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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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
MMN and Schizophrenia

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

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

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

Pregnant Wistar rats

- GD10
  - GD10 Control
  - GD10 MIA
  - Poly (I:C)
- GD19
  - GD19 Control
  - GD19 MIA
  - Poly (I:C)

Birth

Weaning

Adulthood
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 (0.5mg/kg)

- 5 days washout

MK-801 session 1 (0.3mg/kg)
Study Design – MMN Sequence

Oddball Sequences – Flip-Flop Design

- 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

<table>
<thead>
<tr>
<th>Stimulus type</th>
<th>Presentation rate (P)</th>
<th>Frequency (Hz)</th>
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</thead>
<tbody>
<tr>
<td>deviant</td>
<td>0.125</td>
<td>8137</td>
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<tr>
<td>standard</td>
<td>0.875</td>
<td>6636</td>
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<tr>
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<td>8137</td>
</tr>
<tr>
<td>deviant</td>
<td>0.125</td>
<td>6636</td>
</tr>
</tbody>
</table>

Control Sequence – Many-Standards Design

<table>
<thead>
<tr>
<th>Stimulus type</th>
<th>Presentation rate (P)</th>
<th>Frequency (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
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<tr>
<td>control</td>
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<td>3600</td>
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</tbody>
</table>
MMN in control rats

![Graph showing MMN in control rats with annotations for P13, N18, P30, N55, and N85 peaks similar to Nakamura et al. 2011.](image)

- **P13**: 11-15ms
- **N18**: 15-22ms
- **P30**: 22-43ms
- **N55**: 43.5-65.5ms
- **N85**: 65.5-105.5ms

Similar to Nakamura et al. 2011
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
Effect of MIA

Adaptation amplitude (V)

Control
GD10 MIA
GD19 MIA

Adaptation = Response to control – Response to standard
Effect of MK-801 (Controls)

0 mg/kg

0.1 mg/kg

0.3 mg/kg

0.5 mg/kg

Time (ms)

High Deviant
High Control
High Standard

\( \mu V \)
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 amplitude (V)

MK-801 (mg/kg)
0.0 0.1 0.3 0.5

Adaptation =
Response to control –
Response to standard

Effect of MK-801 on Adaptation:
- Increased
- Increased (low dose)
- Reduced
- No effect
# Effects of two models of schizophrenia

## Deviance detection

<table>
<thead>
<tr>
<th>Effect of MIA</th>
<th>Effect of MK-801</th>
<th>Effect of MIA x MK-801</th>
</tr>
</thead>
<tbody>
<tr>
<td>P13 ↑ (GD19)</td>
<td>P13 ↑ (mid-dose)</td>
<td>P13 MIA ↑ effect of MK-801</td>
</tr>
<tr>
<td>N18</td>
<td>N18 ↑ (low dose)</td>
<td>N18</td>
</tr>
<tr>
<td>P30 ↑ (GD19)</td>
<td>P30 ↑ (low dose)</td>
<td>P30</td>
</tr>
<tr>
<td>N65 ↑ (GD10)</td>
<td>N65 ↓ (high dose)</td>
<td>N65</td>
</tr>
<tr>
<td>N85 ↑ (both)</td>
<td>N85 ↓ (high dose)</td>
<td>N85 MK801 ↓ effect of MIA</td>
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</tbody>
</table>

## Adaptation

<table>
<thead>
<tr>
<th>Effect of MIA</th>
<th>Effect of MK-801</th>
<th>Effect of MIA x MK-801</th>
</tr>
</thead>
<tbody>
<tr>
<td>P13</td>
<td>P13 ↑</td>
<td>P13</td>
</tr>
<tr>
<td>N18</td>
<td>N18 ↑</td>
<td>N18</td>
</tr>
<tr>
<td>P30</td>
<td>P30 ↑ (low dose)</td>
<td>P30</td>
</tr>
<tr>
<td>N55</td>
<td>N55 ↓</td>
<td>N55</td>
</tr>
<tr>
<td>N85</td>
<td>N85</td>
<td>N85</td>
</tr>
</tbody>
</table>
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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