

# Optimized 40Hz ASSR in rodent cortical EEG - validation using a ketamine model of NMDA receptor hypofunction

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# What is the 40Hz ASSR?

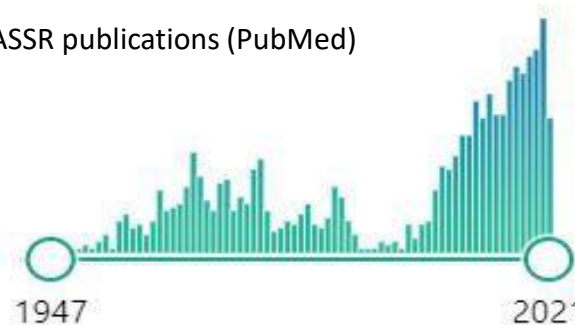
- ✦ Originally designed to test hearing loss in 1981
  - A successor to the auditory brainstem response (ABR)
- ✦ An evoked EEG response entrained to “click” sounds presented at 25ms intervals
- ✦ Requires the integrity of cortical GABAergic neural networks
- ✦ 40Hz ASSR abnormalities are well-characterised in people with schizophrenia
- ✦ Disruptions probably reflect a failure of cortical networks to rapidly integrate auditory sensory information

## ✦ ASSR is in clinical trials for:

- Schizophrenia
- Autism
- Down Syndrome
- Hearing loss

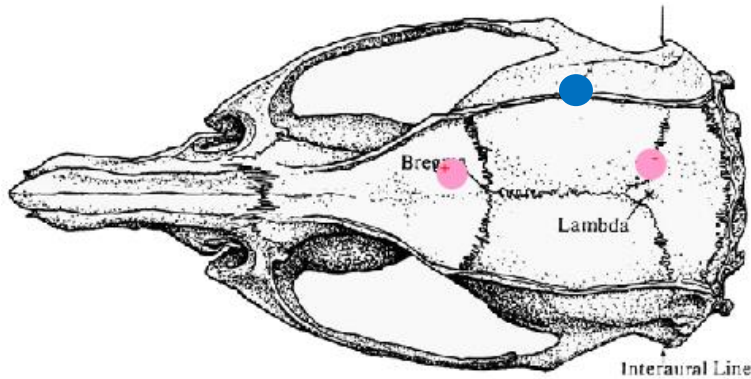


ASSR publications (PubMed)



# ASSR for pharmacology using midline EEG

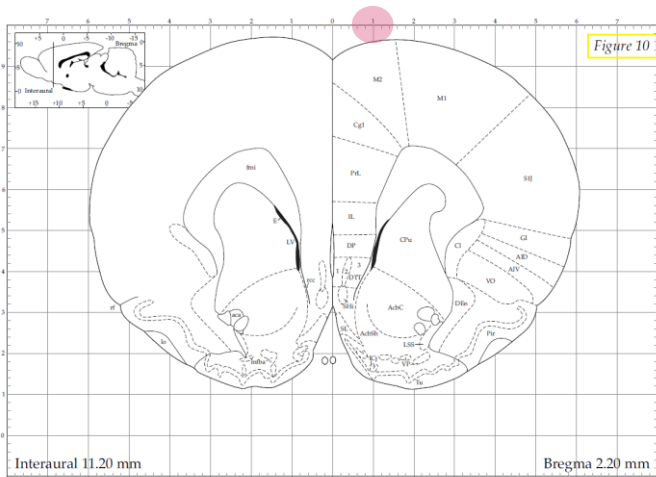
## Epidural electrode placements



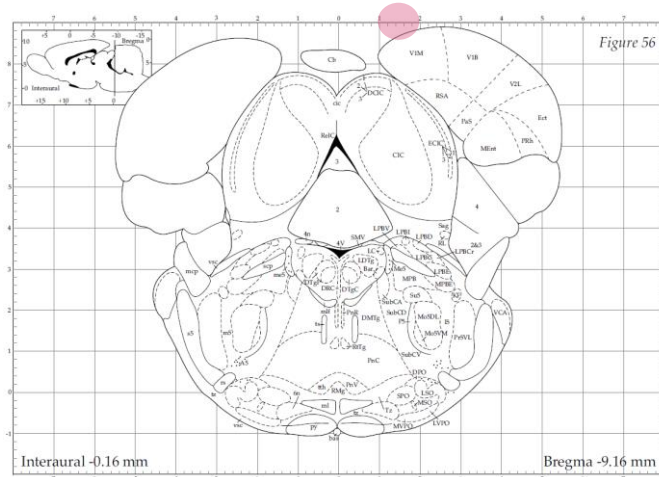
- **Typical auditory cortex placement**
- **Frontal (positive):** Bregma +2.0 mm AP, 1.0 mm ML.
- **Occipital (negative):** Lambda 0.0 mm AP, 1.5 mm ML.

Differential EEG signal acquired at 500Hz with a 0.5-100Hz hardware band-pass filter.

### Frontal: over M2/CG1/PFC



### Occipital: over V1M



## The stimulus used to evoke ASSR

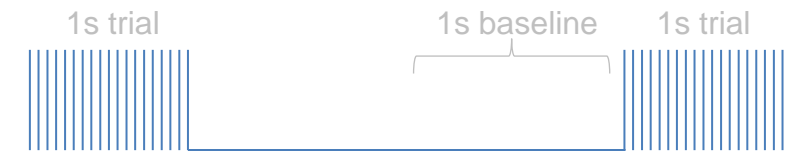
(this is the final protocol)

1ms, 1V (80dB) click



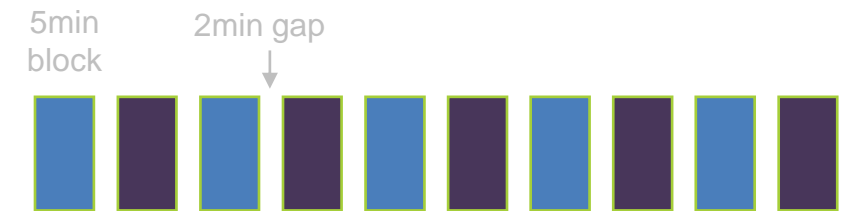
x40

Long enough trial for FFT



x120

Sufficient number of trials for meaningful averaging



68min recording session

Sufficiently short blocks to capture 1-hour pharmacodynamics

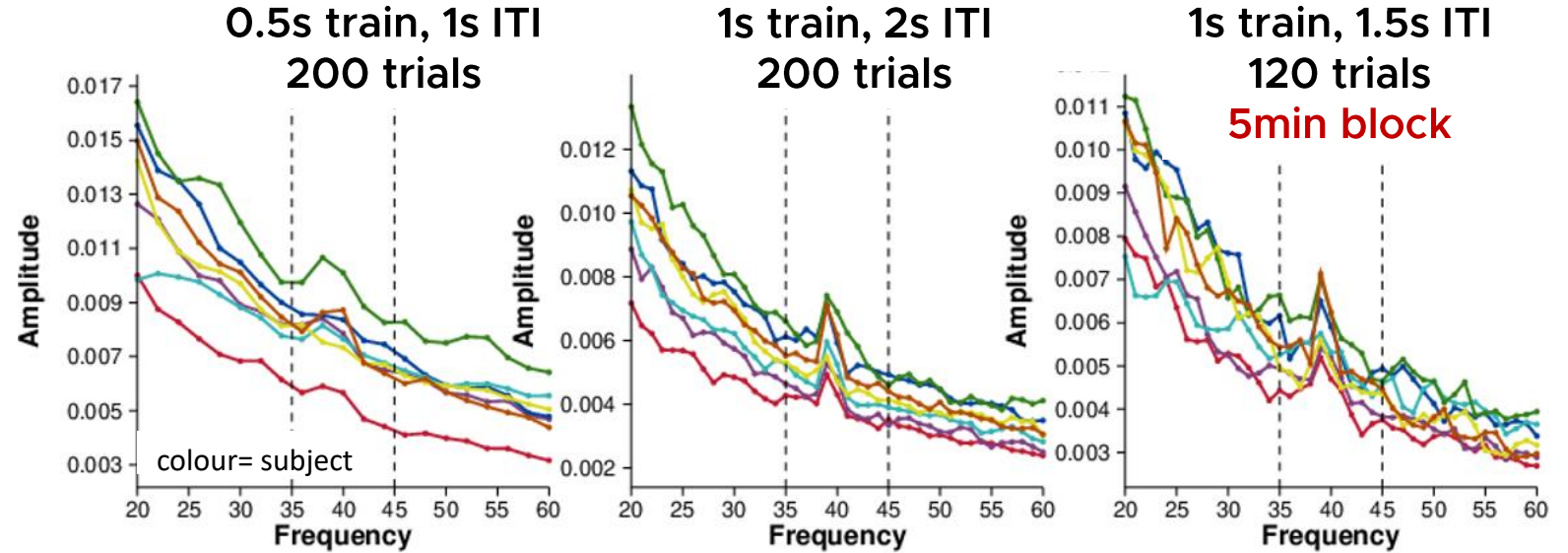


# Detection of ASSR with sleep-EEG montage

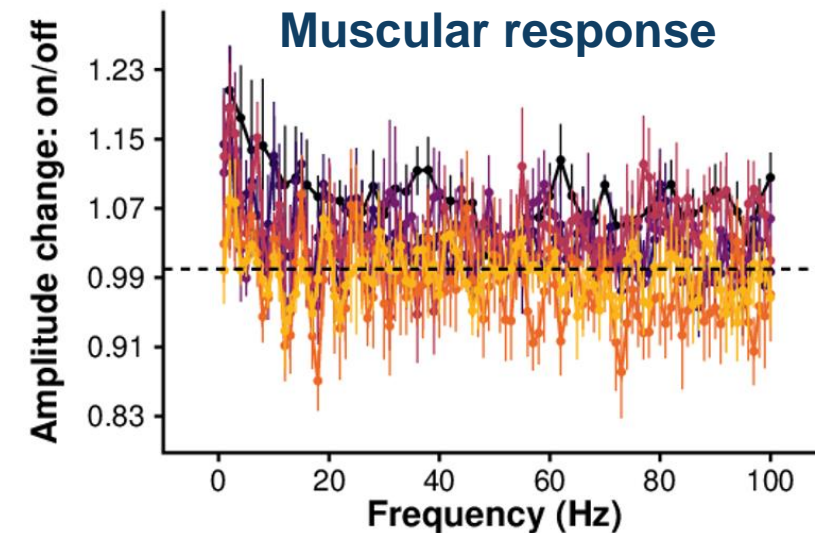
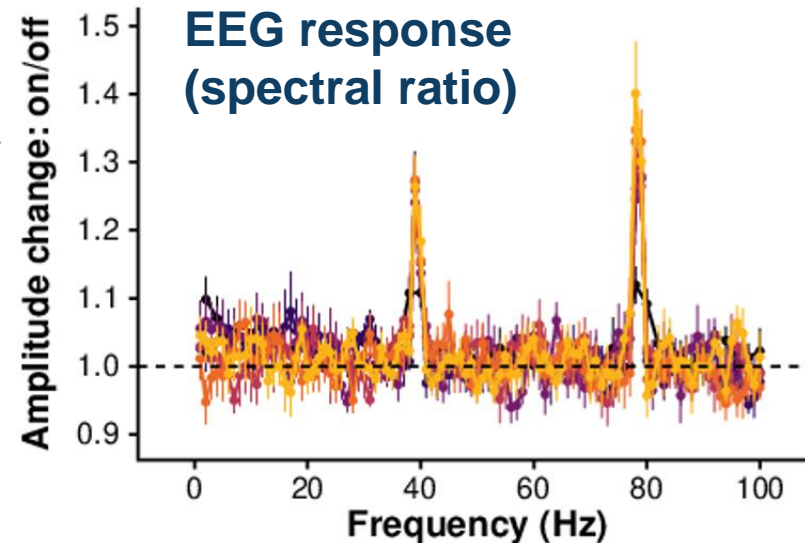
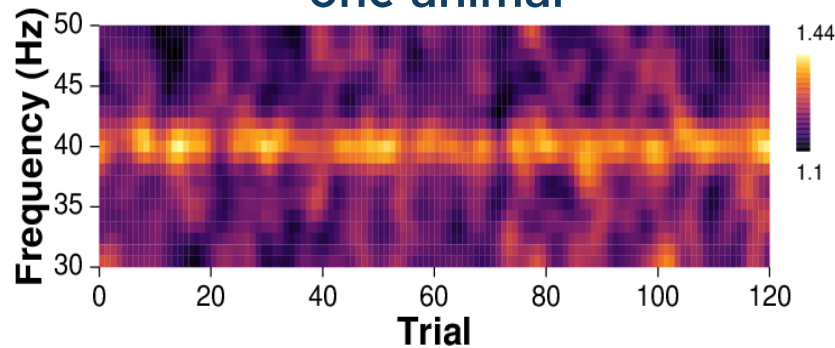
## Analysis

For each trial:

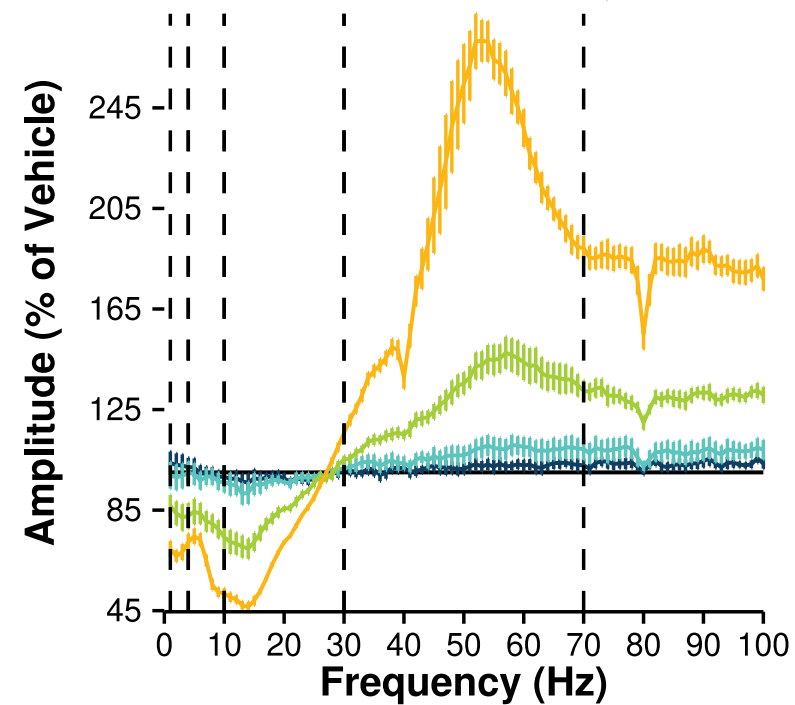
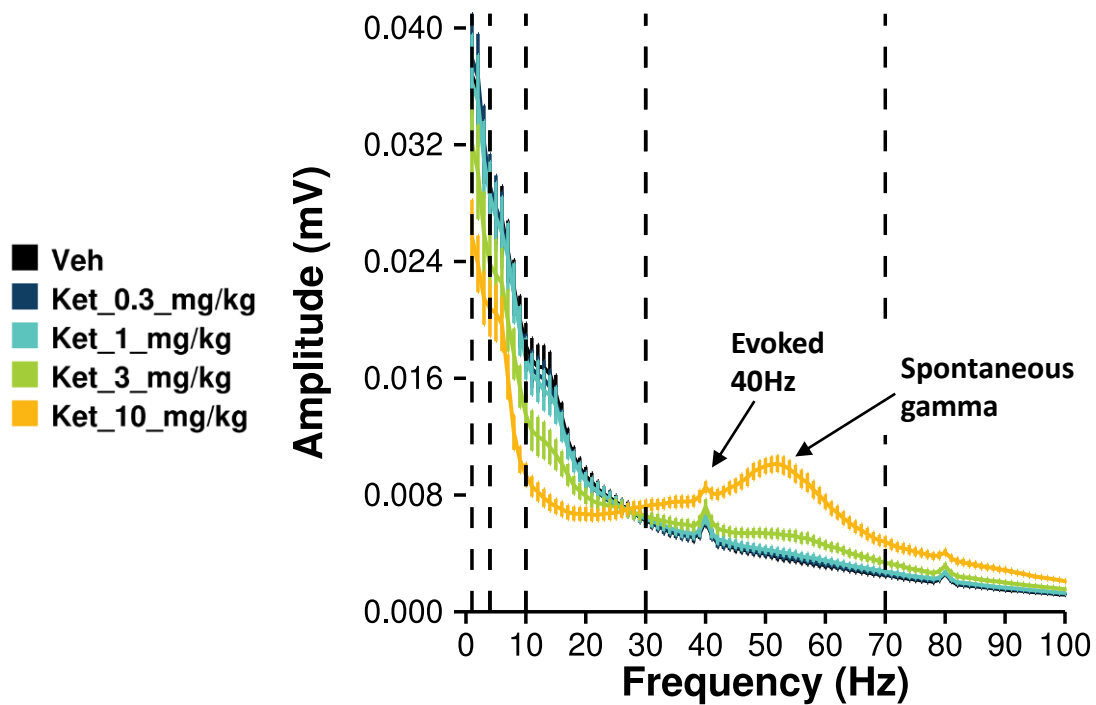
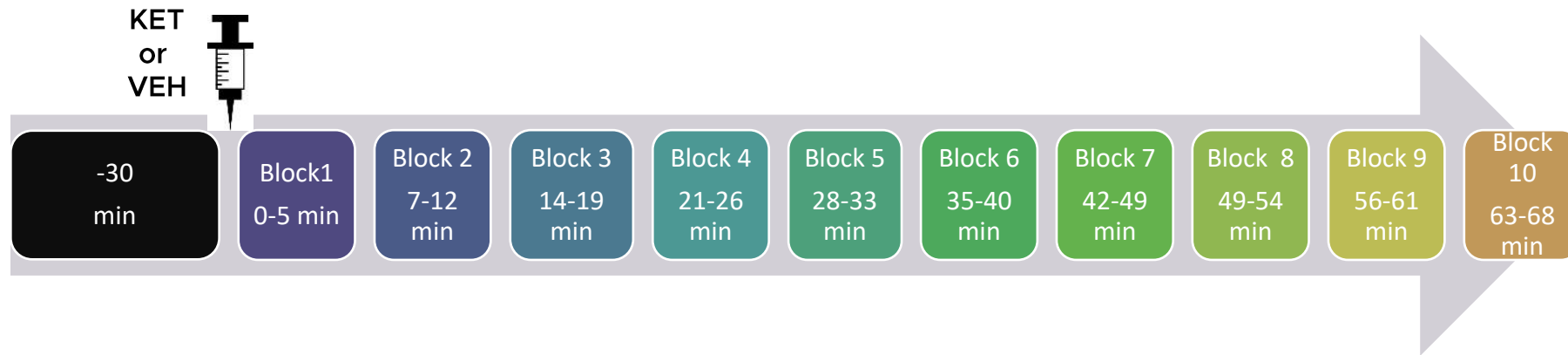
- Power spectrum for the trial (stim)
- Power spectrum for the baseline (pre)
- Focus on the spectral value at 40Hz
- $ASSR = 40Hz(stim) / 40Hz(pre)$



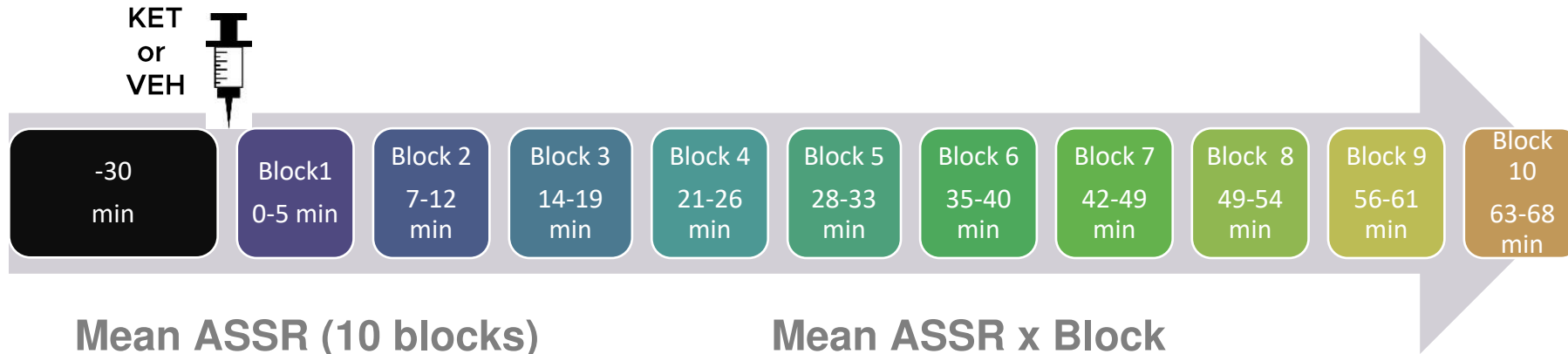
Typical 40Hz response,  
one animal



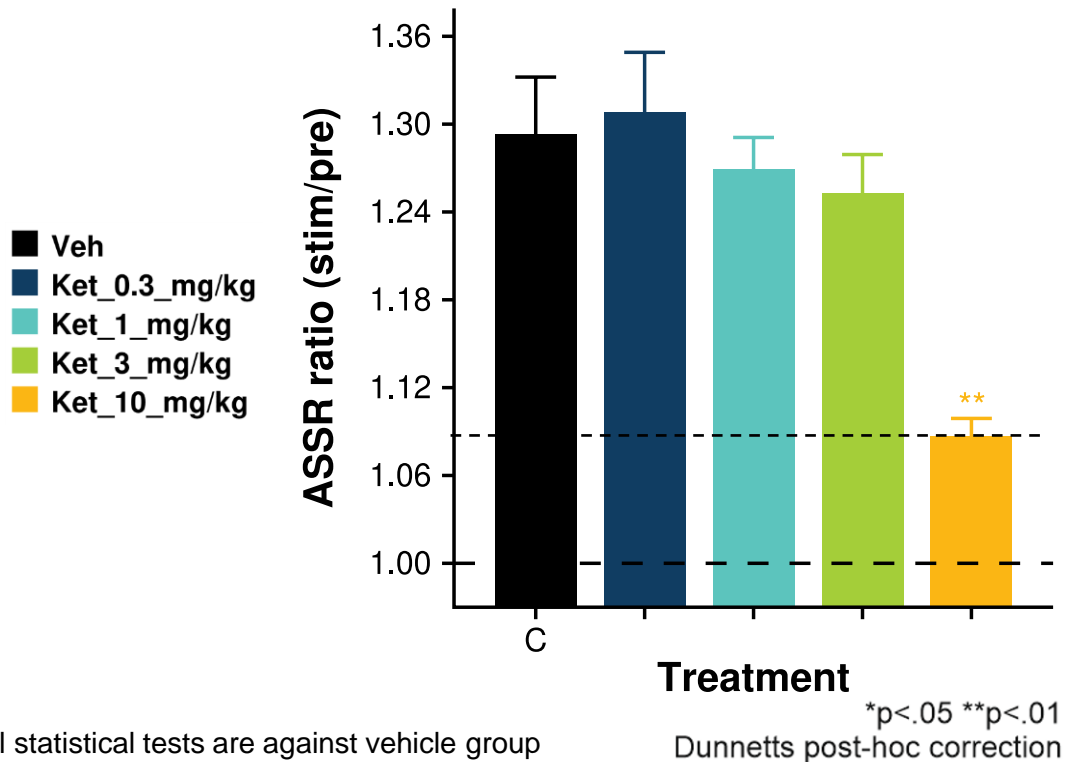
# Induction of a deficit using subanaesthetic ketamine



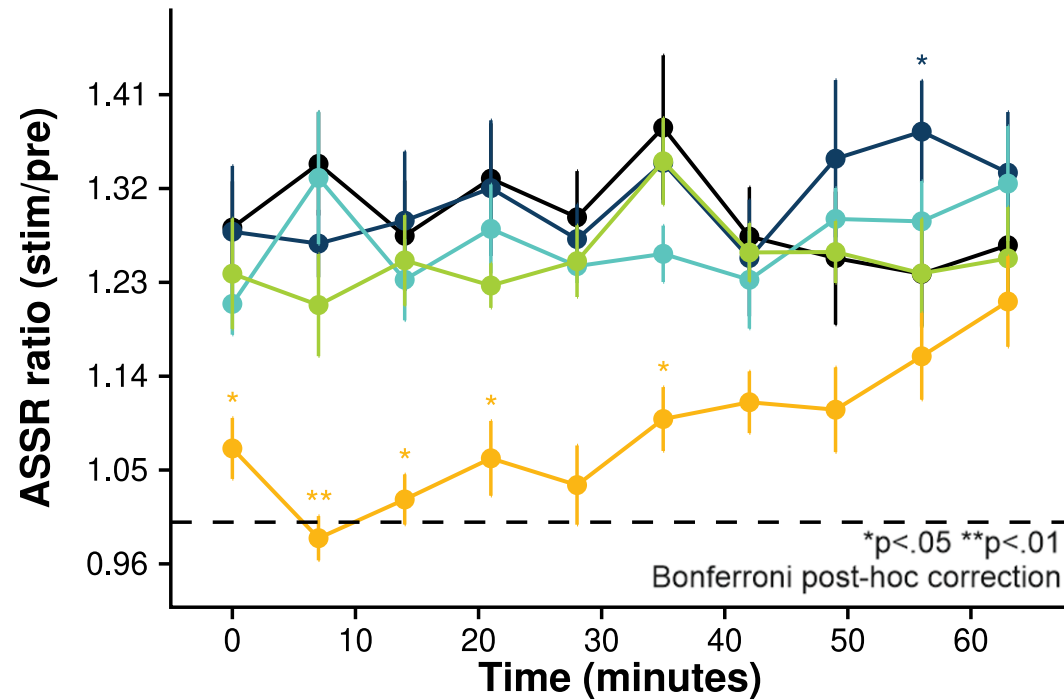
# Induction of a deficit using subanaesthetic ketamine



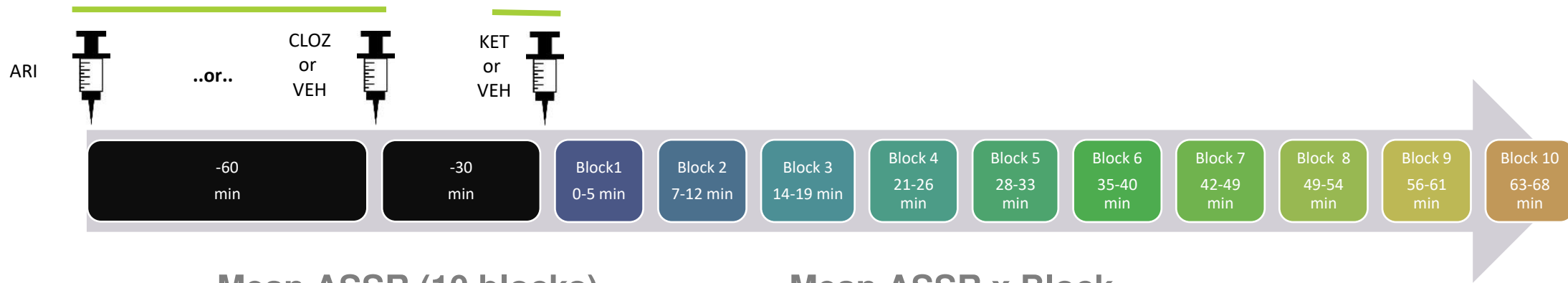
Mean ASSR (10 blocks)



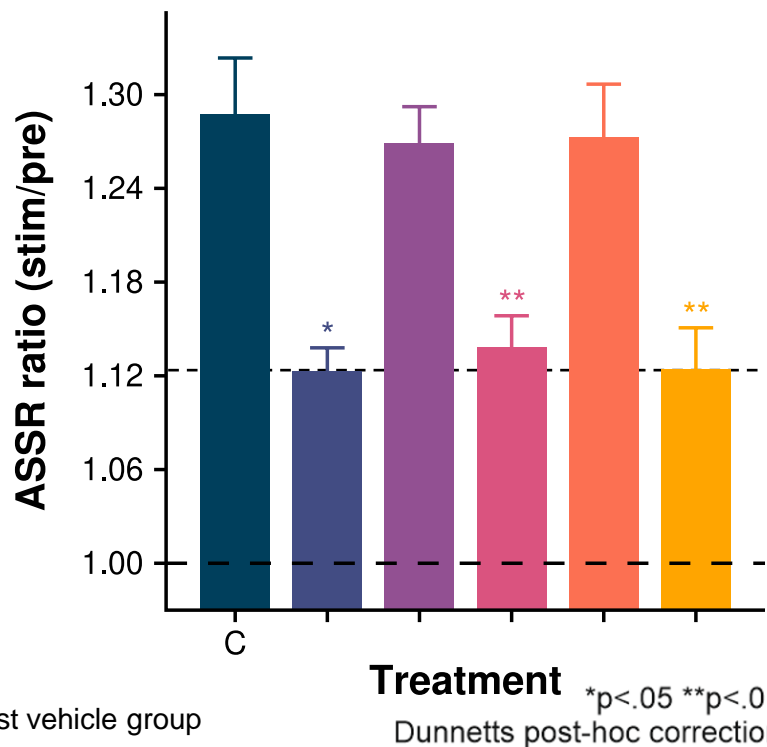
Mean ASSR x Block



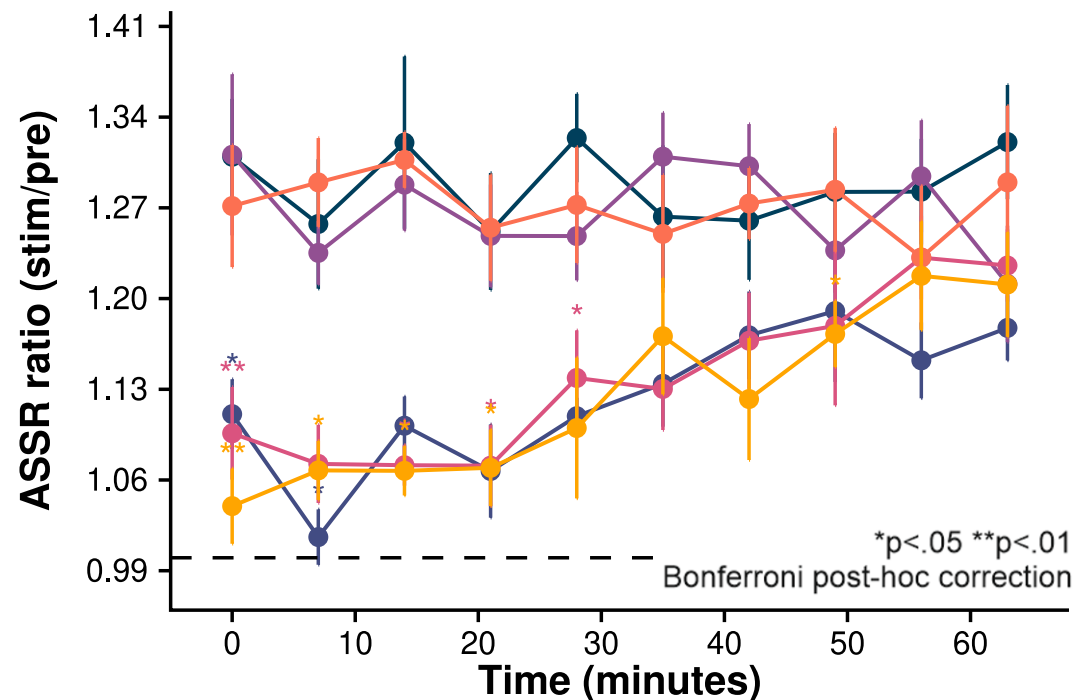
# The deficit was not reversed using atypical antipsychotics aripiprazole or clozapine



Mean ASSR (10 blocks)



Mean ASSR x Block



All statistical tests are against vehicle group



- ASSR in the rat is detected by near-midline epidural EEG recordings that do not specifically target auditory cortex
  - Detection is optimised by presenting 1-second click-trains normalised to the 1-second before each trial
  - 5-minute blocks of trains provide stable estimates of ASSR
- 10 mg/kg ketamine induces a reliable, temporary deficit, pointing to relevance for symptomatic models of schizophrenia
- Atypical antipsychotics targeting 5-HT<sub>2</sub> receptors do not reverse this deficit at the tested doses
- Future efforts will...
  - Investigate other pharmacological routes of reversing deficits induced by NMDAR antagonists
  - Explore other disease models
  - Test ASSR evoked by quieter tones, which may be more easily impaired and more easily recovered



# Thank you.



**John Huxter**  
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Operations Lead  
Associate Director

## References & Recommended Reading

Galambos, R., Makeig, S. & Talmachoff, P. J. A 40-Hz auditory potential recorded from the human scalp. *Proc. Natl. Acad. Sci. U. S. A.* 78, 2643–2647 (1981).

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Franowicz, M. N. & Barth, D. S. Comparison of evoked potentials and high-frequency (gamma-band) oscillating potentials in rat auditory cortex. *J. Neurophysiol.* 74, 96–112 (1995).

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