Latent state space of the nucleus accumbens BOLD activity indicates internal feedback mechanisms for learning temporal regularity

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Abstract

Statistical learning (SL) is an unconscious cognitive process in which the brain extracts regularities from the environment through repeated exposure. Because of its implicit nature and potentially high individual variability, SL posts a major challenge for studying its neural mechanisms. In this work, we investigate the latent brain states that drive multivoxel patterns of functional neuroimaging data during the learning of temporal regularity embedded in sequential visual inputs. This approach allows the latent states to be individual-specific while preserving meaningful group-level consistency. We found that, consistently across individuals, a state in the nucleus accumbens was associated with the perceptual facilitation effect as the subjects were learning the temporal pattern implicitly. This state occurred more frequently during random sequences than structured sequences, suggesting a potential error-driven feedback signal for training the internal prediction. These findings open the door to further elucidating network dynamics using the found latent states as guidance.

Keywords: Statistical learning; fMRI; Hidden Markov model; Striatum; Internal prediction error

Introduction

Uncovering the neural mechanisms underlying SL is challenging due to the implicit nature of the learning process. To achieve the learning goals, the brain engages distributed regions that are related to both domain-general and modality-specific processing, allowing expectations to be generated from learned regularities (Conway, 2020; Reber, 2013; Karuza et al., 2013; Thothathiri & Rattinger, 2015; Frost, Armstrong, Siegelman, & Christiansen, 2015). To capture brain activities that support the emerging expectations is difficult with noninvasive neuroimaging methods. On one hand, learning-induced plasticity produces gradually changing signals in SL tasks, which the traditionally contrast-based methods (e.g. general linear models) are not particularly good at capturing. On the other hand, nonstationarity in task data has been a standing challenge for network analysis with functional magnetic resonance imaging (fMRI). Here, we apply hidden markov models (HMMs) (Baldassano et al., 2017; Bishop, 2006) to study SL-induced plasticity in a set of distributed brain regions. We explore the latent brain states that drive the blood-oxygenation-level-dependent (BOLD) activity during the learning of embedded temporal structures in sequential visual stimuli. Even though the multivoxel pattern of latent states may vary among individuals, their presence/absence pattern during the task can reveal important learning-related processing. Moreover, the HMM framework is not affected by nonstationarity, and the interdependency of found states among different brain regions provide a novel way to investigate network interactions.

Methods

Participants Twenty-three adults (mean age = 20.79 years, SD = 2.89 years, 7 males) participated in this study. All participants gave written consent.

Stimuli & procedure Participants viewed sequentially presented images while responding to target images embedded in each sequence (Fig. 1). The stimuli in each sequence were (1) *Letters* or *Pictures* and (2) temporally arranged into triplets ("S-block") or presented in random order ("R-block") (Fig. 1A). The target location followed no systematic pattern in each block either within- or across-participants. Subjects were not informed of the embedded temporal structure.

MRI data acquisition & preprocessing MRI data were acquired on a Siemens 3T Magnetom Prisma scanner with a 64-channel head coil. Functional images used simultaneous multi-slice, T2*-weighted echo-planar scans (TR=800 ms, TE=32 ms, flip angle=61°, FOV=21 cm, matrix=64 x 64, acceleration factor=6, in-plane resolution=2.5 x 2.5 x 2.5 mm^3). Preprocessing steps involved dropping the 4 initial frames, despiking, slice time correction, motion correction, removal of linear and quadratic trends, and artifact detection based on movement or deviation in intensity. Because of the subsequent autocorrelation and HMM analyses, no smoothing was applied to avoid distortion in the BOLD time series.

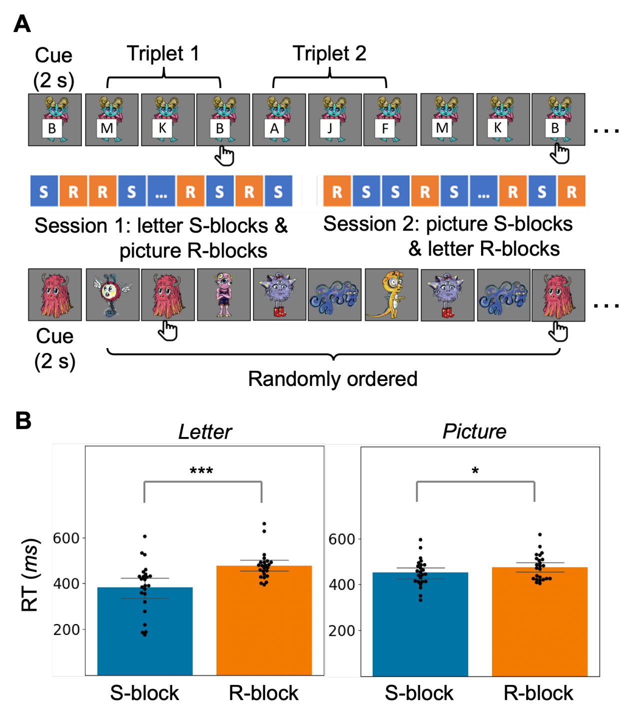

Figure 1: Behavioral sensitivity to temporal structures in sequentially presented visual stimuli. (A) Schematic of task design. (B) RT shown as median ± s.e. across subjects. Black dots represent individual subject data. ***: Wilcoxon test, $p < 0.001$, *: $p < 0.05$.

ROI definition A threshold-free clustering algorithm was applied to find voxels with high lag-1 autocorrelation in 4 regions: the hippocampal formation (HF), caudate (Caud), NAcc and V1, under the assumption that persistent responses to the task would lead to increased lag-1 autocorrelation in the BOLD signal.

HMM design and inference We hypothesized that the multi-voxel BOLD time series can be described by a finite set of latent brain states. Each stimulus in the input sequence corresponded to a brain state, and one state transitioned to another following the transition among stimuli. The latent states were linked to the observed BOLD activity via an emission probability function (Bishop, 2006), which was set to a multivariate Gaussian distribution with dimensions matching the number of voxels in the ROI. The hidden states were estimated using the standard Baum-Welch algorithm (Bishop, 2006). We systematically varied the total number of states in each region and chose the number that led to the best model fitting under Akaike information criterion.

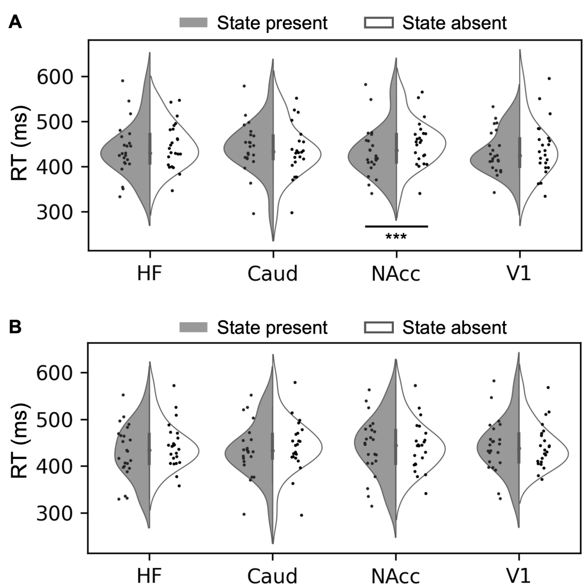

Figure 2: Violin plots of cross-trial median RT when a particular state was present/absent during target presentation. Scattered dots represent individual data. (A) RT associated with the most frequent state. ***: surviving 1000 permutation tests. (B) RT associated with all the other states, presented as mean across states.

Results

Behavior Subjects completed the task with an average hit rate of 97.4 ± 4.7% (cross-subject median ± s.d.), false-alarm rate of 0.2 ± 0.2%, and reaction time (RT) of 446 ± 52 ms. Comparisons of RT between S- and R-blocks showed a facilitation effect of structured sequences on target detection. For both types of stimuli, RT was significantly lower in S-blocks than in R-blocks (Fig. 1B; *Letter*: Wilcoxon signed-rank W = 23.0, $p < 0.00028$; *Picture*: W = 71.0, $p < 0.024$).

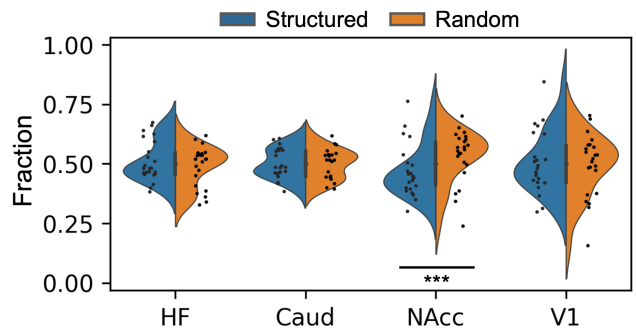

Figure 3: Violin plots of the fraction of trials when the target-associated state occurred during the presentation of structured or random stimuli. Scattered dots represent individual data. ***: surviving 1000 permutation tests.

Brain states during target presentation In each subject and each ROI, we located the brain state that occurred the most frequently during target presentation (referred to as ”critical state” hereafter). We calculated the median RT across trials separately for when the critical state was present and when it was absent. The cross-subject mean of trial-averaged RT was significantly lower when the critical state was present in the NAcc than when the state was absent (observed difference greater than 1000 out of 1000 state-permuted trials) (Fig. 2A). We did not observe such difference in RT with the other ROIs (Fig. 2A). The presence/absence of any other single state did not differentiate the trials by RT either (Fig. 2B).

Critical state in S- & R-blocks Across subjects, the NAcc showed significantly higher (greater than 1000 out of 1000 state-permuted trials) fraction of the critical state in R-blocks than in S-blocks. We did not observe this S/R contrast with the other regions (Fig. 3).

Interdependency of brain states between ROIs We tested whether the state distributions in the HF, Caud and V1 were contingent on the presence/absence of the critical state in the NAcc. Caud but not HF or V1 showed significant contingency (HF: $\chi^2_3 = 7.17, p < 0.200$; Caud: $\chi^2_1 = 11.34, p < 0.00228$; V1: $\chi^2_4 = 5.77, p < 0.651$; Bonferroni corrected for three comparisons).

Discussion

The fact that the critical state consistently differentiated RT across individuals was strong evidence that NAcc activity was closely related to learning. Moreover, the more frequent occurrence of the critical state during R-blocks than S-blocks could be due to error-driven feedback loops between the NAcc and other brain regions. The current work will naturally extend to further exploring network dynamics using these brain states as guidance.

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