Dopaminergic and cholinergic modulation of brain connectivity during working memory, perceptual and reward learning

S. Tomiello*[1], D. Schöbi*[1], L. Weber*[1], J. Heinzle[1], S. Iglesias*[1], G. Stefanics[1,2], K. E. Stephan[1,3]

[1]Translational Neuromodeling Unit (TNU), Institute for Biomedical Engineering, University of Zurich & ETH Zurich, Switzerland
[2]Laboratory for Social and Neural Systems Research, Department of Economics, University of Zurich, Switzerland
[3]Wellcome Trust Centre for Neuroimaging, University College London, UK

* These authors contributed equally to this poster.

1 Introduction

Dysfunction of neuromodulatory action is thought to be involved in many psychiatric diseases. For example, a potential central mechanism for the pathogenesis of schizophrenia is an aberant modulation by dopamine (DA) and acetylcholine (ACh) of N-methyl-D-aspartate receptor (NMDAR) dependent plasticity. We aim to develop generative models that can infer these quantities from electroencephalography (EEG) data and can discriminate between DA and ACh effects on synaptic plasticity in individual subjects. The present study will provide crucial data for validating such models, using three tasks with proven/likely dependence on DA and ACh under selective pharmacological manipulations.

Here we present preliminary analyses of an ongoing study that is not yet unblinded.

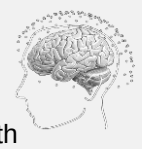
2 Data Acquisition

Sample: 81 healthy, male participants

Tasks: Stimulus Reward Learning (SRL), Auditory Mismatch Negativity (MMN), Working Memory (WM)

Pharmacology:

- Amisulpride[1]:(antagonistic (D2/D3) effect on the dopaminergic system)
- Biperiden[2]:(antagonistic (M1) effect on the cholinergic system)
- Placebo

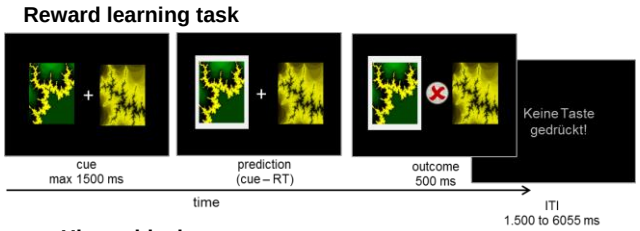


EEG data acquisition: 64-channels cap (EASYCAP GmbH) with electrodes arranged according to the international 10-20 system

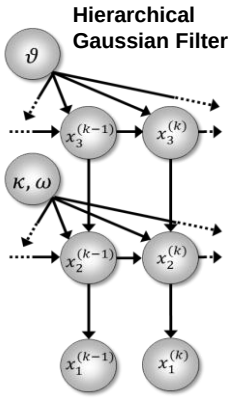
3 Methods

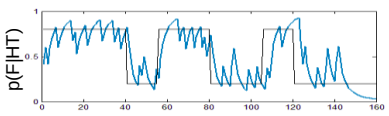
3.1 Stimulus Reward Learning (SRL)

Reward learning task

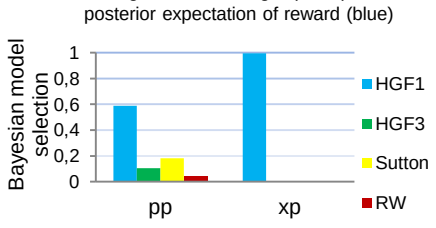


Hierarchical Gaussian Filter [3]





Changes in cue strength (black), and posterior expectation of reward (blue)

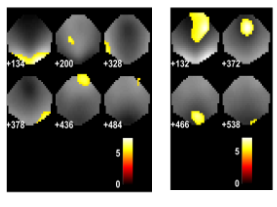


The winning model was then used to compute trial-wise prediction errors (PEs) at two different levels (whole-brain FWE-corrected):

- the choice PE about reward outcome, $c\delta_1$, and
- at a higher level the PE about cue-outcome contingency, δ_2.

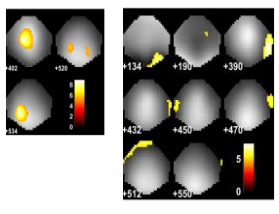
$c\delta_1$, choice PE

positive *negative*



δ_2, volatility PE

positive *negative*



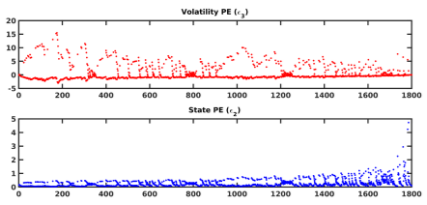
Hypotheses:

- Dopaminergic modulation of choice PEs [4]
- Cholinergic modulation of volatility PEs [5]

3.2 Mismatch Negativity (MMN)

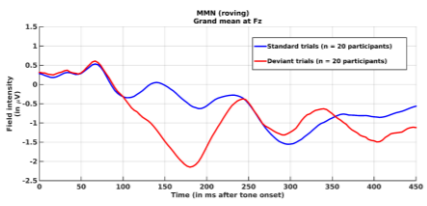
Subjects are exposed to a roving-like sequence of two tones, where the roles of ‚standard' and ‚deviant' tone change continuosly over the course of the session. We model participants' perceptual inference using the three-level HGF for binary inputs (see SRL task) and extract estimates of two PEs: state and volatility PE.

We use these PE's as regressors of interest in a multiple regression of the EEG data in a time window of 100 to 450 ms poststimulus.



Preliminary Results (n = 20)

Using a roving definition (standard = 6th presentation, deviant = 1st presentation of a tone), we find a clear MMN effect between 130 and 230 ms.



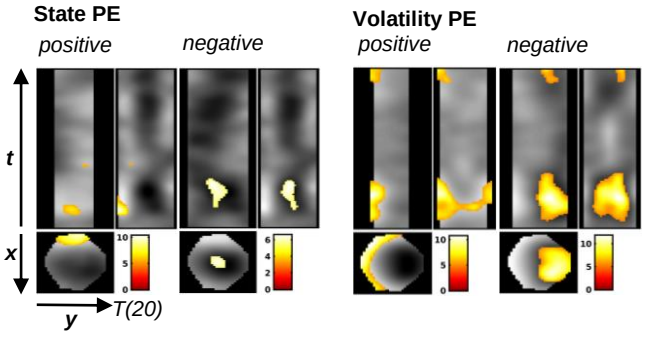
After correcting for multiple comparisons across channels and time points, we find significant correlations of the EEG signal with the PE estimates as shown in the figures (whole-brain FWE-corrected, cluster- & peak-level: p < .05):

State PE

positive *negative*

Volatility PE

positive *negative*

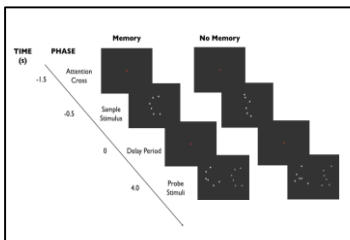


We hypothesize to find a reduced representation of volatility PEs in the ACh antagonist group (as compared to placebo), and no changes with DA.

3.3 Working Memory (WM)

Task:

2 tasks divided into 2 blocks, with 110 trials each



(Choosing 'right' would be correct in these trials)

Memory Block:
Sample Phase: Remember the relative position of six squares.

Probe Phase: Retrieve the remembered stimulus (2AFC)

No Memory Block:
Sample Phase: Nothing

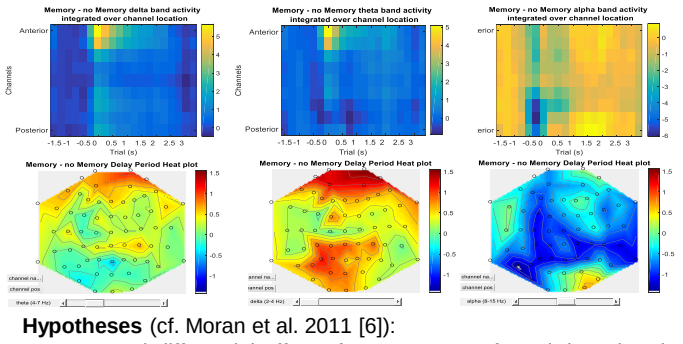
Probe Phase: Decide, which of the two stimuli is darker. (2AFC)

Preliminary Results (n = 18, collapsed over drug conditions):

We performed a Fourier analysis on a sliding window of size 750 ms and step size of 250 ms over the region of interest (Attention Cross, Sample Stimulus and Delay period). Consistent with Moran et al. 2011 [6], we find:

- *Qualitative increase in delta band activity in PFC during the delay period (Note that the window size is too small to estimate the delta band exactly)*
- *Increase in theta band activity in PFC during the delay period*
- *Increase in occipital alpha band activity in the delay period*

→ With the current sample size (and without taking into account pharmacological effects) there is still a lack of statistical power.



Hypotheses (cf. Moran et al. 2011 [6]):

- Expected differential effect of L-Dopa on prefrontal theta band activity
- cbDCM shows an increase in the NMDAR/AMPAR conductance ratio under L-Dopa compared to placebo

6 References

1 Freedman, S. B., Beer, M. S., Harley, E. A. (1988). Muscarinic M_1, M_2 receptor binding. Relationship with functional efficacy. *European Journal of Pharmacology, 156*, 133-142

2 Kerwin, R. (2000). From pharmacological profiles to clinical outcomes. *International Clinical Psychopharmacology, 15*, 1-4

3 Mathys, C., Daunizeau, J., Friston, K. J., Stephan, K. E. (2011). A Bayesian foundation for individual learning under uncertainty. *Frontiers in Human Neuroscience, 5,* 39

4 Schultz, W., Dayan, P., Montague, P. R. (1997). A Neural Substrate of Prediction and Reward. *Science, 275*, 1593-1599

5 Iglesias, S., Mathys, C., Brodersen, K. H., Kasper, L., Piccirelli, M., den Ouden, H. E. M., Stephan, K. E. (2013). Hierarchical Prediction Errors in Midbrain and Basal Forebrain during sensory Learning. *Neuron, 80*(2), 519-530

6 Moran, R., Symmonds, M., Stephan, K. E., Friston, K. J., Dolan, R. J. (2011). An In Vivo Assay of Synaptic Function Mediating Human Cognition. *Current Biology, 21,* 1320 - 1325