Mismatch Responses To Frequency Deviants In The Surface EEG Of Awake, Freely Moving Rats:
A Platform For Examining Pharmacological And Developmental Animal Models Of Schizophrenia

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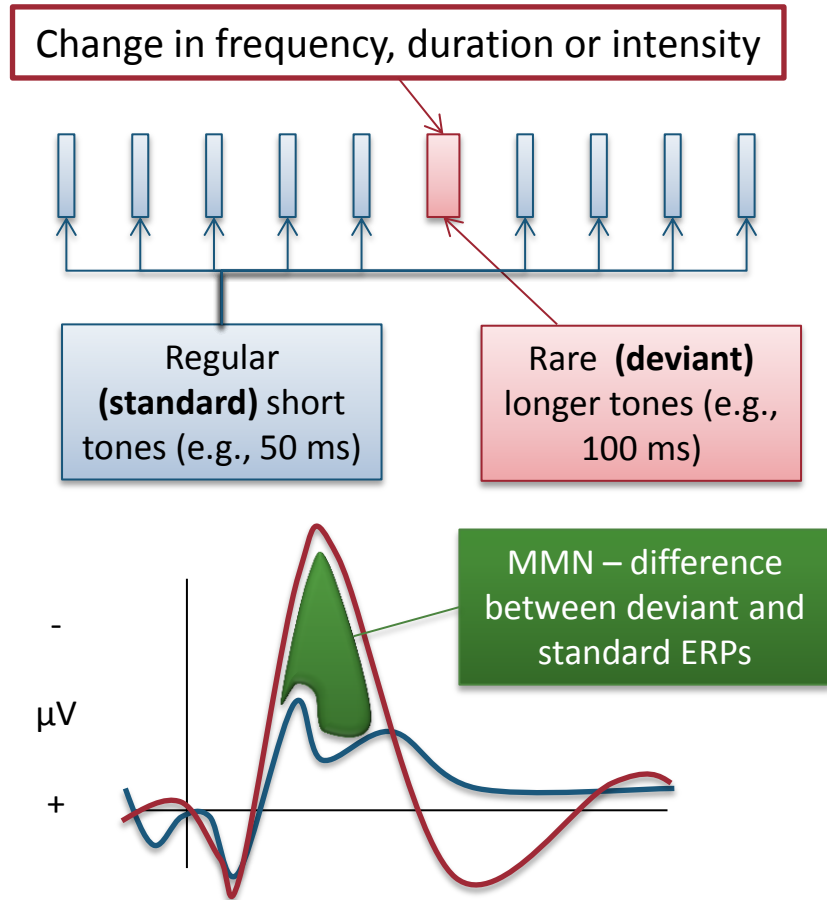
Laboratory of Neuroimmunology

SCHIZOPHRENIA RESEARCH INSTITUTE

Australian Government
National Health and Medical Research Council

HMRI
Hunter Medical Research Institute

Mismatch Negativity (MMN)

- EEG
- Change in the ERP (event-related potential) in response to an unexpected stimulus
- Train of repeated, expected stimuli (Standards) interrupted by a rare, unexpected stimulus (Deviant)
- Negative deflection in ERP

Change in frequency, duration or intensity

Regular **(standard)** short tones (e.g., 50 ms)

Rare **(deviant)** longer tones (e.g., 100 ms)

MMN – difference between deviant and standard ERPs

- µV +

MMN and Schizophrenia

Mismatch Negativity: An Index of a Preattentive
Processing Deficit in Schizophrenia

A. M. Shelley, P. B. Ward, S. V. Catts, P. T. Michie,
S. Andrews, and N. McConaghy

LONG DURATION DEVIANT   **SHORT DURATION DEVIANT**

MEDICATED SCHIZOPHRENIA PATIENTS

- *Reduced* size of MMN in schizophrenia
- MMN reductions correlate with impairments in global functioning
- NMDA receptor hypofunction
  - Ketamine in humans
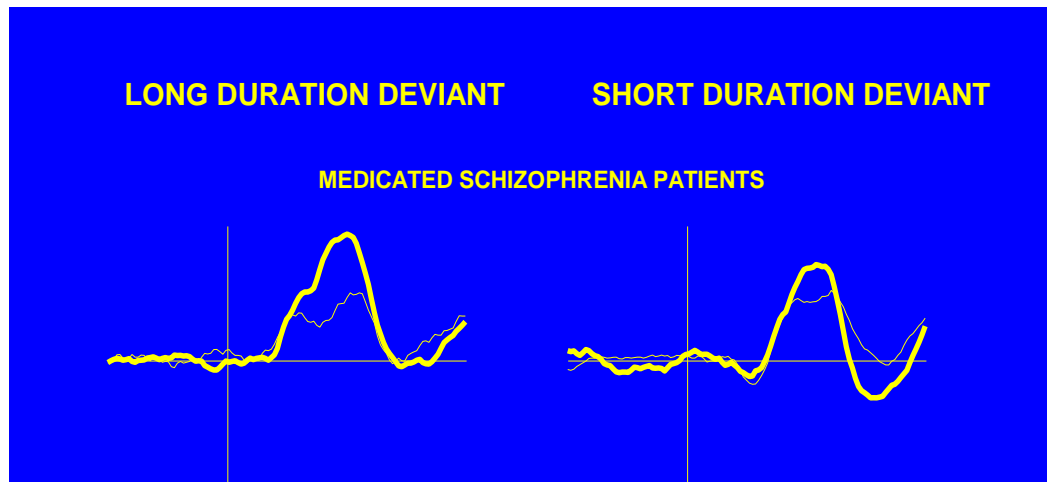
An Animal Model of MMN

Mechanistic hypotheses

- Which regions are responsible for the generation of MMN?
    - Auditory cortex, inferior frontal gyrus
- Which neurotransmitters /receptors contribute toward MMN
    - NMDAR?

Preclinical drug development

- Do animal models of schizophrenia have reduced MMN?
- What interventions can reverse reductions in MMN?

Major Questions

1. NMDAR Antagonists

- Ketamine in human studies
- MK801 – more selective, longer lasting
- Does MMN in rats respond to NMDAR Antagonists as MMN in humans?

2. Animal Model of schizophrenia

- Maternal Immune activation (MIA)
- Good construct, face and predictive validity
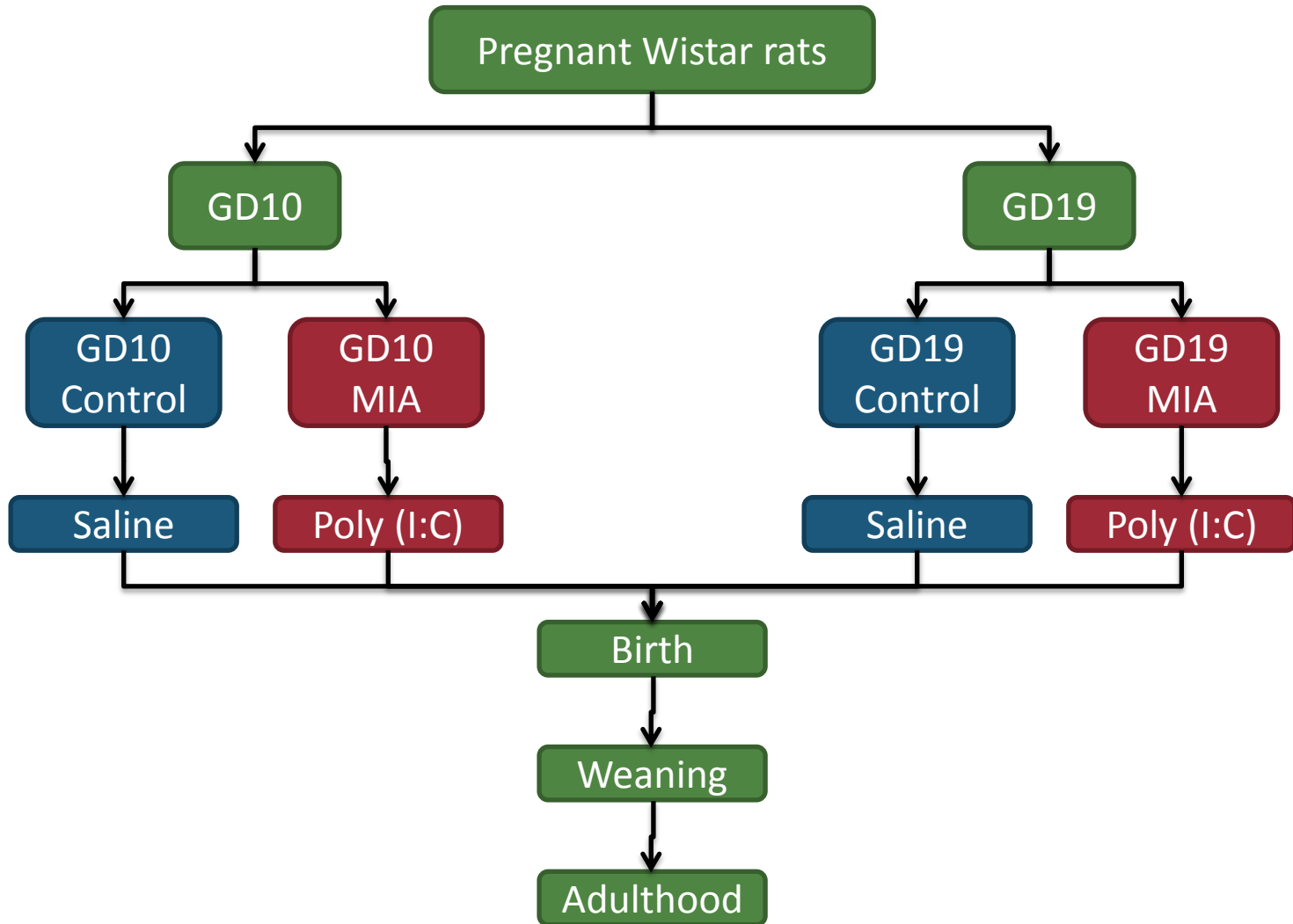- Does this extend to MMN impairments?

The Maternal Immune Activation (MIA) Animal Model

- Epidemiological findings: maternal infection during gestation associated with increased risk of schizophrenia
- Viral infections
- Viral mimic: Poly (I:C)
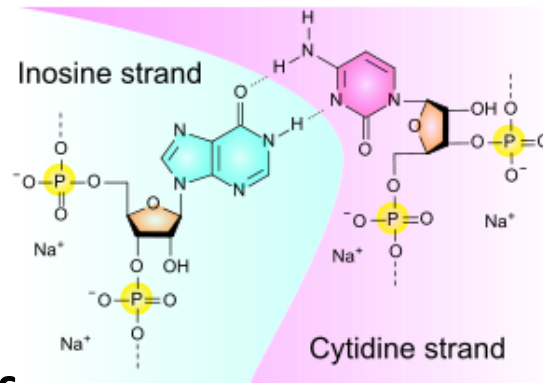
- Mouse model:
  - Early gestation (GD9) – dopamine?
  - Late gestation (GD17) – glutamate/NMDA/GABA

Study Design

Study Design

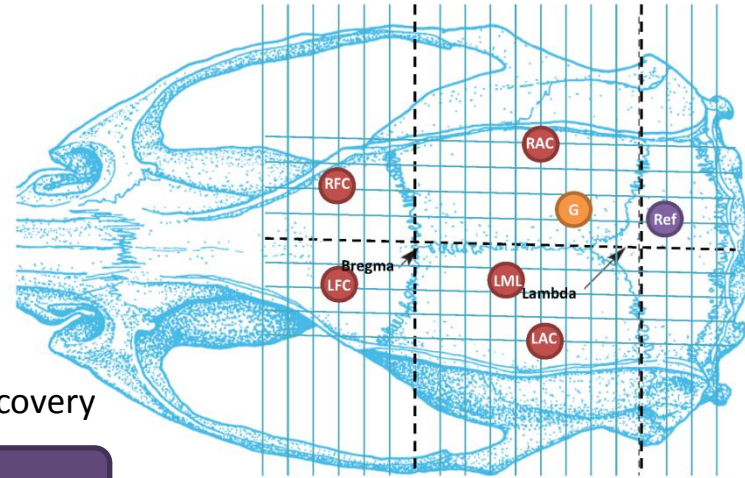Adulthood (12 weeks) → Surgery → (1 week recovery) → MMN baseline session 1 → MMN baseline session 2 → MMN baseline session 3 → MK-801 session 1 (0.1mg/kg) → (5 days washout) → MK-801 session 1 (0.3mg/kg) → (5 days washout) → MK-801 session 1 (0.5mg/kg)

Study Design – MMN Sequence

Oddball Sequences – Flip-Flop Design

Ascending

Descending

Control Sequence – Many-Standards Design
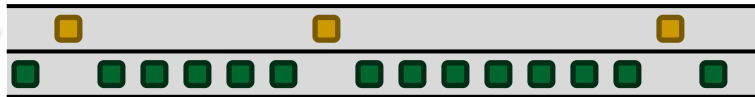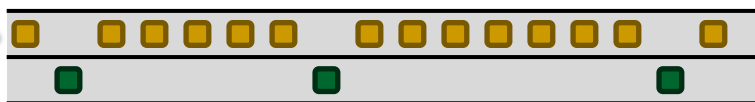
Stimulus type	Presentation rate (*P*)	Frequency (Hz)
deviant	0.125	8137
standard	0.875	6636
standard	0.875	8137
deviant	0.125	6636
	0.125	15000
	0.125	12233
	0.125	9977
control	0.125	8137
control	0.125	6636
	0.125	5412
	0.125	4414
	0.125	3600

- All flip-flop controlled (only compare response to 8kHz tone to responses to other 8kHz tones)

- Can extract:
  - Oddball effects
  - Adaptation effects
  - Deviance detection/ 'true' MMN effects

MMN in control rats
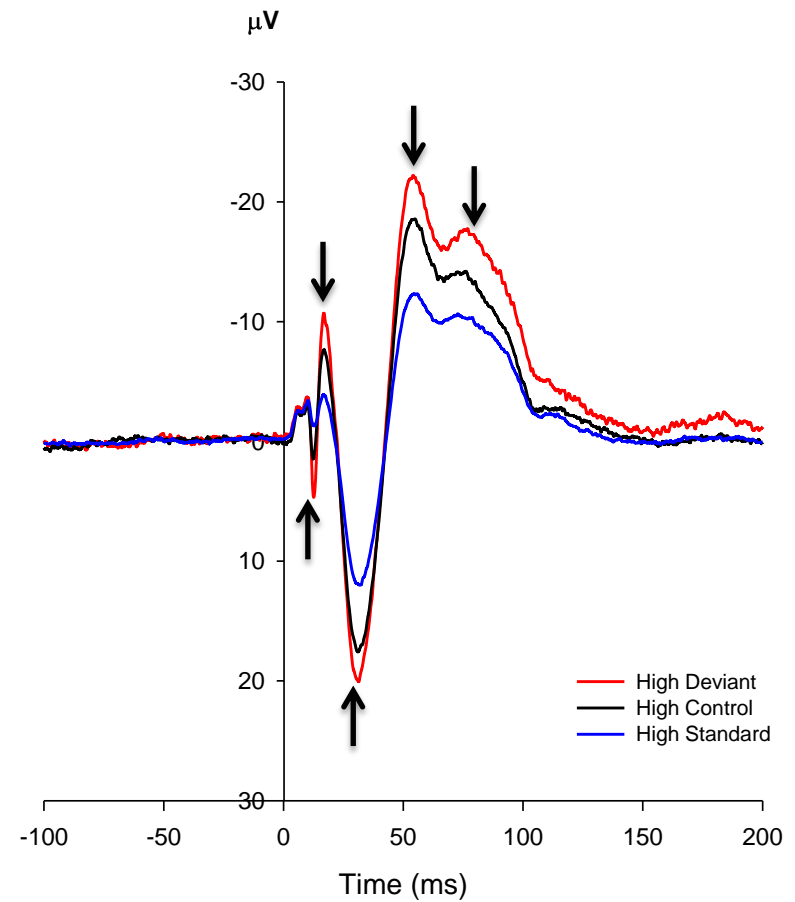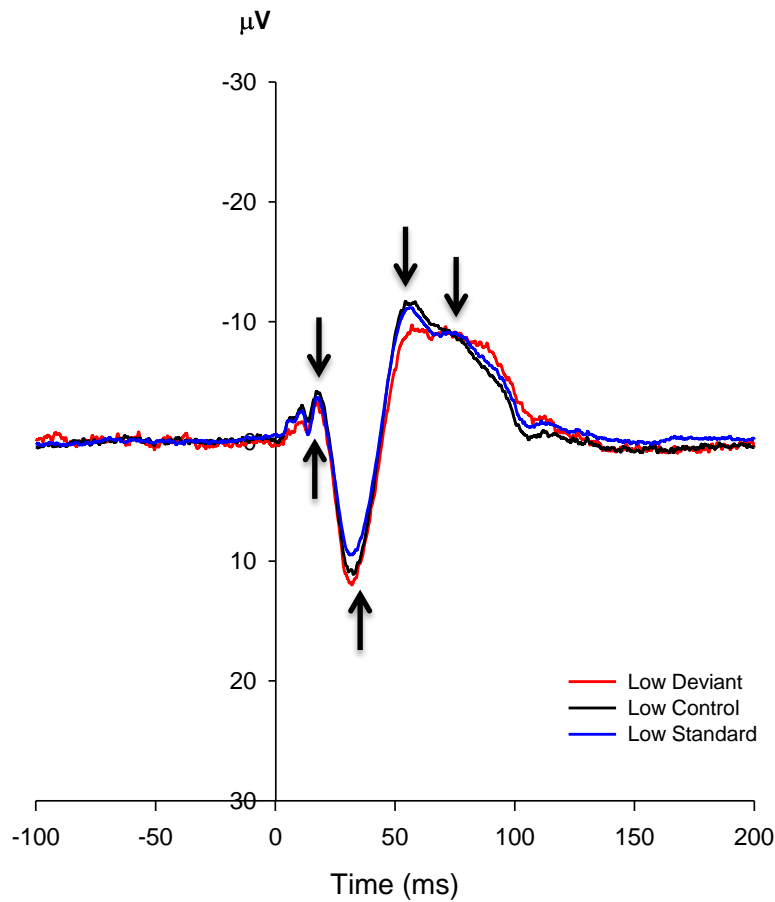
Similar to Nakamura et al. 2011
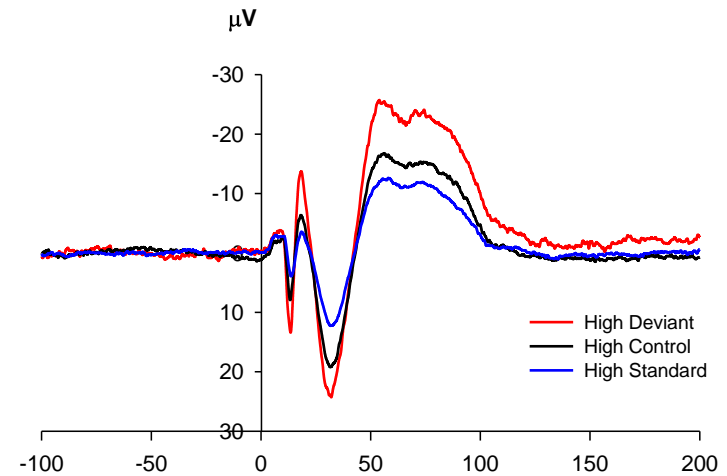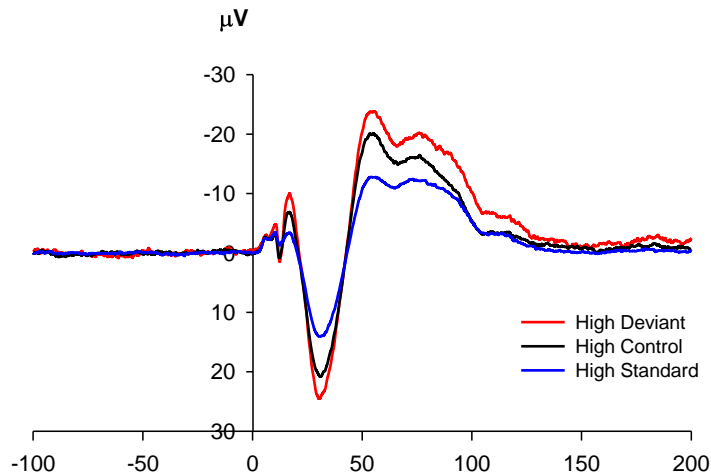
P13: 11-15ms   **N18:** 15-22ms   **P30:** 22-43ms   **N55:** 43.5-65.5ms   **N85:** 65.5-105.5ms
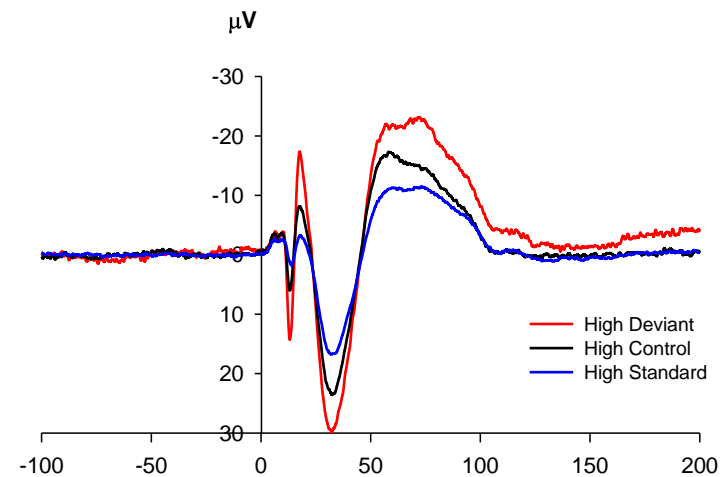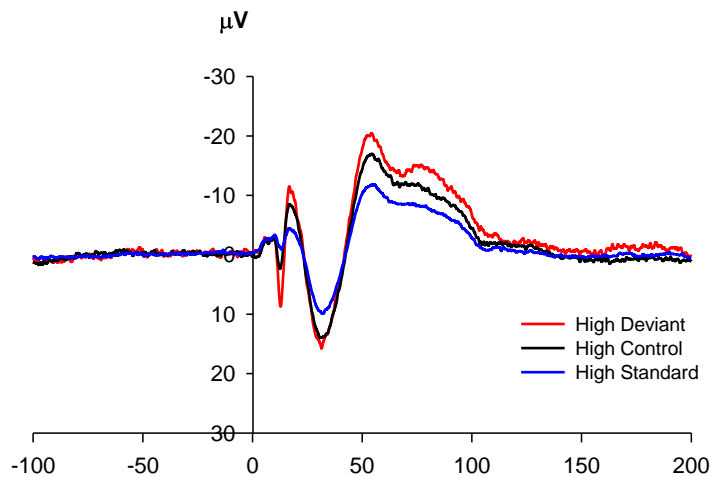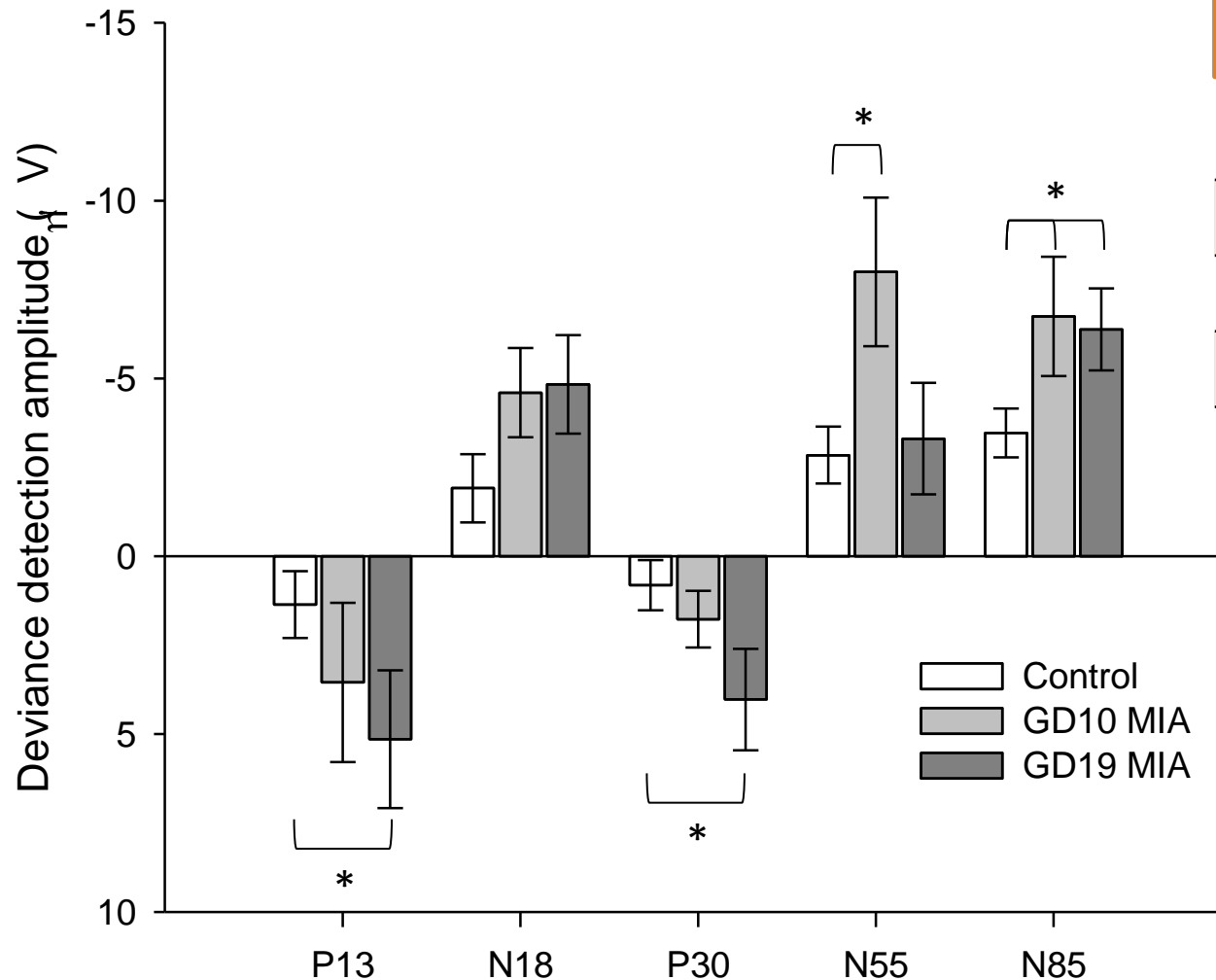
MMN in MIA-exposed rats

Effect of MIA

Effect of MIA on Deviance Detection:

P13	Increased (GD19)
N18	No effect
P30	Increased (GD19)
N55	Increased (GD10)
N85	Increased (both)

Deviance detection = Response to deviant – Response to control

Legend: Control, GD10 MIA, GD19 MIA

Y-axis: Deviance detection amplitude (μV)

X-axis: P13, N18, P30, N55, N85

Effect of MIA

Adaptation =
Response to control –
Response to standard

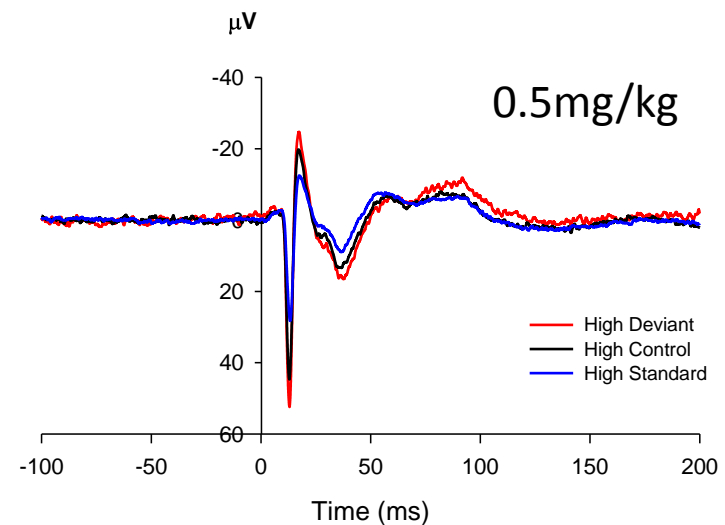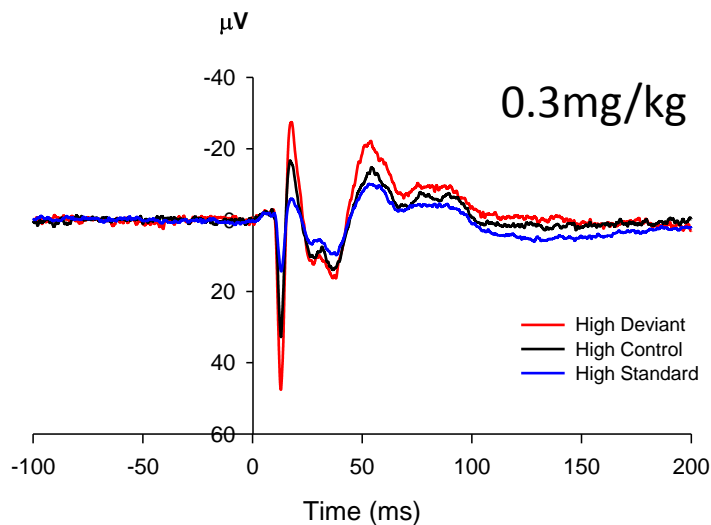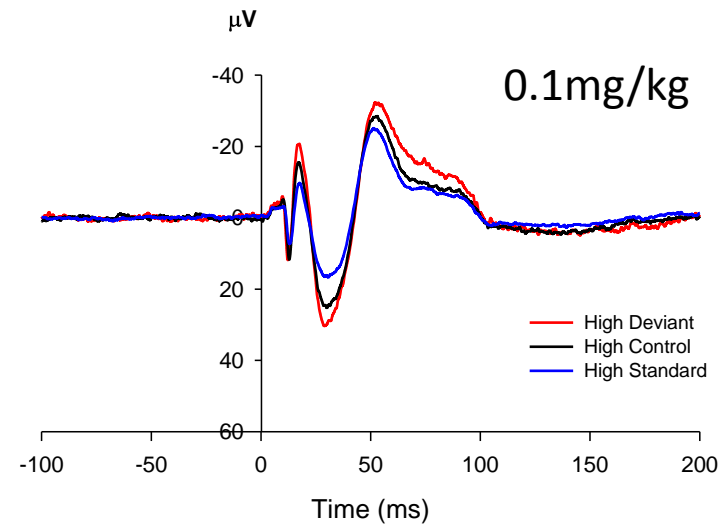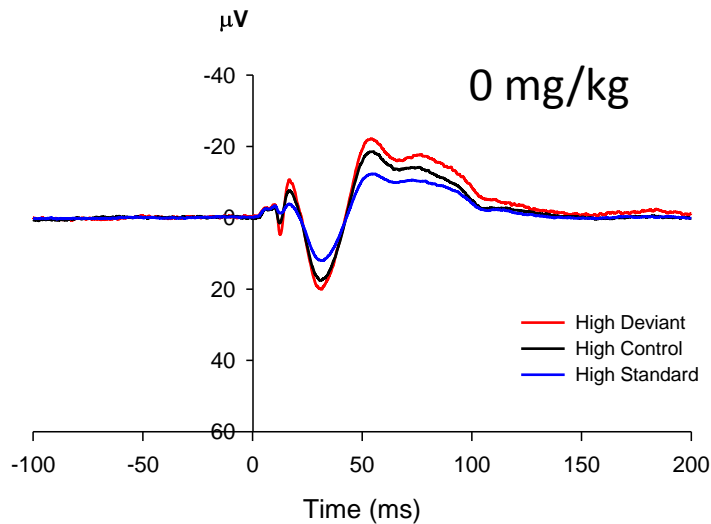# Effect of MK-801 (Controls)

Effect of MK-801 (Controls)

Deviance detection =
Response to deviant –
Response to control

Effect of MK-801 on Deviance Detection:

- P13 — **Increased (mid-range dose)**
- N18 — **Increased (low dose)**
- P30 — **Increased (low dose)**
- N55 — **Reduced (high dose)**
- N85 — **Reduced (high dose)**

Effect of MK-801 (Controls)

Adaptation =
Response to control –
Response to standard

Effect of MK-801 on
Adaptation:

P13 — Increased
N18 — Increased
P30 — Increased (low dose)
N55 — Reduced
N85 — No effect

Effects of two models of schizophrenia

Deviance detection

	Effect of MIA		Effect of MK-801		Effect of MIA x MK-801
P13	↑ (GD19)	P13	↑ (mid-dose)	P13	MIA ↑ effect of MK-801
N18		N18	↑ (low dose)	N18	
P30	↑ (GD19)	P30	↑ (low dose)	P30	
N55	↑ (GD10)	N55	↓ (high dose)	N55	
N85	↑ (both)	N85	↓ (high dose)	N85	MK801 ↓ effect of MIA

Adaptation

	Effect of MIA		Effect of MK-801		Effect of MIA x MK-801
P13		P13	↑	P13	
N18		N18	↑	N18	
P30		P30	↑ (low dose)	P30	
N55		N55	↓	N55	
N85		N85		N85	

Conclusions

- The role of NMDA receptors in the generation of MMRs is more complicated than previously thought

- Deviance detection is differently affected in animal models of schizophrenia for different components of the ERP:

- MIA doesn't model schizophrenia-related impairments in MMN

Next Steps

- Can MMRs be observed for other types of deviance: intensity, omission?

- Where are the generators located for different components of deviance detection?

- Can we observe reduced MMN in other models of schizophrenia?

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