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Translational Neuromodeling Unit

DOPAMINERGIC AND CHOLINERGIC MODULATION OF REWARD LEARNING: A COMPUTATIONAL TRIAL-WISE EEG ANALYSIS

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Introduction

Action optimization relies on learning about the success of past decisions and on accumulated knowledge about the (in)stability of the environment [1]. In hierarchical Bayesian models of learning and decision-making, belief updating is informed by **multiple precision-weighted prediction errors (PEs) that are related hierarchically** [2].

Previous work has examined these computational quantities with fMRI, suggesting that hierarchically different precision-weighted PEs may be encoded by specific neurotransmitters such as dopamine (DA) and acetylcholine (ACh) [3]. By contrast, the **timing** of these different PEs is **poorly understood**.

Using a reward-based associative learning task in which the contingency between cues and rewards changed over time, we inferred, from subject-specific behavioral data, a low-level choice PE ($c\delta_1$) about the reward outcome, a high-level PE (δ_2) about the probability of the outcome as well as the respective precision or uncertainty weights and used them, in a **trial-by-trial analysis**, to explain EEG signals.

Furthermore, the current study employed **pharmacological interventions and genetic analyses (COMT and ChAT) to probe DA and ACh modulation** of these quantities.

Experimental Procedure

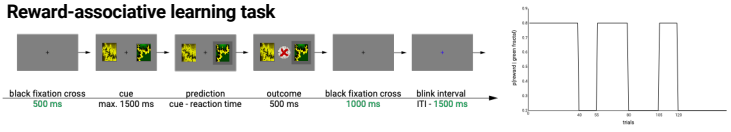
Sample: 73 healthy, male volunteers.

Pharmacological Interventions:
- Amisulpride (400 mg): antagonistic effects on D2/D3 dopaminergic receptors
- Biperiden (4 mg): antagonistic effects on M1 cholinergic muscarinic receptors
- Placebo

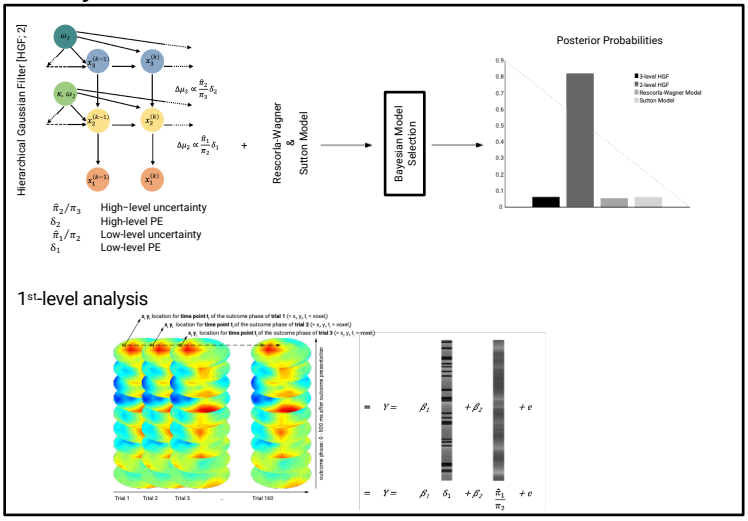
Double-blind, between-subject, placebo-controlled design

EEG data acquisition: 64-channels cap (EASYCAP GmbH), 10-20 system. Subject-specific electrode positions.

Reward-associative learning task



Analyses



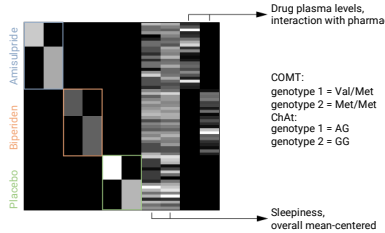
1st-level analysis

Analyses

2nd-level analyses

1-way ANCOVA
Factor: pharmacological group

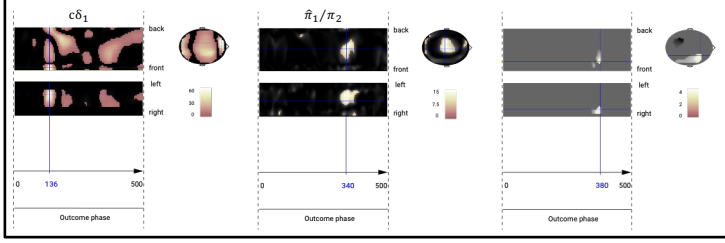
2-way ANCOVA
Factor 1: pharmacological group
Factor 2: genetics



Results

1-way ANCOVA, whole-brain analysis

2-way ANCOVA, mask analysis



Conclusions

Our computational trial-wise EEG analysis captures hidden mechanisms of learning and allows for examining the temporal relation of different computational quantities. Furthermore, employing EEG permits us to inspect pharmacological effects on the electrophysiological measure independent of possible drug-induced changes in vascular responses, a major confound for pharmacological fMRI studies.

Whole-brain EEG results from the 1-way ANCOVA suggest an early processing of choice prediction error at the first level $c\delta_1$ (136 ms after outcome presentation) at antero-frontal sensors. These results could be related to the time course of PE signalling by DA neurons [4]. In a later time window (340-368 ms after outcome presentation), precision-weight at the first level ($\hat{\pi}_1/\pi_2$) related activity is seen at central and frontal channels. Together, this suggests a temporal succession in the encoding of the low-level PE and its precision-weight.
Reducing the search volume to the clusters that showed a significant representation in the EEG signal (negative and positive t-contrast) of the low-level precision weight, disclosed an interaction between the pharmacological substance and ChAt (2-way ANCOVA). In particular, compared to placebo, biperiden diminished the representation of the low-level precision-weight, $\hat{\pi}_1/\pi_2$, for the AG genotype of ChAt (compared to the GG genotype) at 380 ms post-feedback. This finding suggests that the low-level precision-weight might be modulated by ACh, genetically and pharmacologically.
On the other hand, no significant results were detected for the other computational quantities or for the DA-related gene COMT.

Future analyses will focus on biophysical models for discriminating between DA and ACh effects on synaptic plasticity in individual subjects. In clinical studies, this may prove useful for detecting pathophysiological subgroups (e.g. within the schizophrenia spectrum [5]) and to generate individual treatment predictions [6].

References

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