

PERCEPTION: Gain Control & Integration

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Perception – Integration

- **Integration:** The processes linking the output of neurons – that individually code local (typically, small) attributes of a scene - into global (typically, larger) complex structure, more suitable for the guidance of behavior.
- Tasks nominated for further development:
 - Coherent Motion Detection Task
 - Contour Integration Task
 - Modified to optimize assessment of integrative processes

Integration Tasks

- **Coherent Motion Detection Task**
- **Contour Integration Task**
- Both human tasks only in visual modality
 - Behavioral and imaging measures
- Analogous tasks in cats and monkeys. Some proposed for rodents (e.g. Visual Discrimination of direction of motion)
 - Most use electrophysiological, not behavioral measures
- Minimal pharmacology literature
- Perhaps rodent touch-screen methods could be used?

Perception – Gain Control

- **Gain control:** The processes whereby neurons adapt their response levels to take into account their immediate context, in order to make best use of a limited dynamic signaling-range.
- Tasks nominated for further development:
 - Contrast-Contrast Effect (CCE) Task
 - Contrast Sensitivity + Steady state visual evoked potentials to magnocellular vs. parvocellular biased stimuli.
- Already mature tasks:
 - Mismatch Negativity (MMN)
 - Prepulse Inhibition of Startle (PPI)

Gain Control Tasks

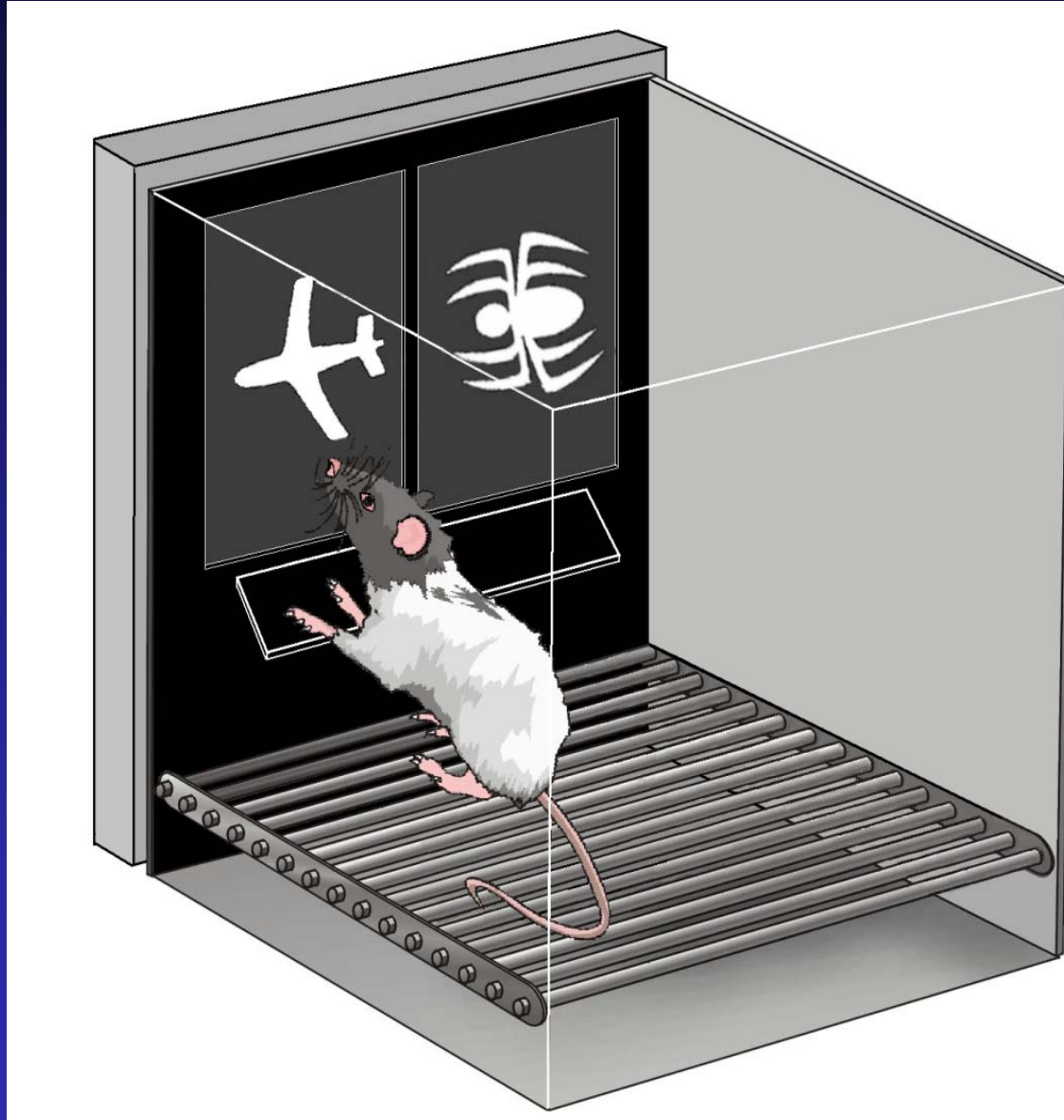
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- **Contrast Sensitivity + Steady state ERPs**
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Rodent Touch Screen Tasks



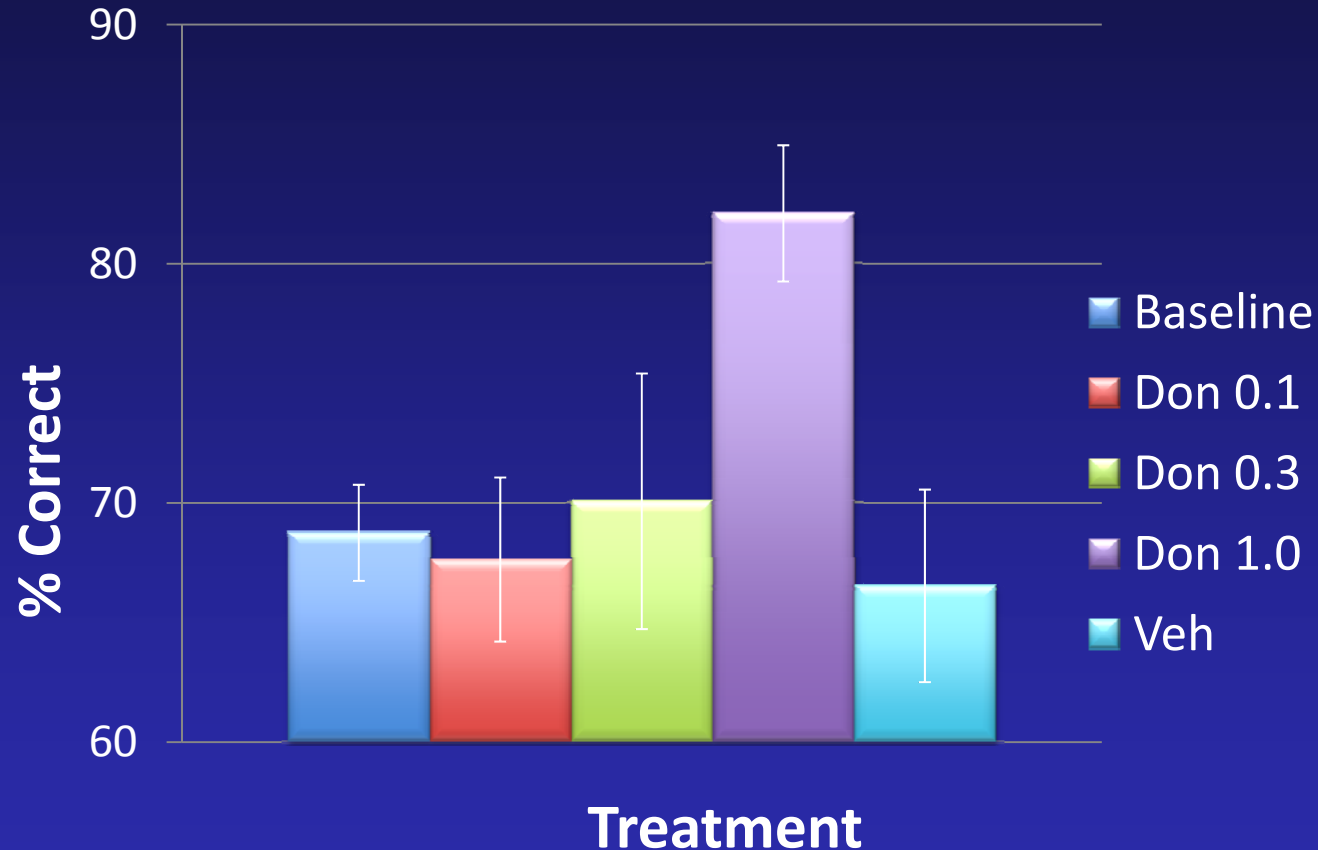
Courtesy of Tim Bussey, Cambridge

Visual Discrimination Learning



Courtesy of Tim Bussey, Cambridge

Donepezil Facilitates Visual Discrimination



McCarthy, Owens, Bansal, McTighe, Bussey and Saksida (2011)
Pharmacology, Biochemistry & Behavior

Gain Control Tasks

■ Mismatch Negativity (MMN)

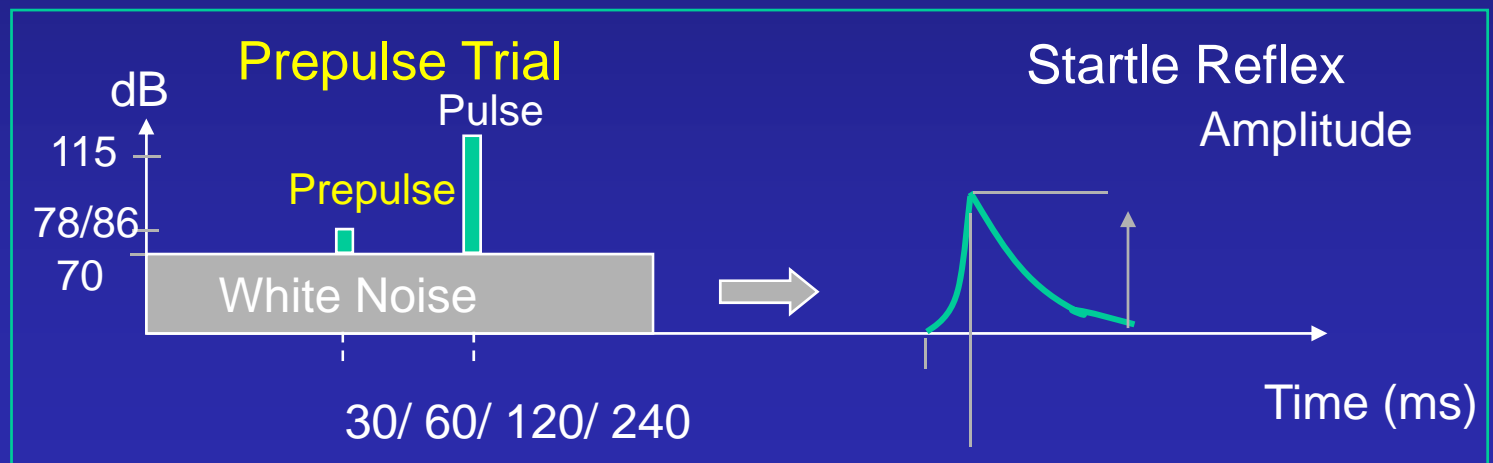
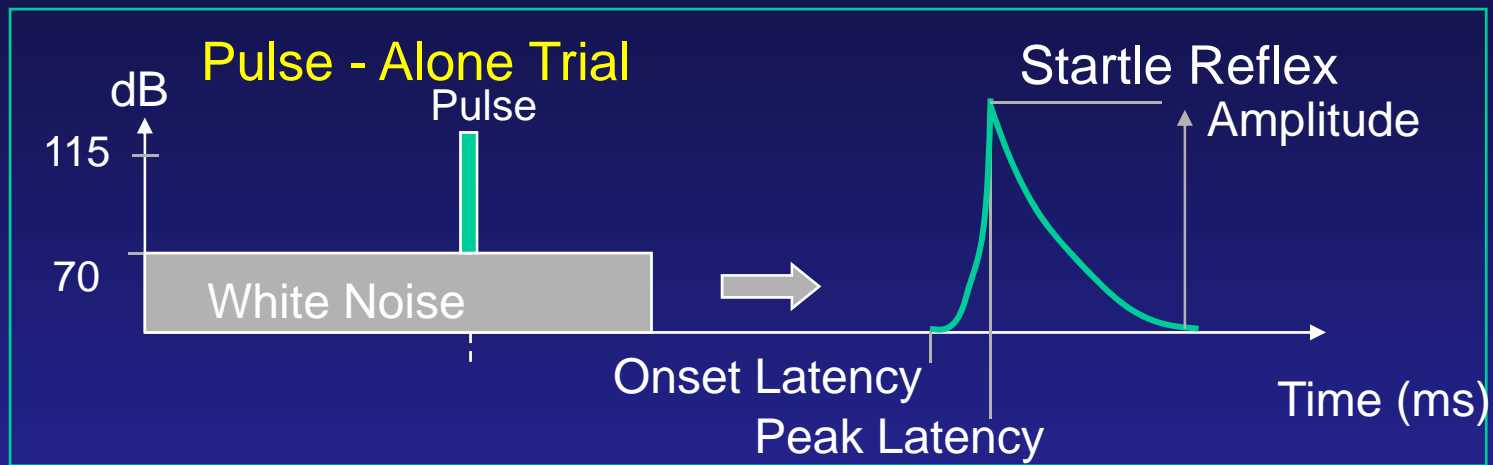
- Human task in auditory modality
 - Electrophysiological and imaging measures, not behavioral
- Analogous electrophysiological task in mice, cats, and monkeys
- Limited pharmacology literature
 - NMDA antagonists reduce MMN in humans, monkeys, and mice
- “Well developed” task:
 - True for assessing deficits in schizophrenia
 - Limited work in other disorders or rodent applications
 - Not true in terms of use for testing improvements in gain control.

Gain Control Tasks

■ Prepulse Inhibition of Startle (PPI)

- Human task in auditory, tactile, or cross-modal modalities
 - Behavioral, electrophysiological, and imaging measures
- Homologous behavioral task in many species
- Enormous pharmacology literature in rodents; modest literature in humans
- “Well developed” task:
 - True for assessing antipsychotics.
 - Not true in terms of PPI-fMRI as a potential imaging biomarker
 - Not true in terms of use for testing improvements in gain control.

Prepulse Inhibition & Latency Facilitation



Prepulse Inhibition of amplitude is disrupted in Schizophrenia
Latency Facilitation is normal in Schizophrenia

Cross-species Homology: Startle/PPI



The Deficient Gating Construct

NORMAL

Sensory & Cognitive Information



Pre- and Attentional Filters



Information Processing



Coherent Cognitive Schema

SCHIZOPHRENIA

Sensory & Cognitive Information



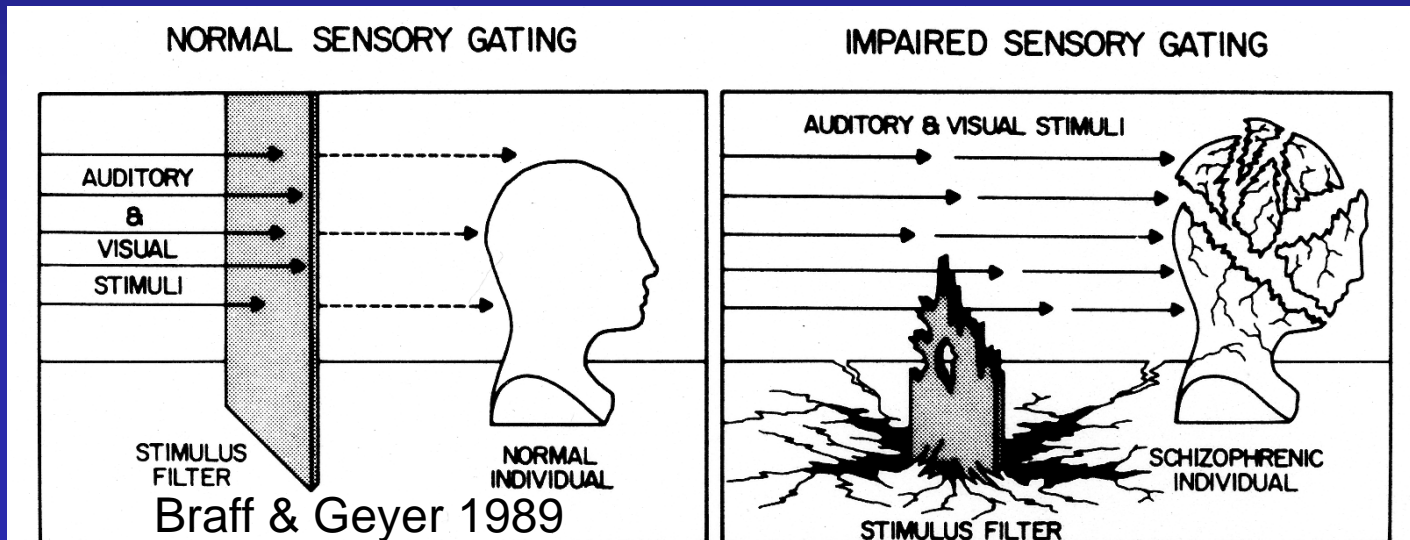
Deficient Filters



Information Overload



Disorganized Cognition



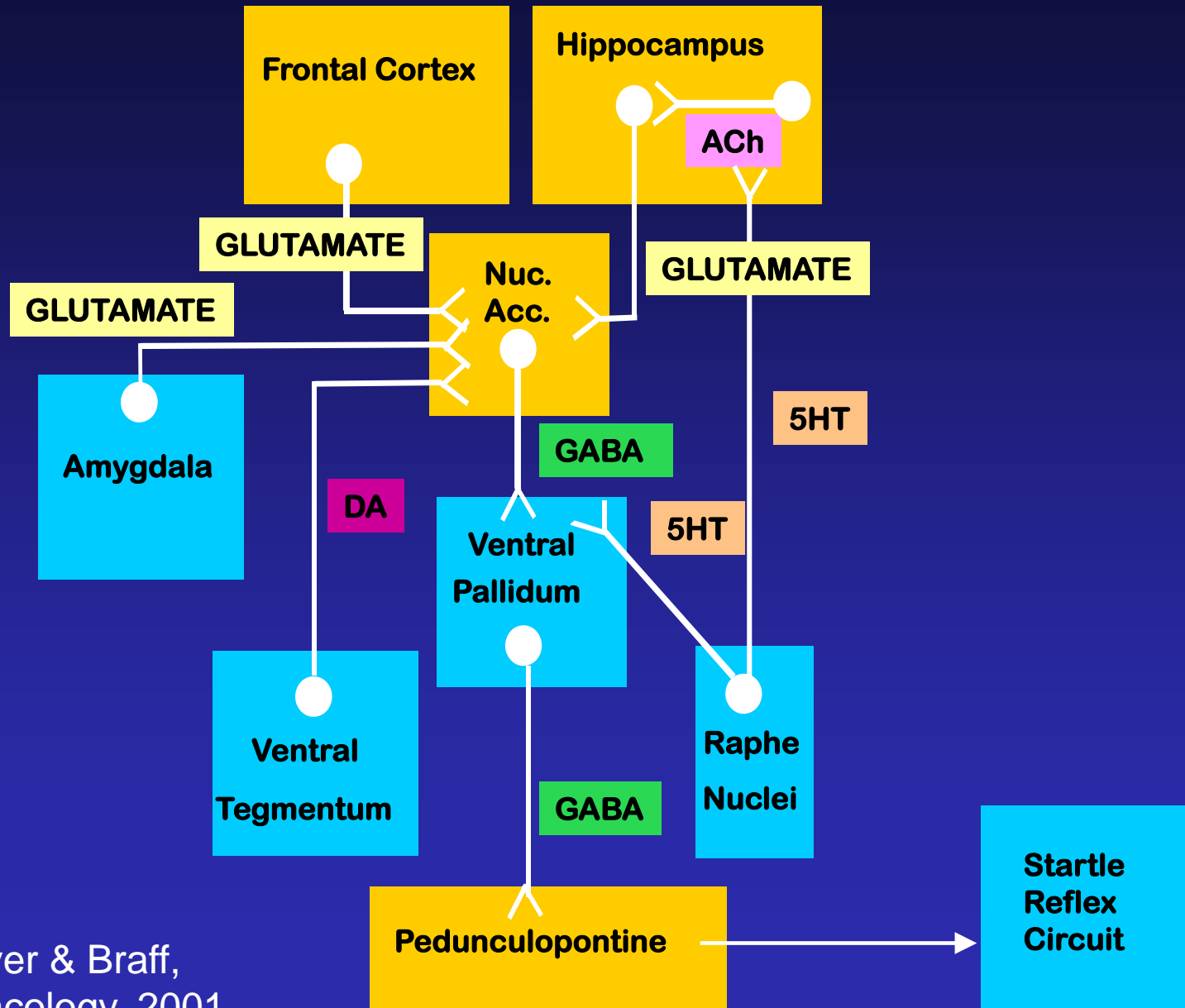
PPI is NOT Correlated with Other “Gating” Measures:

In Mice, Rats, Healthy Humans, or
Schizophrenia Patients

- Other operational measures of GATING:
 - Startle habituation
 - P50 auditory gating
 - Latent Inhibition

The more specific construct of Gain Control
in perceptual processing fits well with the
original pre-attentional filtering construct for PPI

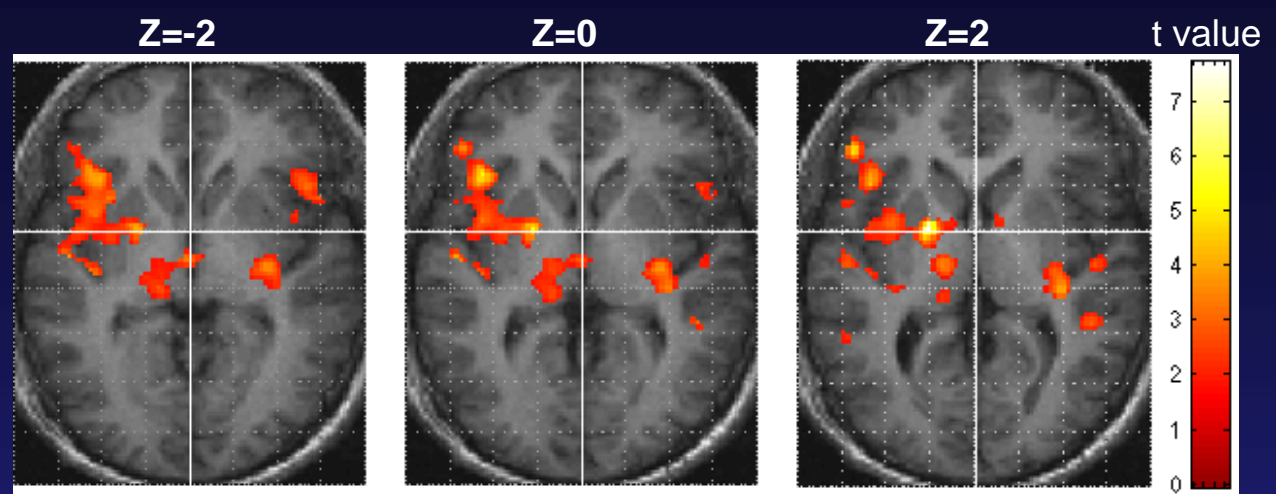
Circuits Modulating PPI in Rats



Adapted from
Swerdlow, Geyer & Braff,
Psychopharmacology, 2001

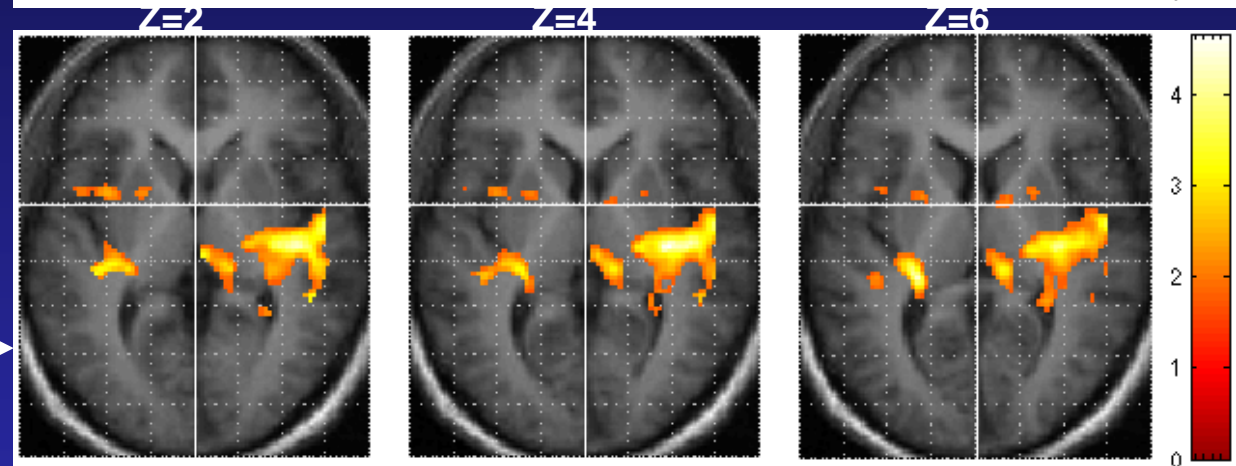
fMRI PPI

Controls →



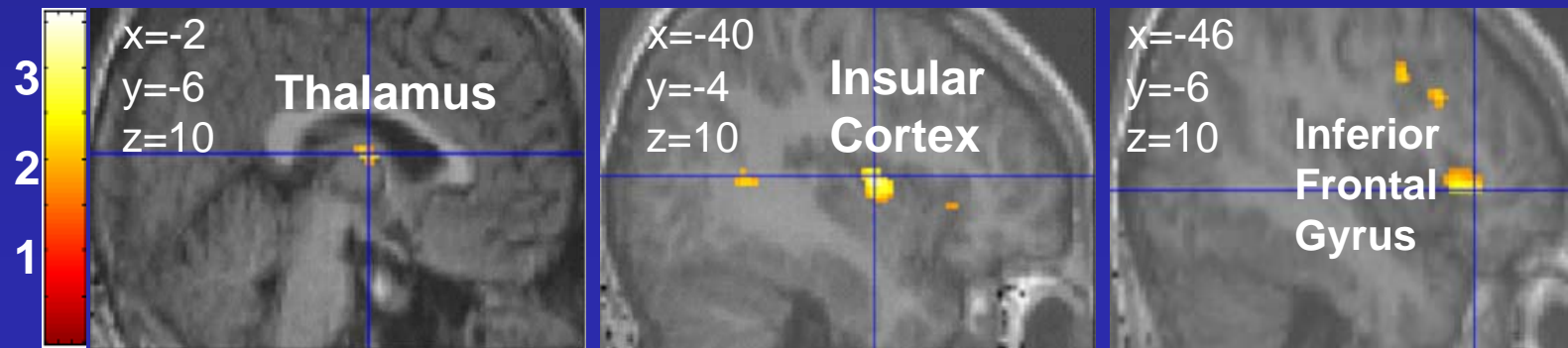
Increases in
prepulse
condition
relative to
startle-alone.

SZ Patients →



Less
activity in
patients
than in
controls.

t value



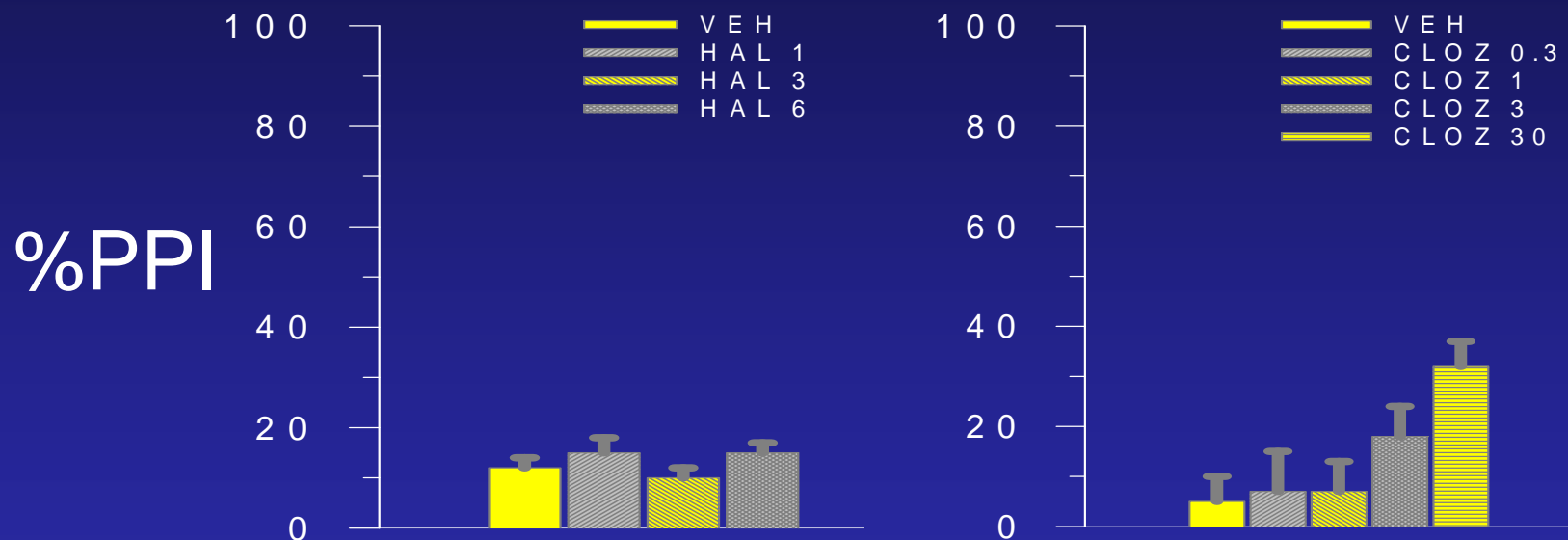
Four Rat Models of Deficient PPI

- **Psychostimulant Dopamine Agonists**
 - Apomorphine, Amphetamine
- **Hallucinogenic Serotonin-2A Agonists**
 - DOI, Mescaline, LSD
- **Psychotomimetic NMDA Antagonists**
 - PCP, Dizocilpine, Ketamine
- **Developmental Disturbances**
 - Prenatal MAM, Isolation Rearing, Neonatal Lesions, Early postnatal PCP

Antipsychotic Effects in Four Rat Prepulse Inhibition Models

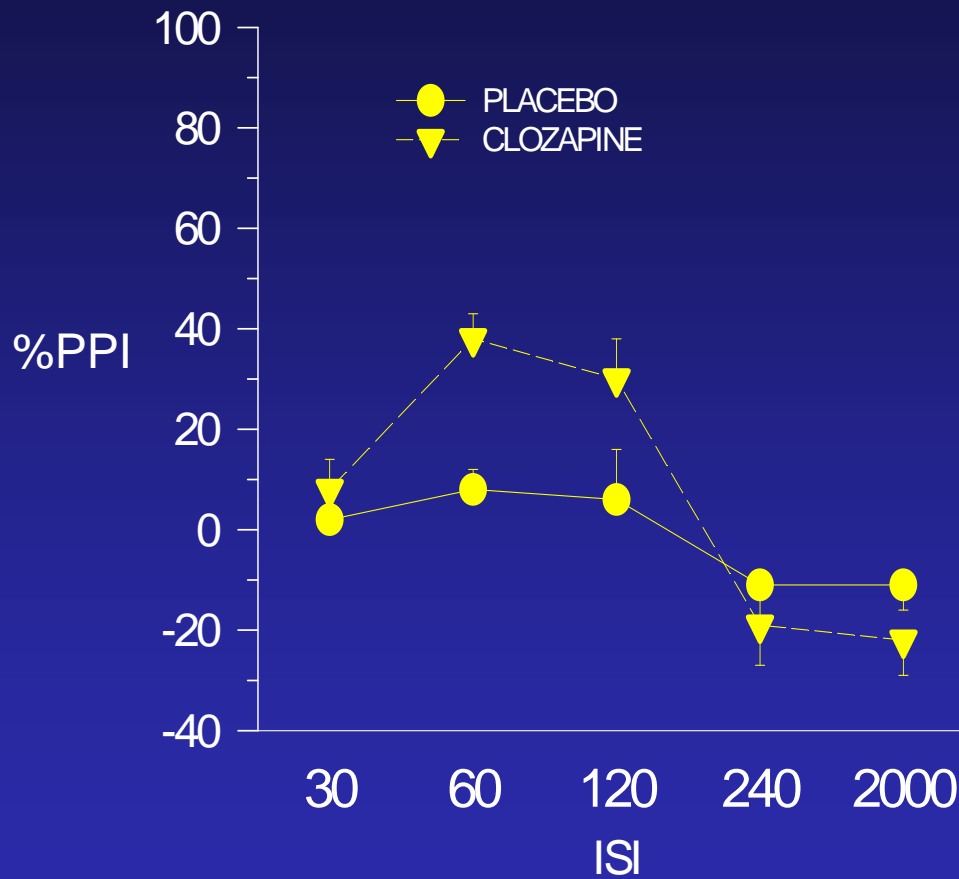
Disrupting Manipulation	Typical APDs	Atypical APDs	Others
Dopamine D2 Agonists	Yes	Yes	Some
Serotonin 2A Agonists	No	Some	No?
NMDA Antagonists	No	Some	Some
Developmental Perturbations	Yes	Yes	Yes?

Clozapine Increases Low PPI in C57BL/6J Mice

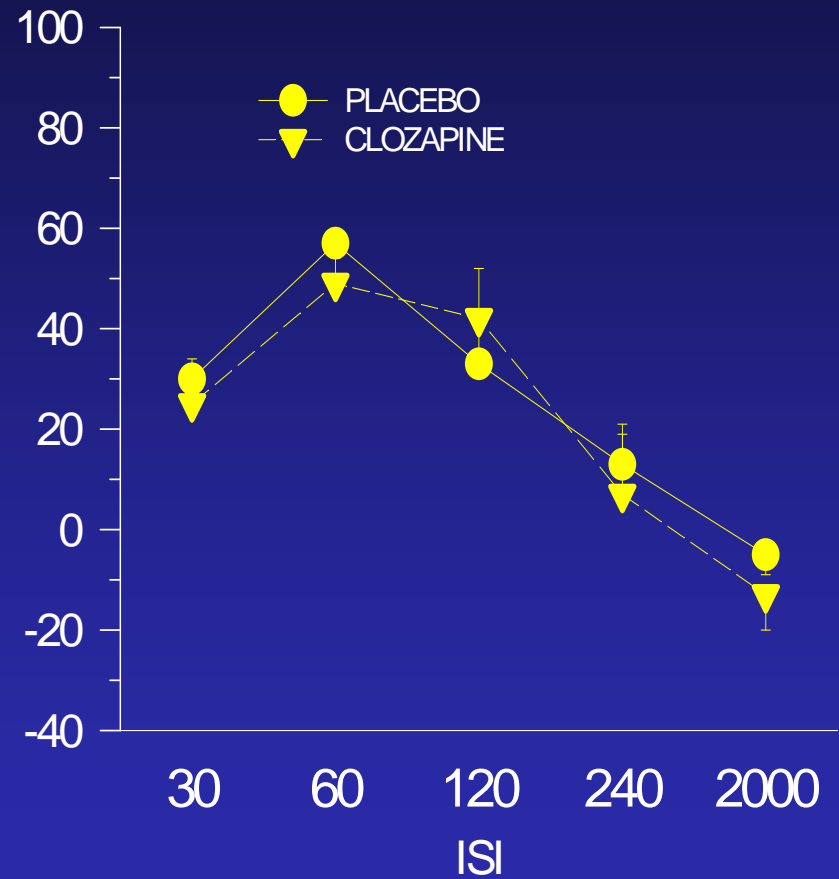


Clozapine failed to increase PPI in the high PPI strain of mice (129Sv/Ev)

Clozapine Increases PPI in Low but not High PPI Subjects



Low PPI Subgroup



High PPI Subgroup

CONCLUSIONS

- Perceptual abnormalities may impact performance on cognitive tests and cognitive functions in patients.
- Cross-species tasks to assess Integration and Gain Control in visual and auditory domains are feasible.
- Developing visual modality tasks in rodents may help.
- Global constructs such as “Gating” may be less useful than specific constructs such as “Gain Control”.
- Tasks that are “well developed” for some purposes may require further development for assessing the constructs of Integration and Gain Control.
- Though beyond the scope of this meeting, combining a specific task with different disrupting manipulations will lead to different pharmacological profiles.

