Neuromodulatory systems partially account for the topography of cortical networks of learning under uncertainty

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Abstract

Human learning in a dynamic and stochastic environment relies on computational variables such as confidence and surprise. If the learning process is shaped by neuromodulation, then the spatial distribution of receptors and transporters across the brain could put constraints on the spatial distribution of learning-related neural activity. Here, using fMRI data from four probabilistic learning studies and a Bayesian ideal observer model, we reveal a strong spatial invariance across tasks for the functional correlates of confidence, and to a lesser extent, surprise. Using 20 PET receptor/transporter density maps, we then show that this invariance could be partly explained by the chemoarchitecture of the cortex. We identified multiple receptors and transporters whose distribution aligned with the spatial distribution of neural activity in the cortex. While many of these receptors/transporters are in line with previous proposals of neuromodulation of learning, the results also revealed novel associations that can be targeted in experimental studies.

Keywords: neuromodulation; learning; confidence; surprise; fMRI; receptors; Bayesian inference; PET; brain mapping

Introduction

In uncertain and dynamic environments, we continuously adjust our probabilistic expectations based on new observations, distinguishing between random fluctuations and meaningful changes—an adaptive process well-characterized by Bayesian inference. This framework suggests that surprising events, particularly those that diverge from confident predictions, should drive stronger learning updates, a principle reflected in both human behavior and neural data (Peterson & Beach, 1967; Gallistel et al., 2014; McGuire et al., 2014; Meyniel, 2020). Neuromodulators such as dopamine, serotonin, acetylcholine, and norepinephrine have been proposed to mediate this adaptive learning, influencing neural circuits by altering synaptic strength, excitability, and network dynamics (Doya, 2002; Yu & Dayan, 2005; Celada et al., 2013). These effects depend on the diverse characteristics and distribution of neurotransmitter receptors and transporters across the brain (Goulas et al., 2021; Shine, 2019), possibly influencing how learning signals like confidence and surprise are represented. This study tests whether the topography of learning-related neural activity is constrained by the spatial distribution of receptors, using fMRI and PET data across various learning tasks to assess (1) the consistency of learning-related brain activity, (2) its relationship to receptor density, and (3) the identification of neuromodulators specifically linked to confidence and surprise.

Methods

To test whether the brain's response to learning under uncertainty exhibits a consistent spatial pattern across tasks—and whether this relates to neurotransmitter receptor distributions—we generated effect maps for surprise and confidence from four fMRI datasets spanning diverse tasks and modalities. These included three probability learning tasks (Studies 1–3) and one reward-based decision task (Study 4), all involving unpredictable changes in latent variables (e.g., probabilities, rewards) to drive adaptive learning. All data were preprocessed with a unified pipeline, and neural responses were modeled using a general linear model (GLM) with trial-by-trial regressors for surprise and confidence, derived from an ideal Bayesian observer model.

To assess spatial invariance of confidence and surprise representations, we computed group-level effect maps for each variable per study, examined the extend of overlap between maps, and correlated each map with the same latent variable from other studies. Correlations were tested for significance against spin-based null distributions (e.g., Alexander-Bloch et al., 2018; Blaser & Fryzlewicz, 2016; Markello & Misic, 2021).

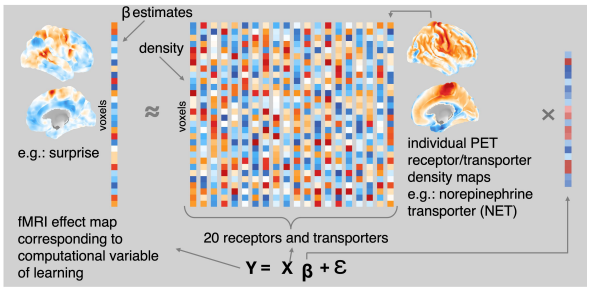

Figure 1: Analysis framework. Do fMRI effects of computational learning-related variables align with cortical receptor/transporter distributions?

We next asked whether this spatial distribution could be predicted from cortical neurotransmitter receptor distributions (Figure 1). We used PET-derived density maps for 20 receptors/transmitters across 10 neurotransmitter systems from Hansen et al. (2022), including an α_2 receptor map from Laurencin et al. (2023). For each subject and task, we used cross-validated multiple linear regression to predict fMRI effect maps from receptor densities. Model performance was assessed against spin-based null model distributions.

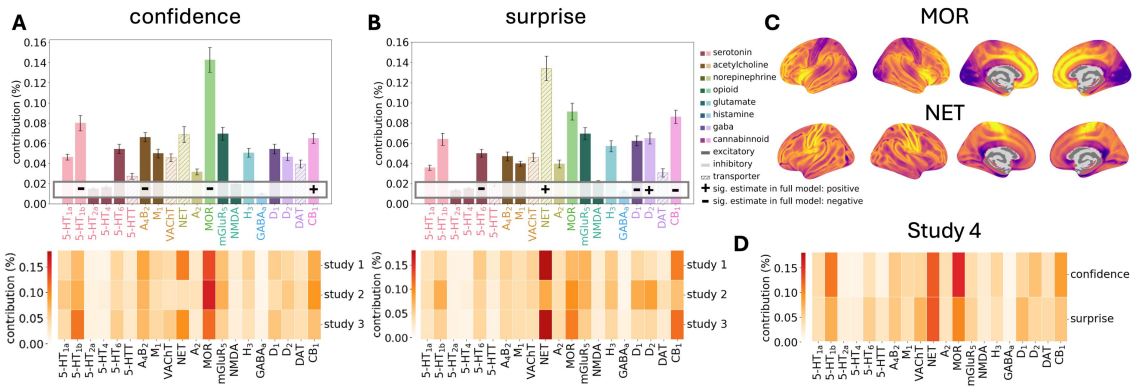

Figure 2: **Predicting fMRI effects from receptor distributions**. Dominance analysis revealed the contribution of each receptor and transporter to the model fit. The percent contribution of each receptor reflects the variables dominance normalized by the model fit (R^2. The top row in **A** (confidence) and **B** (surprise) depicts the mean percent contribution across all subjects from all probability studies (studies 1-3). Error bars reflect the SEM. The signs across the bottom of the bar plot indicate consistent signs and significance across subjects in each study in the full regression model. The heat maps illustrate the dominance results by study. **C**: Example receptor density distributions across the cortex for MOR and NET. **D**: Dominance results for surprise and confidence for the reward learning study (Study 4).

To identify key contributors, we ran a dominance analysis which reveals the contribution of each receptor/transporter to model fit. Dominance scores were normalized by total model fit for comparison across tasks and variables.

Results

We observed consistent spatial patterns for both confidence and surprise effects across studies (all correlations $p<0.001$). Confidence-related effects overlapped across all four tasks, especially in the posterior intraparietal sulcus, precuneus, and anterior insula. Surprise-related activations also showed overlap across the probability learning studies, particularly in the right precentral sulcus and inferior frontal gyrus.

Next, we tested whether the spatial distribution of neuromodulatory receptors could account for the invariant patterns in fMRI effect maps. Cross-validated models using receptor density distributions significantly outperformed null models (all $p<0.001$) in all study-variable combinations except surprise in Study 2. Focusing on individual receptor contributions (Figure 2), dominance analysis revealed that the spatial distribution of the mu-opioid receptor (MOR) consistently explained the largest share of variance in confidence-related brain effects across probability learning tasks. MOR was significant in all three studies, with a negative coefficient—indicating increased activation in areas of low MOR density under high uncertainty. Other receptors (e.g., 5-HT_{1B}, A_4B_2, CB_1) contributed modestly. For surprise, the norepinephrine transporter (NET) showed the strongest and most consistent contribution across probability learning studies, particularly in Studies 1 and 3. Areas with high NET density showed greater activity in response to unexpected outcomes. In contrast, in the reward learning task (Study 4), the contributions of MOR and NET flipped: surprise-related activations emerged in regions with low NET and high MOR density.

Discussion

Our results show that cortical representations of confidence are highly consistent across probabilistic learning tasks, despite differences in sensory modality (visual, auditory), statistical structure (Bernoulli, transitions), and even task type, extending to reward learning. This invariance is partly explained by receptor distributions. Across probability learning tasks, confidence-related activity aligned with several neuromodulator systems, notably 5-HT_{1b} (serotonin), A_4B_2 (acetylcholine), and unexpectedly, μ-opioid receptor (MOR). MOR's strong and consistent contribution may reflect its modulation of the locus coeruleus and dopamine system (Curtis et al., 2001; Gysling & Wang, 1983).

Surprise-related effects were also partly consistent across probability tasks, though more variable and modality-dependent. The strongest correlation across studies was with norepinephrine transporter (NET) density, supporting its role in learning under uncertainty (Yu & Dayan, 2005). Associations with serotonin (5-HT_6) and dopamine (D_1, D_2) receptors also align with existing models of neuromodulation of learning (Doya, 2002). In contrast, surprise effects in the reward task showed limited overlap with other tasks and different receptor contributions, likely due to differences in task demands and the reduced relevance of unsigned surprise.

Together, these findings suggest that cortical effects related to computational learning variables— confidence and surprise—show robust cross-task similarity, partly shaped by receptor distributions. Some receptor associations support previous hypothesis, while others suggest novel neuromodulations of learning.

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