

Computational fMRI Reveals Separable Representations Of Stimulus and Choice In Auditory Cortex: A Tool for Studying the Locus Coeruleus Circuit

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Abstract:

The locus coeruleus (LC) influences many cognitive functions (e.g., arousal, attention, and perception) due to its broad noradrenergic projections throughout the brain. However, the computational mechanisms of LC's influence are complex and so constitute an area of active investigation. One promising approach would be to observe how LC engagement changes stimulus encoding in sensory cortex. As a preliminary step towards this goal, we combined a novel auditory oddball discrimination task with high-resolution fMRI (2mm³ isotropic voxels) and multivariate pattern analysis in humans. Even with modest trial counts (~24-70 trials per condition), sparse logistic regression classifiers could decode both auditory stimulus identity and behavioral choices above chance in auditory cortex, in single subjects and in each of six oddball stimulus levels. Further, stimulus decoders were highly specific to each oddball level, but choice decoders generalized across levels; there was also little overlap between stimulus and choice decoders. These findings suggest that our paradigm and computational analyses provide a promising approach for investigating LC influences on sensory neural representations in humans in the future.

Keywords: MVPA; fMRI; decoding; perception; auditory cortex; locus coeruleus

Introduction

The diverse efferent noradrenergic projections of the locus coeruleus (LC) nucleus suggest that this structure may be essential for maintaining normal cognitive abilities (Freedman, Foote, & Bloom, 1975; Moore & Bloom, 1979). A substantial factor in the challenge of studying LC-norepinephrine (LC-NE) system's modulation of cognition arises from three key factors: the bi-directional relationship between LC activity and multiple interacting cognitive functions (Aston-Jones & Cohen, 2005; Aston-Jones, Rajkowski, & Cohen, 1999; Berridge & Waterhouse, 2003; Clewett, Huang, Velasco, Lee, & Mather, 2018; Nieuwenhuis, Aston-Jones, & Cohen, 2005;

Rajkowski, Kubiak, & Aston-Jones, 1994; Sara, 2009; Tomlinson, Irving, & Blessed, 1981; Usher, 1999), LC's broad projections throughout the brain (Aston-Jones & Cohen, 2005), and the non-monotonic influence of LC engagement on cognition (Yerkes & Dodson, 1908).

One approach to addressing these challenges in the perceptual domain would be to investigate the computational consequences of LC engagement on the neural encoding of perceptual stimuli in relevant areas of sensory cortex. To do so in humans would require sophisticated characterization of neural representations with a high degree of spatial precision, in conjunction with appropriate behavioral paradigms. Here, we took a first step towards this goal by aiming to develop and optimize an appropriate auditory perception experimental paradigm and analytical approach using high-resolution functional neuroimaging in humans and machine learning decoding.

We modified the traditional auditory oddball behavioral paradigm -- often used as a modulator of arousal via LC engagement and an activator of auditory cortex (Clewett et al., 2018) -- to include a sensitivity manipulation. Our auditory oddball discrimination task thus includes multiple levels (i.e., distance from the frequent tone) of oddballs. We then used state of the art machine learning decoding (sparse logistic regression) to decode frequent versus oddball trials and subjects' behavioral choices with low trial counts, and evaluated the similarity in neural representations for different oddball levels and across decoders for stimulus identity versus choice. To anticipate, our results provide converging evidence that our novel paradigm, high-resolution fMRI, and sophisticated computational analytic approach is appropriate for characterizing LC modulation of neural representations in future studies.

Methods

Subjects

Seven healthy undergraduate students from the University of California, Riverside (2 males, 5 females, mean age = 29.4, SD = 13.3) provided written informed consent to participate in this study. Participants reported normal or

corrected-to-normal vision and hearing, had no history of psychiatric/neurological disorders, and were compensated for their participation. The study was approved by the University of California, Riverside Institutional Review Board.

Auditory oddball discrimination task

During fMRI scanning, subjects listened to a series of tones that were either frequent or oddball. A frequent trial contained a sequence of five consecutive beeps of the same frequency (1000 Hz), and an oddball trial consisted of five consecutive beeps with one odd tone [1004, 1008, 1016, 1032, 1064, or 1128 Hz] embedded (Figure 1). Subjects indicated their choice on each trial (“oddball or frequent?”) using a 4-button MRI-compatible response device. We interspersed “blank” trials (no tones) pseudorandomly with the oddball and frequent trials as controls; on these trials, subjects were instructed which button to press.

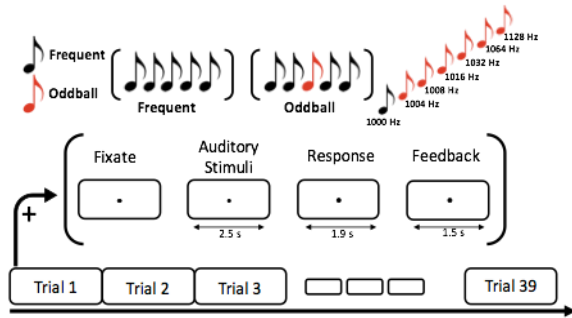


Figure 1: **Auditory oddball discrimination task.** Auditory sequences of five consecutive tones made up “frequent” (five 1000 Hz tones) and “oddball” trials (single odd tone [1004, 1008, 1016, 1032, 1064, 1128Hz] embedded in four 1000 Hz tones). The odd tone was never first or last.

Neuroimaging data acquisition and preprocessing

BOLD data were acquired on a 3T Siemens PRISMA scanner (TR/TE = 2000 ms/ 32 ms, flip angle (FA) = 69°, FOV = 220 x 220 mm², voxel size 2x2x2 mm³) using a 64-channel head coil. MR-compatible headphones and a 4-button box were used for stimulus presentation and response recording. We used the SPM12 toolbox in Matlab (www.fil.ion.ucl.ac.uk/spm) to perform standard preprocessing, including realignment anatomical segmentation, and coregistration. All EPI images and the structural (T1: TE/TR/inversion time = 3.02 ms/ 2600 ms/ 1060 ms, flip angle (FA) = 8°, and a 0.8 mm isotropic voxels) were registered to the first functional scan. For the purposes of decoding, we performed all analyses in individual brain space (i.e., did not standardize to MNI or Talairach) and did not perform any spatial smoothing. A standard hemodynamic response function (HRF) was subsequently fitted to the BOLD response in each trial time-locked to stimulus onset, following standard

approaches (<http://www.pymvpa.org>), which yielded beta weight patterns for all voxels on a trial-by-trial basis. HRF fitting was done via custom-written Python scripts utilizing the PyMVPA2 toolbox.

Automated gray matter parcellation was completed using the FreeSurfer software (recon-all). An auditory cortex ROI for each subject was then constructed combining the G_temp_sup-G_T_transv, G_temp_sup-Lateral, and S_temporal_transverse Freesurfer labels (Desikan-Killiany Atlas) across left and right hemispheres.

Decoding stimulus identity and behavioral choice

Prior to any classification, we normalized all single-trial betas via z-score. To characterize the neural representations of different oddball levels in comparison to frequent tones, we first performed simple dimensionality reduction by using a one-way ANOVA on trial types (oddball levels, frequent, and blank) to select 1000 informative voxels within the combined auditory ROI, based on their single-trial beta weights. We next trained a series of sparse logistic regression classifiers (Krishnapuram, Carin, Figueiredo, & Hartemink, 2005) on these informative features (betas) -- one classifier in each oddball level (48 trials per condition: 24 oddball, 24 frequent) -- to discriminate the two trial types based on stimulus identity. We also trained a second series of classifiers to discriminate subjects’ choices on a trial-by-trial basis, also within each oddball level (~70 trials per condition, unevenly spread across choices). Classifier performance was quantified using the bias-free metric of area under the receiver operating characteristic curve (AUROC) across six-fold cross-validation.

Results

As expected, subjects’ behavioral performance (hit rate) increased as a function of auditory oddball level (Figure 2a). The sparse logistic regression classifiers were able to decode both stimulus and choice above chance, despite the relatively few trials in each condition (Table 1).

A 2 (stimulus/choice) x 6 (oddball level) repeated measures ANOVA revealed that the stimulus decoder performed better than the choice decoder across oddball levels, despite lower trial numbers in each condition ($F(1,6) = 43.799, p < .001$) (Figure 2b). We observed no significant main effect of oddball type in this top-level omnibus ANOVA ($F(5,30) = 1.908, p = .123$) and no interaction between decoder type and oddball level ($F(5,30) = 1.553, p = 0.20$). However, because our overall number of subjects is low, to better evaluate the appropriateness of our novel behavioral paradigm and computational neuroimaging approach for the purposes of future studies, we also elected to conduct two step-down one-way ANOVAs on oddball level within each decoder. Within the stimulus decoders we observed no main effect of oddball level ($F(5,30) = 0.493, p$

= 0.799), but within the choice decoders we observed a significant main effect of oddball level ($F(5,30) = 2.650, p = .042$). This suggests meaningful differences may exist between the stimulus and choice decoders overall, and also suggests that choice decoding increases as a function of behavioral performance whereas stimulus decoding appears insensitive to behavioral factors.

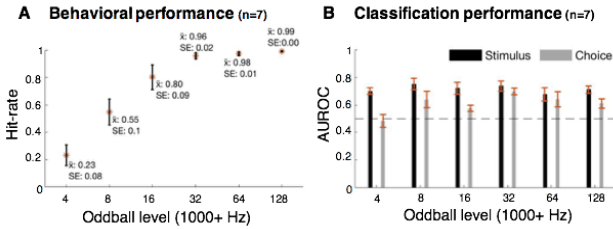


Figure 2: **Behavioral and decoding results.** (A) Subjects’ performance (hit-rate) on the auditory oddball discrimination task during fMRI scanning rose as a function of oddball level. (B) Classification accuracy (AUROC) for both stimulus and choice was above chance for most oddball levels, and was overall higher for stimulus than for choice.

Table 1: **t-values (two-tailed) for all conditions.**

| Oddball | Stimulus | Choice |
|-------------|----------|--------------|
| 1004 | 8.678*** | 0.353 (n.s.) |
| 1008 | 5.844** | 2.280† |
| 1016 | 5.129** | 3.480* |
| 1032 | 6.323*** | 8.515*** |
| 1064 | 3.740** | 2.608* |
| 1128 | 7.649*** | 3.278* |

† $p < .07$, * $p < .05$, ** $p < .01$, *** $p < .001$.

We next examined the similarity of the classifiers across different *pairs* of oddball levels within each subject separately. The goal of this representational similarity analysis (Diedrichsen & Kriegeskorte, 2017; Kriegeskorte, Mur, & Bandettini, 2008) was to evaluate whether there is differential similarity in decoder pairs when decoding stimulus identity versus choice, i.e. whether the representation of “oddballness” in auditory cortex is more similar when we care about a subject’s choices than when we care about the representation of the stimulus-specific properties. For example, we compared the weights placed on informative voxels for the 1004 Hz stimulus decoder versus the 1008 Hz stimulus decoder, 1004 Hz vs 1016 Hz, and so on. We did this for all pairs of stimulus decoders and all pairs of choice decoders, as well as across pairs of stimulus and choice decoders. To compare classifier similarity, we only examined voxels that had received a non-zero weight in the sparse logistic regression (which iteratively removes non-informative features from the classifier) across any of the six folds in both oddball levels being compared. We then used Pearson correlations to

evaluate classifier similarity. Correlation coefficients were subsequently Fisher-z transformed.

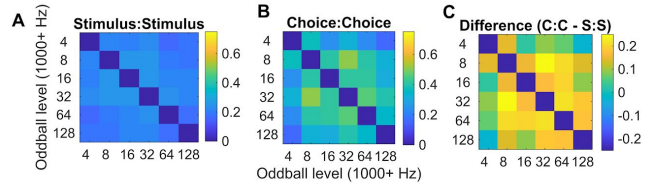


Figure 3: **Generalization of stimulus and choice decoders across pairs of oddball stimulus levels.** (A) Stimulus decoders typically did not generalize from one oddball level to another, but (B) choice decoders demonstrated significantly higher ($t(6), -7.292, p < .001$) generalization. Generalization was also typically higher for more-similar oddball pairs (e.g., 1032 & 1064 Hz) than more dissimilar pairs (1004 & 1064 Hz). Differences in generalization between stimulus and choice decoders are shown in (C).

We found that pairs of stimulus decoders across oddball levels were more *dissimilar* than the same comparisons between choice decoders (Figure 3). That is, there was more overlap in the decoders of 1004 Hz and 1008 Hz choice than there was between 1004 Hz and 1008 Hz stimulus. The mean pairwise similarity for choice decoders was significantly larger than for stimulus decoders across all pairwise comparisons for all subjects ($t(6) = 7.292, p < .001$; Figure 3c), meaning that choice decoders generalize significantly more across oddball levels. We also observed that the similarity between oddball decoders grew slightly as a function of oddball similarity (Figure 3b), which was not observed in the stimulus decoders (Figure 3a). Finally, there was also essentially no overlap between stimulus and choice decoders within each oddball level (data not shown), suggesting unique representations underlie the encoding of each stimulus identity versus the choice to behaviorally respond “oddball”.

Discussion

Our goal with this project was to evaluate the sensitivity of a new approach to studying how LC may modulate neural encoding of perceptual stimuli in sensory cortex. Our novel auditory oddball sensitivity task, in conjunction with high-resolution multivariate fMRI in humans, revealed significant and distinct encoding patterns of stimulus-specific features in the auditory cortex but a more generalized pattern corresponding to choices. Using sparse logistic regression, we were able to decode both stimulus identity and participants’ behavioral responses within each oddball level tested, and further use representational similarity analysis (Diedrichsen & Kriegeskorte, 2017; Kriegeskorte et al., 2008) to quantify the similarity in decoders as a function of stimulus similarity in both classifier types -- even with low numbers of trials in each

condition. These findings suggest a strong promise for our novel paradigm and computational neuroimaging approach in revealing how the LC circuit changes stimulus representations in sensory cortex in future work.

That the stimulus decoders do not generalize from one oddball stimulus level to the next suggests that each stimulus type is encoded in a unique manner within the sensory cortex. In contrast, we observed robust generalization of the choice decoders, which increased as a function of stimulus similarity; we also observed that stimulus and choice decoders are largely distinct from one another, even within the same oddball stimulus level. This pattern of results suggests that choices may be encoded in auditory cortex as a function of top-down influences or feedback projections from higher cortical regions, such as the prefrontal cortex, consistent with previous reports (Gilbert & Sigman, 2007; Mante, Sussillo, Shenoy, & Newsome, 2013). Although the temporal resolution of fMRI is often too poor to differentiate between feed-forward versus feedback projections, future studies may seek to combine our paradigm and approach with more temporally precise neuroimaging modalities.

The present paradigm cannot yet evaluate the computational consequence of LC engagement on the representations in sensory cortex due to the absence of active LC manipulation in our behavioral paradigm. Current work is underway to add these elements to our protocol. Thus, the present work serves to demonstrate the validity of our design and computational analysis approach, paving the way for future studies characterizing the role of LC in driving attention- and arousal-related changes in perceptual representations across a variety of brain regions.

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