# Modeling EEG endophenotypes in a murine NMDAR antagonist model of schizophrenia

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## Introduction

The oscillatory activity of the brain allows the coordinated activity of its parts and the emergence of higher cognitive and executive functions. This coordinated activity is disrupted in schizophrenia and is considered an endophenotype of the illness. Specifically, disruptions in low frequency oscillatory activity [1], elevated noise in gamma band [2] and alterations in brain connectivity [3] have been reported in schizophrenic patients, among other EEG abnormalities.

N-methyl-D-aspartate receptor (NMDAR) hypofunction has been proposed to account for the etiology and pathophysiology of schizophrenia. NMDAR blockage has been used to model schizophrenia in experimental animals. It's been suggested that repeated rather than acute exposure to NMDAR antagonists more likely resembles the positive, negative and cognitive symptoms of the illness [4]. However, to our knowledge, it had not yet been studied which model more accurately represents the EEG endophenotypes of the illness.

## Aim

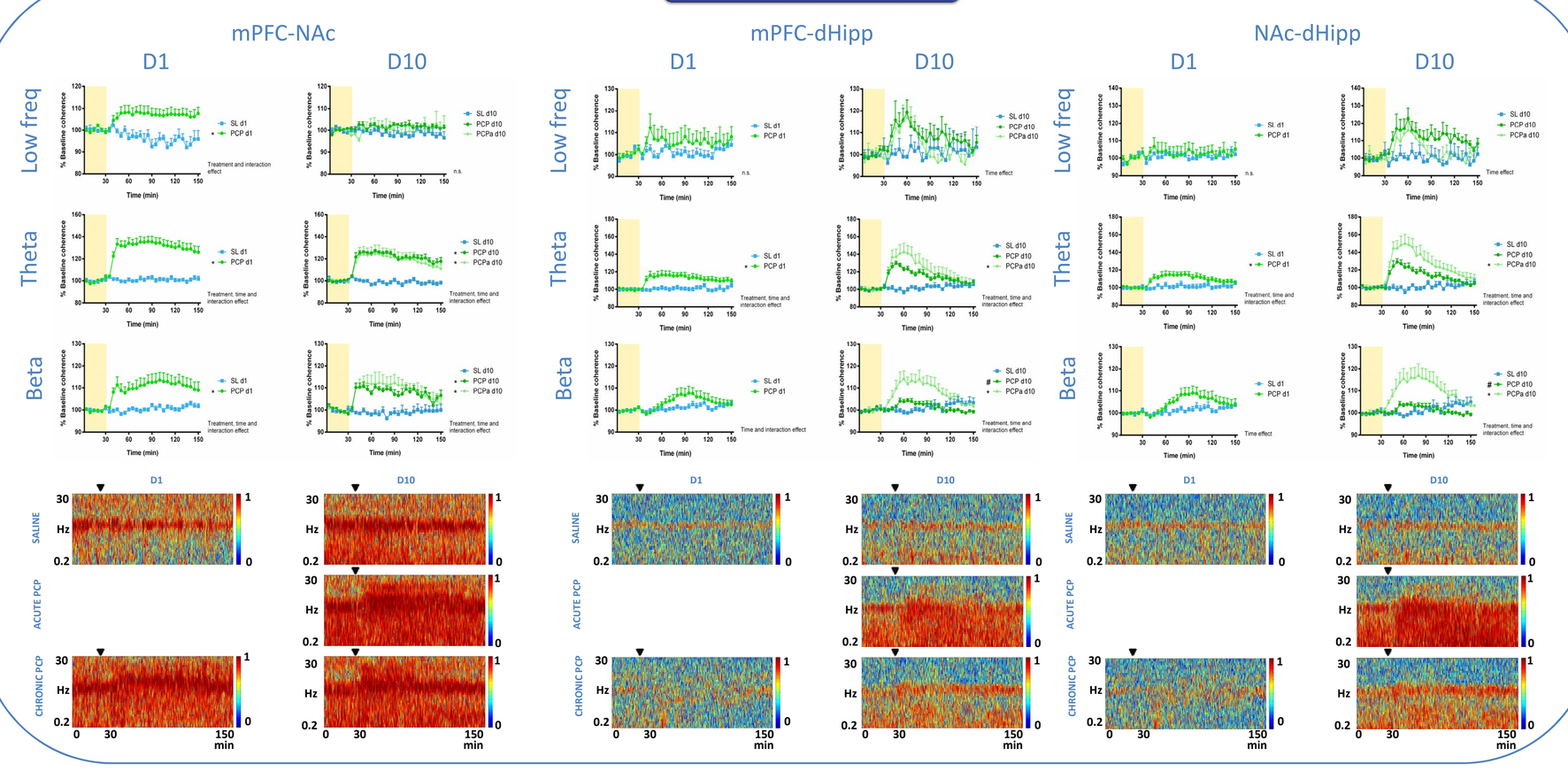
To examine the neurobiological bases of the acute vs. sub-chronic NMDAR antagonists' models of schizophrenia.

To evaluate the possibility to use disruptions in oscillatory activity after NMDAR antagonist treatment as a valid and translational model of the disease.

## Results

### LFP power


### Coherence




## Sumary

**Acute PCP treatment** produced:

- An increase in mPFC LFP power in theta and beta rhythms.
- An increase in NAc LFP power at low, theta and beta frequencies.
- A decrease in dHipp LFP theta and beta power.
- A persistent increase in LFP gamma power in mPFC and a transient increase in dHipp, but a decrease in NAc.
- A persistent increase in HFO power in mPFC and NAc and a transient increase in dHipp.
- A general increase in low frequency, theta and beta mPFC-NAc coherence, as well as an increase in mPFC-dHipp and NAc-dHipp coherence, but to a lesser extent, limited to theta and beta rhythms and in a time dependant manner.
- Acute PCP produced **different effects** when administered in a novel or in a well known environment, showing habituations (delta and theta NAc power) or potentiations (beta mPFC-dHipp and NAc-dHipp coherence) of day 1 acute effects when administered acutely at day 10. In these parameters, sub-chronic PCP administration at treatment day 10 resembled acute PCP effects at day 1.

**Besides the already described effects, sub-chronic PCP treatment** produced:

- An extreme and persistent potentiation of the PCP-induced increase in dHipp gamma and HFO.
- At the same time, a suppression of the effects we saw on dHipp beta oscillations with acute treatment.

## Conclusions

Sub-chronic PCP-induced alterations in oscillatory activity likely underlie behavioural and cognitive effects produced by the model. Some of these alterations resemble those in schizophrenic patients (e.g. disruption in low frequency oscillatory activity, elevated noise in gamma band, alterations in brain connectivity, etc.) [1,2,3]. Overall, these results support the use of sub-chronic NMDAR antagonist as a valid model to study schizophrenia EEG endophenotypes.

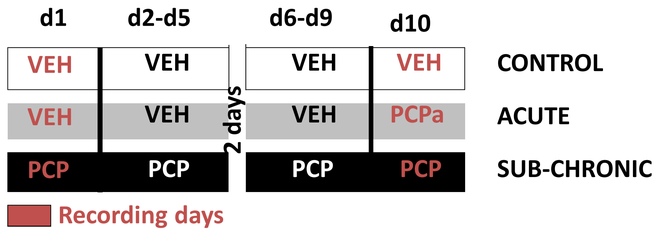
## Materials & methods

**Animals & surgery:** C57BL6J mice were implanted with Plastics One electrodes (Virgina, USA) under isoflurane anesthesia in the following stereotaxic coordinates (in mm from skull): mPFC, AP+2.2, L-0.3, DV-2.5; NAc, AP+1.5, L-0.8, DV-4.5; dHipp, AP-2, L-1.3, DV-1.3. A ground screw and three screws were also implanted. The implant was fixed with dental cement.

**Treatments:** At least one week after the surgery sub-chronic phencyclidine (PCP) treatment (10 mg/kg/day, s.c., 10 days) was used as a pharmacological model of schizophrenia as previously described [5]. Control mice received saline (10 ml/kg, s.c., 10 days). Another control group received saline for days 1-9 and acute PCP (10 mg/kg, s.c.) on day 10.

**Local field potential (LFP) recordings:** Recordings were performed in a 40 x 40 cm open field with a digital Lynx system and Cheetah software (Neuralynx, Montana, USA). The signal was obtained at 3.2kHz sampling rate and filtered between 0.1 and 1000Hz. Recordings were made at treatment days 1 and 10 as follows: 30' of basal condition (yellow shadow), PCP or saline injection (black triangle) and 2 more hours of recording. *Analysis*: Data were imported to MatLab environment (MathWorks, MA, USA) for off-line power and coherence wavelet analysis, using built-in and self-developed routines. Data were analyzed in periods of 5 minutes for comparison with previous behavioural studies. Low freq., 0.2-4Hz; Theta, 4-10Hz; Beta, 10-30Hz; Gamma, 30-80Hz; High Frequency Oscillations (HFO), 80-200Hz. Spectrograms and Coherograms represent Hz in exponential scale.

**Statistical analysis:** Data are shown as mean ± SEM. We used 2-way ANOVA followed by post-hoc Tukey comparisons. Statistical significance was set at 95% confidence level. Asteriscs (*) indicate differences vs. saline; number signs (#) indicate differences vs. acute PCP.




*No potential conflict of interest.*

*Financial support: CIBERSAM (11INT4), EU grant NEWMEDS (IMI Innovative Medicines Initiative) and SAF2012–35183 (Ministerio de Economía y Competitividad, cofinanciado con fondos FEDER). Acknowledgements to Noemí Jurado and Montserrat Carrasco.*

## References

[1] Schulman et al., 2011. Frontiers in Human Neurosci. 5(69):1-11.

[2] Suazo et al., 2012. Prog Neuropsychopharmacol Biol Psychiatry, 38(2):270-5

[3] Medkour et al., 2010. Neuroscience, 169(4):1779-88.

[4] Castañé et al., 2013. Behavioural Pharmacol, 24, A.7.

[5] Hashimoto et al., 2005. Eur J Pharmacol. 519, 114-7.