not exhibit compensations when presented with feedback perturbations. Recent experiments in our laboratory in the common marmoset (Callithrix jacchus), a highly vocal New World primate, showed that they exhibited the Lombard effect in noisy background and were capable of adjusting the timing of calls during vocal exchanges in the presence of interfering noise. In the present study, we investigated whether marmosets are capable of altering acoustic structures of their vocalizations when presented with interrupting noises. Marmosets produce long duration calls known as phee calls and are often engaged in antiphonal calling when visual contact is occluded. Our study was based on phee calls and the antiphonal calling behavior paradigm. We introduced acoustic perturbations by playing interfering noises during a vocalization while a marmoset was producing spontaneous phees or engaged in antiphonal calling. The acoustic perturbations led to vocal alterations not only in call timing but also in its spectral characteristics. Our results showed that: (1) with acoustic perturbations, marmosets produced phee calls with fewer phrases than observed during vocal exchanges in normal conditions; (2) the perturbations resulted in changes in the fine structure of calls (e.g., change in frequency slope was found to be higher in calls with perturbation compared to calls in silent background); (3) when presented with band-pass noise at frequency either below or above the fundamental frequency (F0) of vocalization, marmosets tended to shift their vocalization F0 away from the noise spectrum. Collectively, these results suggest that marmosets rely on auditory feedback to maintain their vocalizations and exhibit voluntary control of the acoustic structures of their vocalizations. [This research is supported by NIH grant DC-8578.]