Sensory Processing Deficits of MK-801 Responds to Risperidone Across ASSR-EEG, PPI and 5-CSRTT

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INTRODUCTION

Difficulty processing sensory information is a untreated symptom of Schizophrenia (SZ). Auditory Steady State Response (ASSR) is an electroencephalography (EEG) based response reflecting ones ability to integrate auditory sensory information by cortical networks[1]. Pre-Pulse Inhibition (PPI) similarly considers cortical processing efficiency by using auditory sensory information and resulting reflex motor output. 5-Choice Serial Reaction Time Task (5-CSRTT) uses sensory stimuli to elicit a learned response and specifically considers processing related to attention and impulse control. The NMDA antagonist MK-801, modulates the rats response and performance across all assays (ASSR, PPI[2] and 5-CSRTT[3]). Atypical antipsychotics such as risperidone aim to overcome processing impairments by primarily targeting the serotonin (5-HT) system.

METHODS

Male Sprague Dawley rats were used in ASSR and PPI studies. Male Long Evans rats were used in 5-CSRRT studies.

ASSR: N=7 (crossover design),

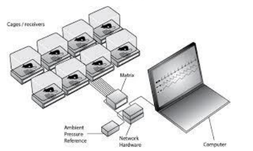
PPI: N=8/group (parallel design),

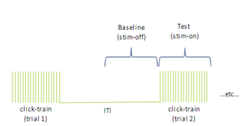
5-CSRTT: N=32 (crossover design).

In these assays, the dose response of MK-801 (0.01-0.2 mg/kg) was established followed by reversal effects of Risperidone.

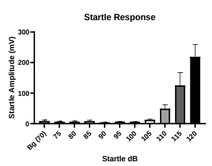
- ASSR: Animals were implanted to DSI telemetry devices and presented with click-train stimuli.
- PPI: Startle response was quantified as %PPI following trial types including, startle pulse alone, startle pulse plus pre-pulse, pre-pulse alone.
- 5-CSRTT: Animals were trained to perform a nose poke into an illuminated aperture to receive a food reward. During testing, a 5s intertrial interval was used over 100 trials.

ASSR

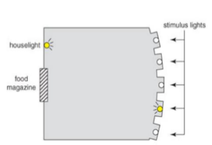




PPI



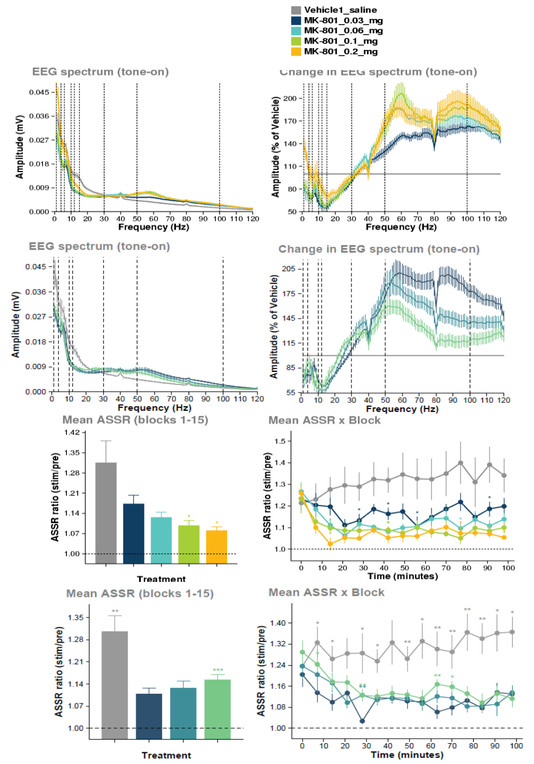
5-CSRTT



Results

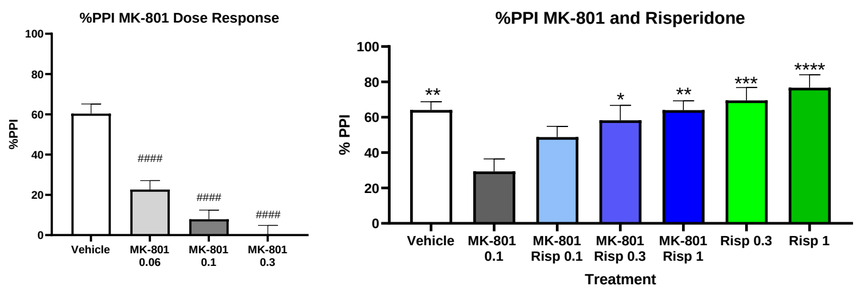
ELECTROENCEPHALOGRAPHY (EEG)

- MK-801 significantly enhanced 50-100 Hz high-gamma power and supressed frequencies below 30Hz.
- Risperidone was able to partially reverse the increased high gamma induced by MK-801 (p<0.001).
- MK-801 dose dependently reduces ASSR.
- Risperidone (0.5mg/kg) partially reverses MK-801 (0.06 mg/kg) deficit.



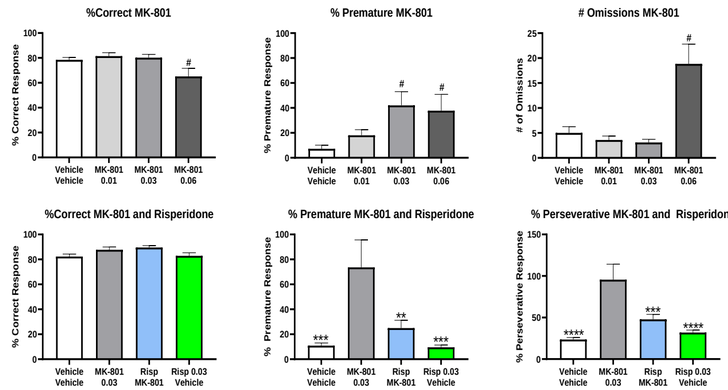
PRE-PULSE INHIBITION (PPI)

- MK-801 reduced % PPI in a dose dependant manner (p<0.001).
- Risperidone dose dependently and effectively reverses the MK-801 induced PPI deficit.
- Risperidone does not affect %PPI alone.



5-CHOICE SERIAL REACTION TIME TASK 5-CSRTT)

- Higher dose of MK-801 (0.06) reduced the number of correct responses and significantly increased omissions
- MK-801 increased premature (p<0.001) and perseverative responding (p<0.001) relating to increased impulsivity and compulsivity respectively.
- Risperidone reversed premature responses (p<0.001) and perseverative responding (p<0.001).



CONCLUSIONS

- The sensitivity of different sensory processing assays varies such that ASSR-EEG and 5-CSRTT are highly sensitive and require low doses of MK-801 to produce a change in response and behaviour.
- PPI requires higher doses of MK-801 to elicit a change in behavioural output.
- In conclusion, MK-801 impairs processing of environmental stimuli across multiple assays including ASSR-EEG, PPI and 5-CSRTT. Risperidone improves some aspects of sensory processing across ASSR-EEG, PPI, and 5-CSRTT.

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