Sensory Gating Measures

Auditory P50 Response
Prepulse Inhibition of Startle (PPI)

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Heuristically, sensory gating denotes the ability to filter out irrelevant or distracting stimuli, in order to focus on task-relevant sensory information.

Physiologically, it refers to the inhibition of the response to a second stimulus when it occurs shortly after a preceding stimulus.

Failure of this inhibitory mechanism is thought to be a core deficit in schizophrenia.
PPI Methodology

Perry et al., *Am J Psychiatry* 159:1375-81, 2002
P50 Gating Methodology

Click

Click

500 ms

10 secs

500 ms

CONTROL

Amplitude (μV)

6

-6

50

0

Time (ms)

100

150

Conditioning Wave

T/C=0.06

Test Wave

PATIENT

Amplitude (μV)

6

-6

50

0

Time (ms)

100

150

Conditioning Wave

T/C=1.56

Test Wave
Robust Endophenotypes of Schizophrenia Pathology:

- Highly heritable
  - P50: 68% (Hall et al., *Behav Genet* 36:845-857, 2006)
- Abnormal in unaffected 1st-degree relatives of patients

Important Features of Both Measures:

- Generally considered to be “pre-attentive”
- Allow direct translation into animal models
- Some understanding of the underlying neurocircuitry
- Extensive characterization of pharmacological effects
- Patient abnormality can be ameliorated by clozapine
PPI and P50 gating deficits are not strongly correlated with each other or with other cognitive measures in schizophrenia

<table>
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<th>Age</th>
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<th>PPI</th>
<th>P50 G</th>
<th>AS</th>
<th>LNS</th>
<th>DS-CPT</th>
<th>CVLT-II</th>
<th>FMEM</th>
<th>SMEM</th>
<th>SPA</th>
<th>S-M</th>
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<tr>
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<td>0.37*</td>
<td>0.34*</td>
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Additional Caveats:

**P50 Gating**

- Test-retest reliability is less than ideal (0.38)
- Nature of schizophrenia deficit is still unclear

- Test-retest reliability of P50 amplitude is quite good (0.76)
- P50 amplitude and PPI are robustly correlated (r=0.68)
  
  Schwarzkopf et al., *Biol Psychiatry* 33:815-28, 1993

**PPI**

- ~30% of subjects are “acoustic nonresponders”
  
  Braff et al., *Arch Gen Psychiatry* 49:206-15, 1992
Animal Model of P50 Gating

Bregma -1.4 AP, -2.75 lateral, -2.75 depth

[Graph showing microvolts vs. seconds with a peak at around 0.2 seconds]

[Image of a rat being monitored]
Neural Substrates of P50 Gating

P50 auditory evoked potential generated primarily in superior temporal gyrus. Response is regulated by a distributed cortical/subcortical network. Most attention has focused on medial septal – hippocampal pathway.
Nicotinic Modulation of P50 Gating Deficit

Smoking transiently normalizes the P50 gating deficit in schizophrenia patients.

Adler et al., *Am J Psychiatry* 150:1856-61, 1993

Genetic analysis in schizophrenia pedigrees has linked the gating abnormality to the alpha-7 nicotinic receptor gene on chromosome 15.

Nicotinic Modulation of P50 Amplitude Deficit

![Graph showing the comparison between Family Members and Controls under Placebo and Nicotine conditions.]
Animal Model of PPI
Neural Substrates of PPI

Acoustic stimulus “S” elicits startle response “R” via simple pontine circuitry; prepulse effects on R are mediated via PPN, which is regulated by descending serial and parallel projections from the forebrain.

Dopaminergic Modulation of PPI

COGS Genetic Association Study – Preliminary Results

1,385 SNPs in 94 Candidate Genes

<table>
<thead>
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<th>PPI</th>
<th>P50 Gating</th>
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</thead>
<tbody>
<tr>
<td>GRiK3</td>
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<td>COMT</td>
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</table>
Evidence of for / against glutamatergic modulation:

**P50 Gating**
- No effect of ketamine in rat model of P50 gating (dBruin et al., 1999)
- No effect of ketamine in healthy human volunteers (van Berckel et al., 1998; Oranje et al., 2002).
- Ketamine combined with haloperidol did impair gating ratio (Oranje et al., 2002).
- NMDA receptor NR1 subunit mutant mice exhibit impaired S2 gating (Bickel et al., 2008)

**PPI**
- Animal models provide strong evidence that PPI is disrupted by NMDA antagonists. (Geyer et al., 2001)
- The effects of NMDA antagonists can be reversed by:
  - clozapine (Yang et al., 2010)
  - glycine transporter I inhibitor, sarcosine (Yang et al., 2010)
  - mGluR1 antagonist (Satow et al., 2009)
- Also disrupted by upregulation of GLT-1; blocked by mGluR2/3 agonist (Bellesi and Conti, 2010)
- Impaired in both NR1 (Bickel et al., 2008) and mGluR5 (Gray et al., 2009) mutant mice
- However, ketamine *improves* PPI in healthy human volunteers, and abnormal PPI is associated with *high* glycine levels in schizophrenia patients. (Abel et al., 2003; Heekeren et al., 2007; Heresco-Levy et al., 2007)
In Sum:

Abnormal PPI and P50 sensory gating are relatively robust markers of schizophrenia pathophysiology and may serve as viable endophenotypes.

The availability of direct animal models makes them excellent tools for translational research studies.

Preclinical data strongly suggest that PPI, in particular, could be used as a biomarker for pharmacological studies of the glutamate system.

However:

Their relationship to patients’ “real world” cognitive and functional deficits have not been established and may be equivocal.

There are some methodological difficulties associated with each measure.

Cross-species applicability of preclinical studies to humans is not clear.