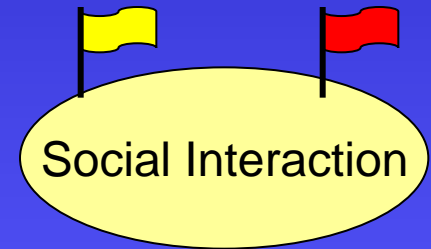
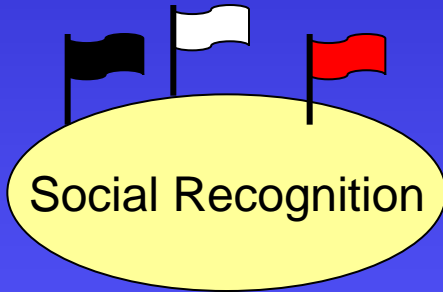
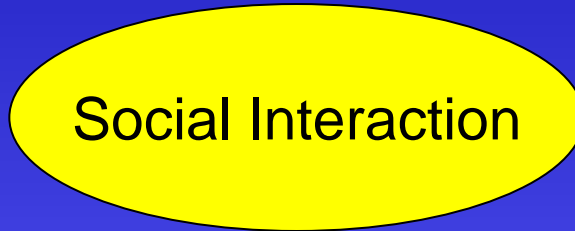
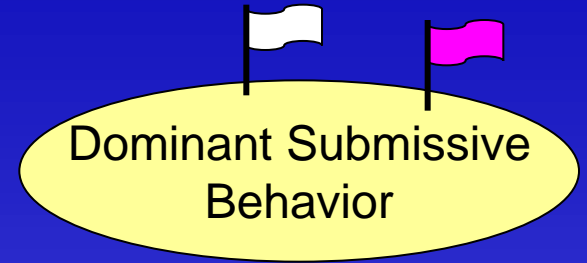
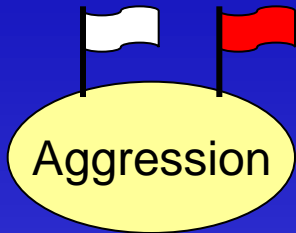


Measuring social interactions in drug discovery

Marcel van Gaalen



Schizophrenia



Depression



Alzheimers Disease



Anxiety Disorders

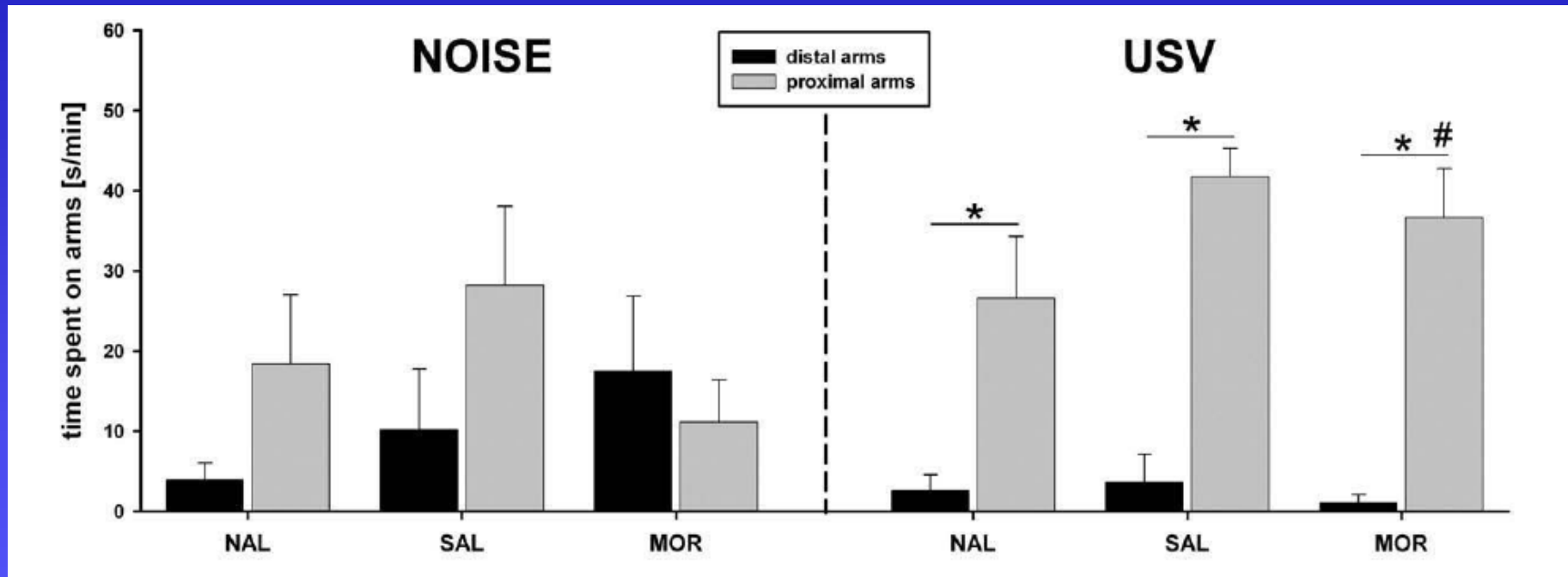


Cognition Defictis



Autism

Ultrasonic communication: emerging method in rats?



Stimulus-directed locomotor activity of juvenile rats. The time spent (s/min) in the distal (black bars) or proximal (grey bars) arms from the loudspeaker is given for presentation of background noise (NOISE, left graphs) and 50-kHz ultrasonic vocalizations (USV, right graphs).

Model development

- Validity: Predictive, construct, face.
- Ease to reproduce: internal and external
 - Robust effect size
 - Measuring window
 - Simple set up
 - Space
- Capacity

Dominant submissive behavior



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Review

Dominant–submissive behavior as models of mania and depression

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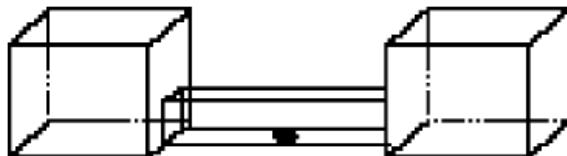


Fig. 3. The RSBM apparatus consists of two plexiglass chambers connected by a passage having a small feeder dish with milk in the center from which only one rat can drink at a time. Reproduced from Malatynska and Kostowski (1984) and Malatynska (1985).

Validity: Predictive, construct, face

Ease to reproduce: internal and external

Robust effect size

Measuring window

Simple set up

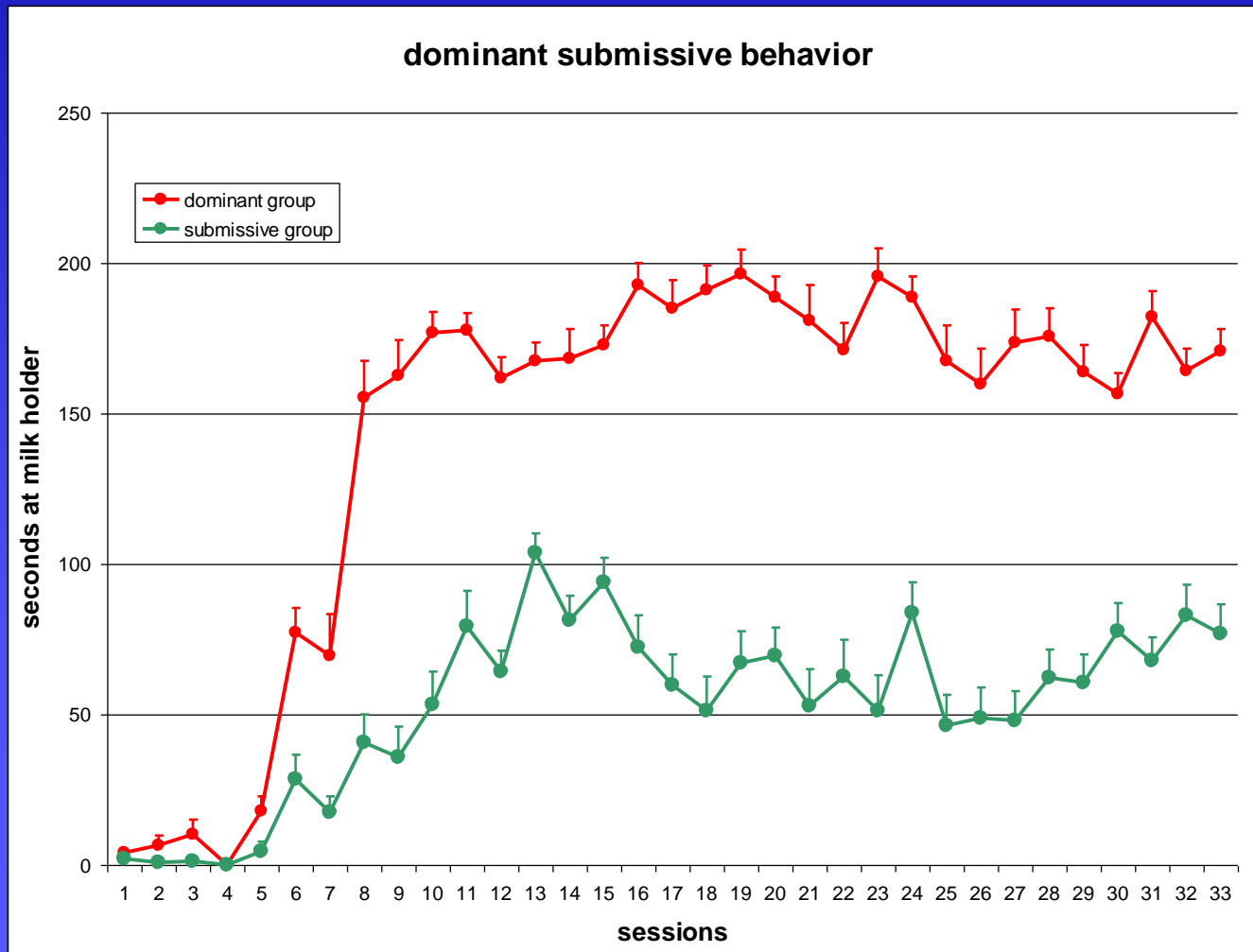
Space

Capacity

Dominant submissive behavior

- Sprague Dawley Rats were housed in pairs
- Two animals were tested per arena from different pairs, but testing was always with the same animal
- Test arena was a type IV cage with a 50 ml beaker glass hanging in the bottom, to which one animals at the time had access.
- Animals had restricted access to food during the week, and full food over the weekend.

Dominant submissive behavior



Dominant submissive behavior

- Stable dominant submissive behavior in rats can be demonstrated with an easy set up.
- Approximately that 60% of the trained pairs show distinct and stable dominant submissive behavior.
- The test can be run in a semi automatic fashion.

Schizophrenia: negative symptoms

- Efficacy of current antipsychotics on negative symptoms is modest at best
- Persistent and clinically significant negative symptoms remain a major unmet therapeutic need
- Regulatory agencies such as the FDA have indicated that they will entertain approval of add-on treatments proven to be effective in specific domains such as negative symptoms but so far, no compound received FDA approval for treatment of negative symptoms (Laughren and Levin 2006)

Negative symptoms: rating scales

SANS Items	SANS	PANSS	BPRS
Affective flattening	X	X	X
Unchanging expression	X	X	X
Decreased movements	X	X	X
Paucity of gestures	X	X	X
Poor eye contact	X	X	—
Affective nonresponsivity	X	X	X
Inappropriate affect	X	—	—
Lack of vocal inflection	X	X	X
Alogia	X	P	—
Poverty of speech	X	X	—
Poverty of content	X	P	—
Blocking	X	—	P
Increased latency response	X	—	—
Avolition/apathy	X	P	—
Poor grooming/hygiene	X	X	—
Impersistence at work/school	X	—	—
Physical anergia	X	—	—
Anhedonia/asociality	X	P	P
Few recreational activities	X	P	—
Decreased sexual interest	X	—	—
Decreased capacity for closeness	X	P	—
Few friends/prefers isolation	X	X	X
Attentional impairment	X	—	—
Social inattentiveness	X	P	—
Inattentiveness on mental status examination	X	—	—
Other items			
Emotional withdrawal	P	X	X
Poor rapport	P	X	—
Poor abstract thinking	—	X	—
Stereotyped thinking	X	X	—
Psychomotor retardation	P	—	X
Lack of sense of purpose	P	P	—
Fatigue	—	—	—
Slowed speech	—	—	X
Depressed appearance	—	—	—
Loose associations/incoherence	—	—	X
Low voice	—	—	P

Hypotheses of schizophrenia

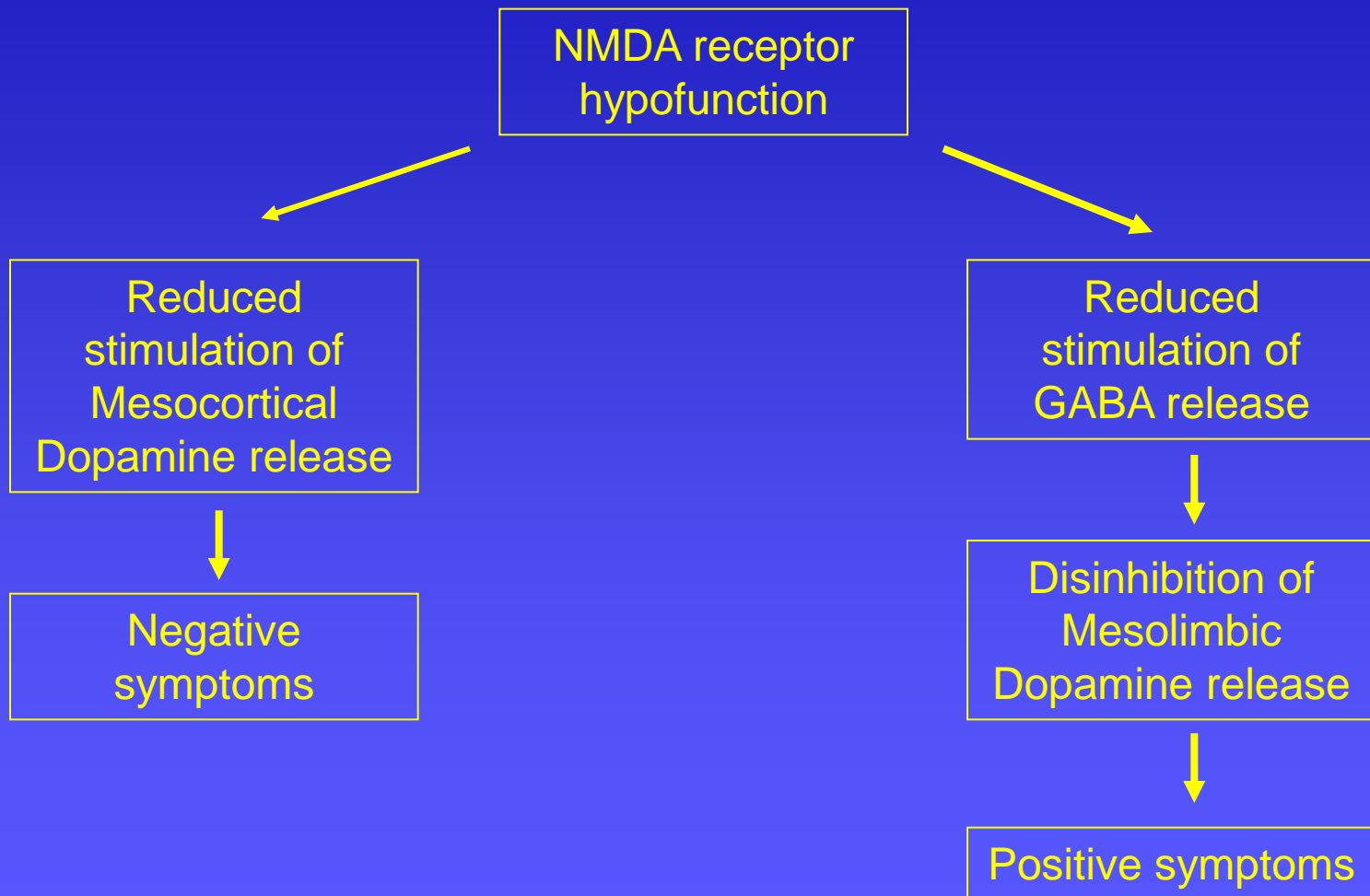
– Dopamine hypothesis

- Dopamine-releasing stimulants cause psychosis
- Current antipsychotics are D2-like antagonists
- Negative symptoms are at best poorly responsive to current antipsychotics
- Dopamine-releasing stimulants do not induce a syndrome that resemble negative symptoms

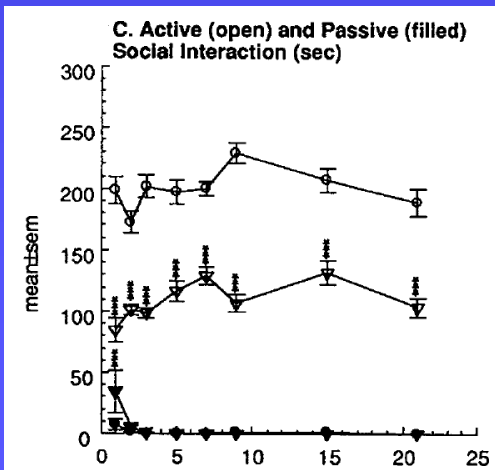
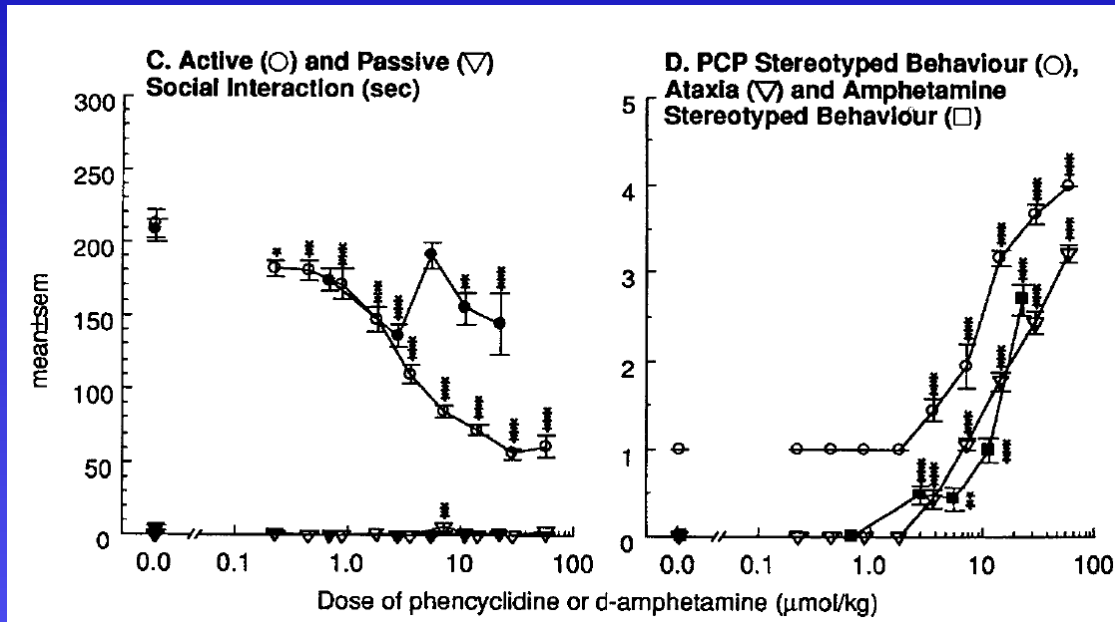
– Glutamate hypothesis

- NMDA antagonists produce a syndrome that is comparable to symptoms of schizophrenia including negative symptoms

Hypothesis of schizophrenia



PCP-induced social interaction deficit

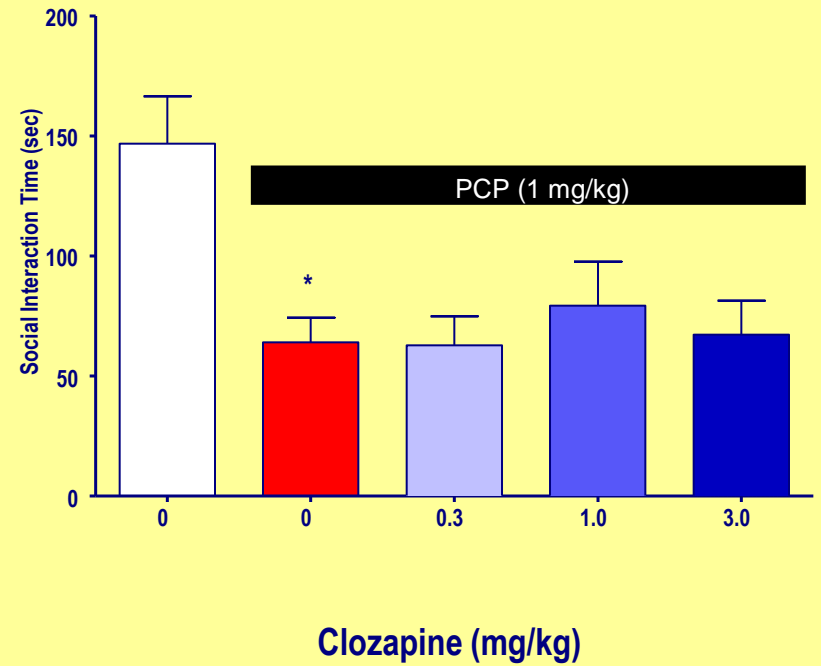
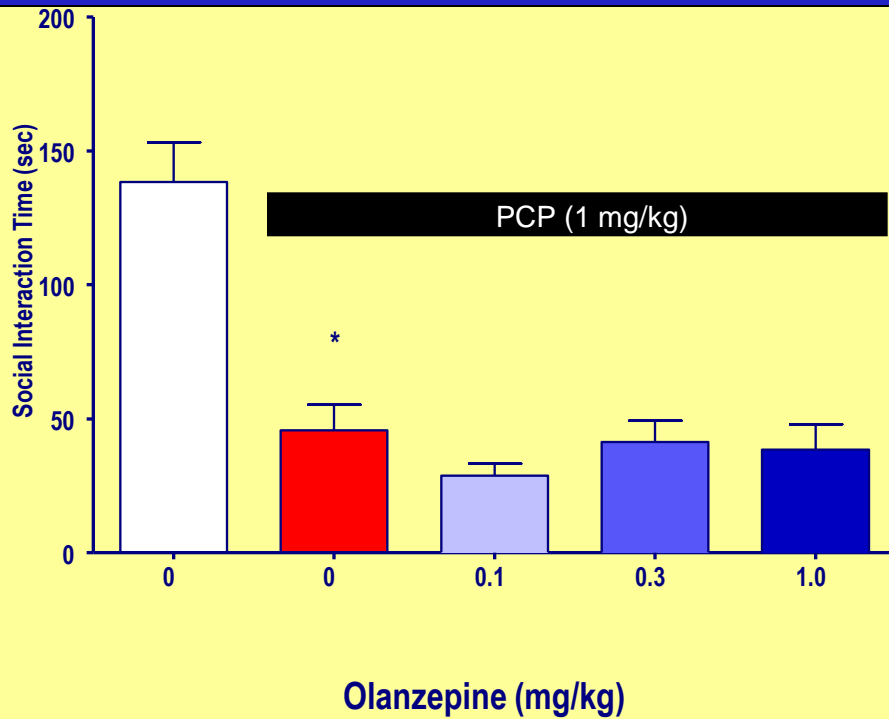


PCP-induced effect on social behavior can be blocked by chronic treatment with clozapine but not by haloperidol

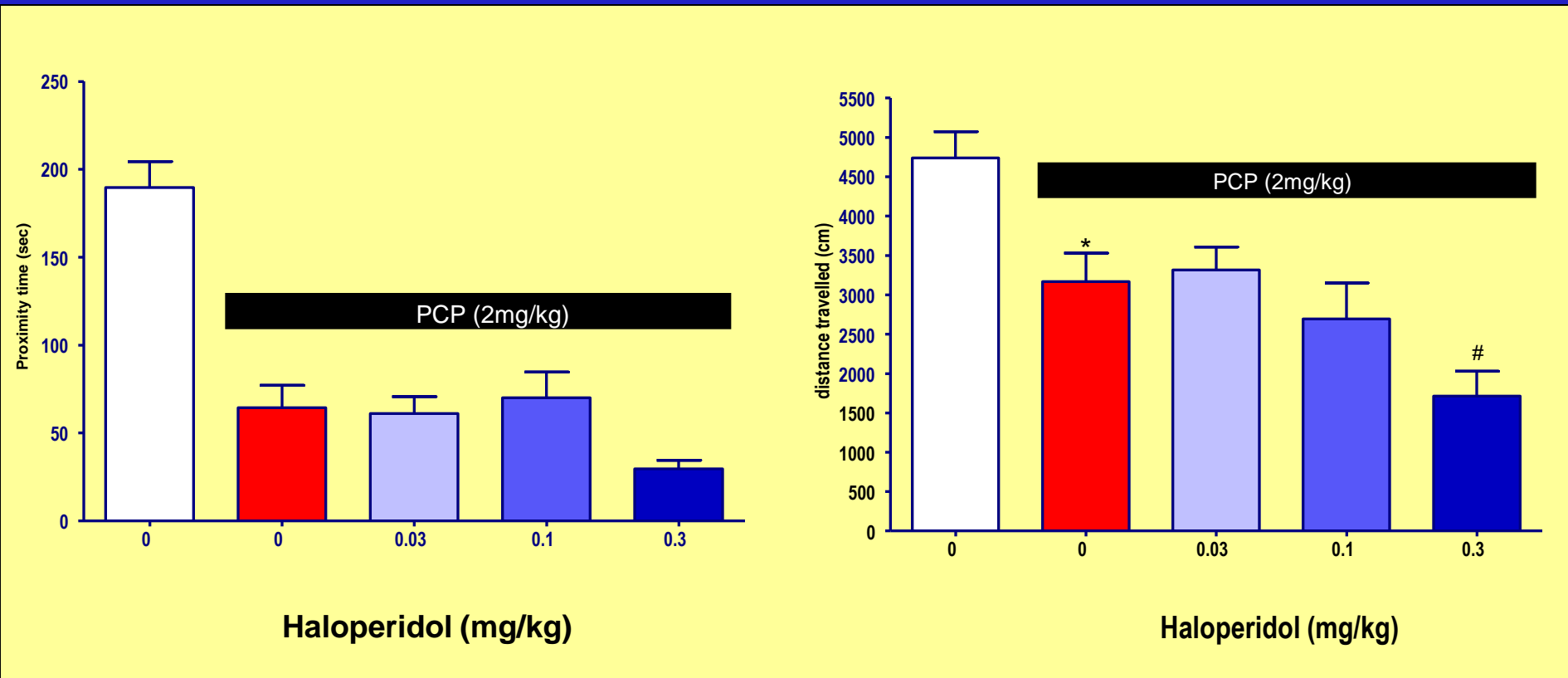
PCP-induced social interaction deficits: protocol

- Rats are housed in pairs in reversed light/dark cycle and handled twice a week for a period of two weeks
- day 1: animals are habituated to an open field (60x60) under red light conditions with a familiar rat
- Day 2: animals are treated with test compound (60 min) or PCP (15 min) before tested with an unfamiliar rats (same treatment) for 10 min
- Proximity is defined as center of gravity is 8 -18 cm apart

PCP-induced social interaction deficits



PCP-induced social interaction deficits



PCP-induced social interaction deficits

Compound	Dose range	Effect
haloperidol	0.03 – 0.3	↓
olanzepine	0.1 – 1.0	↔
risperidone	0.03 - 1.0	↔
clozapine	0.3 – 3.0	↔

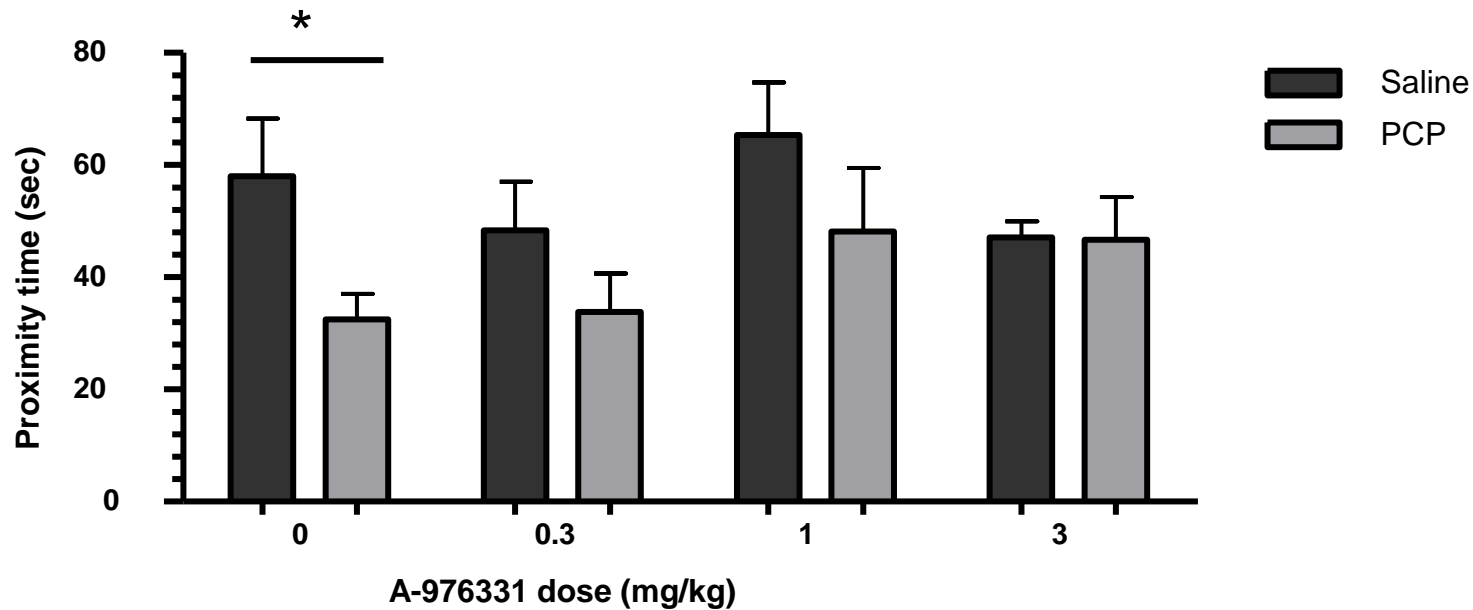
According with or in contrast to clinical findings?

Negative symptoms: Glycine site potentiators

- The strychnine-insensitive glycine binding site is a positive modulatory site for the NMDA receptor
- The full glycine agonists glycine, D-serine and D-alanine and partial agonist D-cycloserine improve negative symptoms
- The glycine transporter-1 inhibitor sarcosine improves negative symptoms

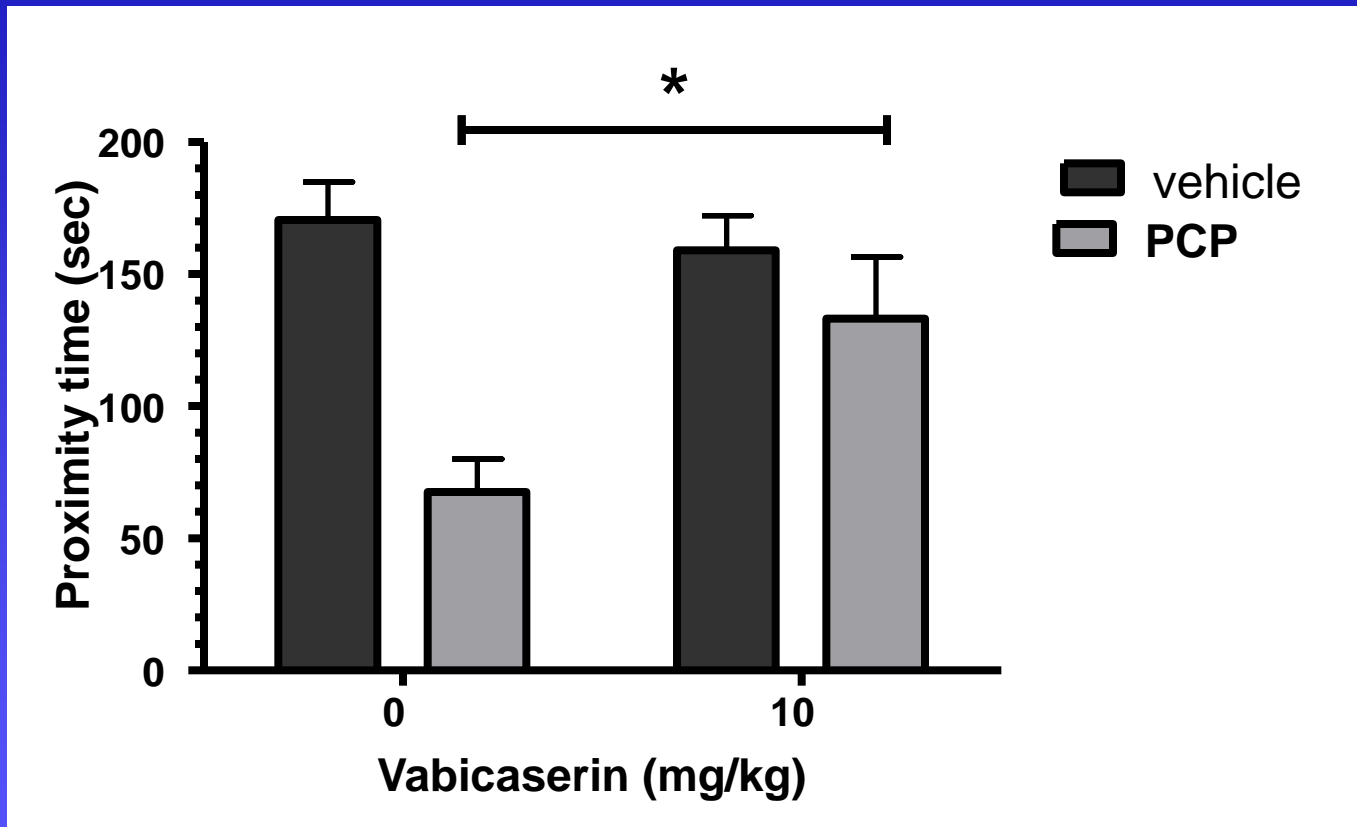
Social interaction: GlyT1 inhibitor A-976331

Social interaction in rats



Social interaction

5-HT_{2C} agonist vabicaserin



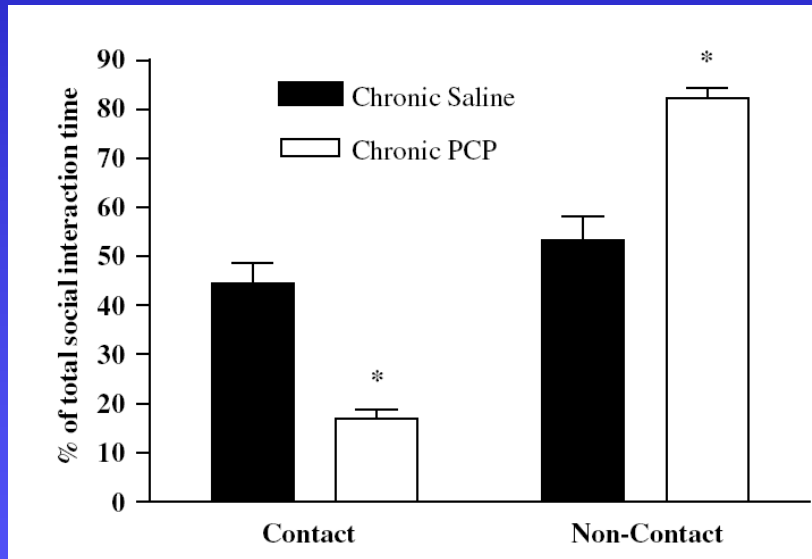
Acute PCP treatment (1.0 mg/kg) induced a reduction in social interaction between adult, unfamiliar rats. Vabicaserin fully reversed this PCP-induced deficit without affecting social interaction time by itself.

Summary

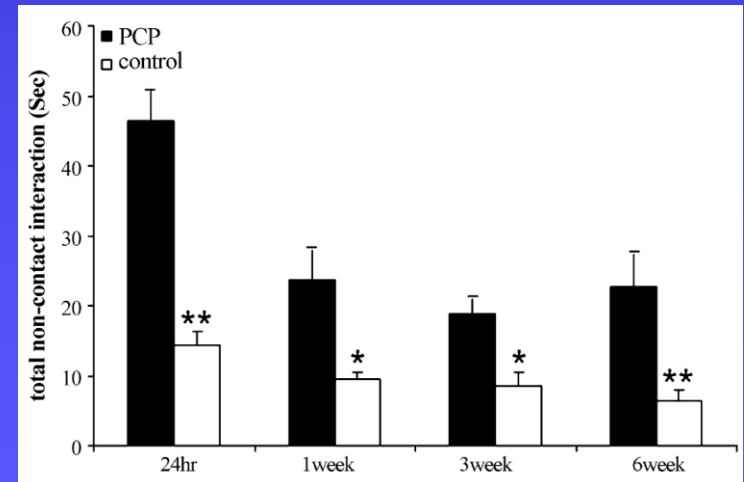
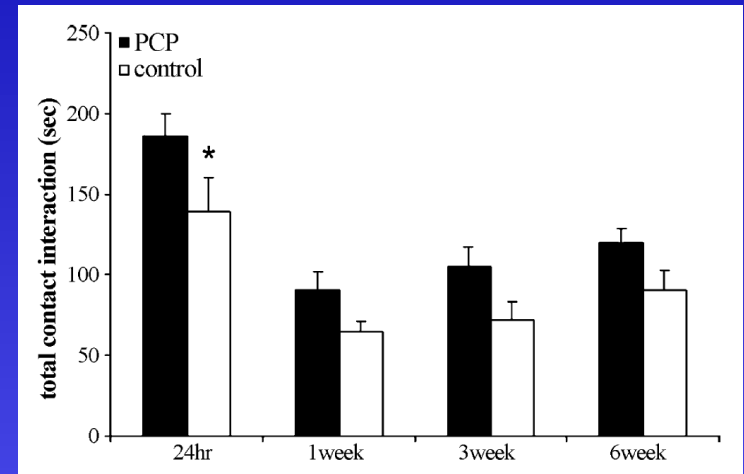
- Social interaction tests are valuable tests for drug development
- New methods, like 50 kHz calling, may allow other aspects of social interaction (susceptibility or interest?)
- PCP-induced deficit in social interaction is a model with face and construct validity for negative symptoms of schizophrenia
 - Predictive validity?
 - 5-HT_{2C} agonist possible treatment?

Backup

Social interaction: Details matter



14 day treatment with PCP
Lee et al 2005



Withdrawal after 7 days treatment with PCP
Jenkins et al 2008

Animal models of schizophrenia

Dopamine agonist-induced behavior	No observation of negative symptoms
NMDA antagonist-induced behavior	What treatment regime leads to induction of negative symptoms?
Chronic NMDA antagonist-induced behavior	
Withdrawal of NMDA antagonist	
Neonatal brain lesion models	Damage to brain is not observed in patients
Neonatal pcpc models	Robustness?
Disrupted neurogenesis (MAM, X-ray)	
Mutant models: (DISC, Reeler mouse, Trace amine 1 receptor knock out mouse)	