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Biological Psychiatry

- Established in 1969
- Published by Elsevier and the Society of Biological Psychiatry (founded in 1945)
- Acceptance rate of approximately 15%
- Latest Impact Factor: 8.926
Ranked 4th out of the 117 Psychiatry titles, and 13th out of 230 Neuroscience titles, on the 2009 Journal Citations Reports® published by Thomson Reuters.

Publishes “peer-reviewed basic and clinical contributions from all disciplines and research areas relevant to the neuroscience, pathophysiology, and treatment, of major psychiatric disorders. The journal publishes only novel reports of current work.”
• Most of the Journal’s output features work with human patients (functional MRI and cognitive evaluations), but rat models are also very common.

Bastiaansen et al. (2011). Age-Related Increase in Inferior Frontal Gyrus Activity and Social Functioning in Autism Spectrum Disorder. 69(9): 832-838

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What is Schizophrenia?

• Mental disorder characterized by disorganized speech and thought patterns, hallucinations, and paranoid or bizarre delusions

• Can also involve “negative symptoms”—lack of motivation, emotional responses, or desire to form relationships.

• Schizophrenia has immense human and economic costs—a 1999 study by the Lancet found active psychosis to be the third-most disabling medical condition.

• Also decreases life expectancy by 12-15 years
Antipsychotic side effects

• “Typical antipsychotics” and “Atypical antipsychotics”

• Associated with movement disorders (extrapyramidal symptoms), considerable weight gain, and diabetes

• Serious issues with drug regimen compliance
What causes schizophrenia?

- Both hereditary and environmental causes have been described.
- The latter include prenatal insults, childhood abuse, and social alienation.
- No single neurobiological cause has been discerned, although there are many candidates.
Current investigations

- Dopamine hypothesis—posits hyperactive and disturbed dopaminergic signal transduction. **Prolonged use of dopamine-increasing drugs can cause schizophrenia-like symptoms: “amphetamine psychosis.”** Certain brain regions of schizophrenics (e.g. the thalamus) have an over-abundance of dopamine-associated transcripts. **The PFC, which integrates sensory, motor, and affective input to shape planned behavior, is densely innervated with dopaminergic neurons.**
Current investigations

• Glutamate hypothesis—hypoactivation of glutamate receptors. PCP (phencyclidine), which functions primarily as an NMDA receptor antagonist, produces many of schizophrenia’s core symptoms.

• GABA—low GABA levels have been described in the amygdala, thalamus, and nucleus accumbens of schizophrenics. GABAergic neuronal density is lower in the limbic system and cortex.
How might GABA loss contribute to schizophrenia?

- One theory holds that GABAergic inhibitory interneurons may be important to stabilizing/regulating the activity of other CNS neurons. These neurons receive input from pyramidal neurons, the primary excitatory units of the prefrontal cortex.

- In other words, schizophrenia may represent (at least in part) an outcome of PFC hyperactivity.
What is GABA?

- Gamma-aminobutyric acid is the chief inhibitory neurotransmitter in the mammalian nervous system.
- Synthesized in the brain from a glutamate precursor.
- Two receptor classes are known—GABA_A (ligand-gated Cl- channels), and GABA_B (G-protein-coupled receptors).
- GABA analogs have anti-anxiety and anti-convulsive properties (benzodiazepines).
Bicuculline

- Competitive antagonist of ionotropic GABA receptors (GABA$_A$ class)
- Produced by several plant species
- High doses mimic epilepsy—this drug has been widely used for in vitro study of seizures

This study used bicuculline methobromide:
Why a rat model?

• “Functionally, the prefrontal cortex of rats has been implicated in working memory, attention, response initiation and management of autonomic control and emotion. In humans, dysfunction of prefrontal cortical areas with which the medial prefrontal cortex of the rat is most likely comparable is related to psychopathology including schizophrenia, sociopathy, obsessive-compulsive disorder, depression, and drug abuse.”

PFC infusions (Figure 1)
Male Long-Evans rats were implanted with bilateral cannulae
Using stereotaxic coordinates
http://www.leica-microsystems.com/news-media

AP=anterior-posterior; ML=from mid-line (usually measured from bregma)
DV=dorsal-ventral
Nissl Stain (3.72mm anterior from bregma) 2\textsuperscript{nd} from top in Fig. 1
Nissl stain (3.0mm anterior from bregma) 4th from top in Fig. 1
Nissl stain (2.76mm anterior from bregma) bottom of Fig. 1
So...

Injected mPFC structures (in dorsal to ventral order)
Cingulate cortex
Prelimbic cortex
Infralimbic cortex
One caveat...

“...although the medial prefrontal cortex is clearly involved in a variety of cognitive and emotional processes, its dorsal and ventral subregions seem to be involved in different aspects of the information processes. Thus, the dorsal part of the medial prefrontal cortex...is mainly involved in the temporal patterning of behavioral sequences. In contrast, the ventral part of the medial prefrontal cortex...appears to be critical for the flexible shifting to new strategies or rules in spatial or visual-cued discrimination tasks, and also... to guide behavior in situations of perceived threat or exposure to aversive stimuli.”
What is being tested?

1. Working Memory

The ability to retain and manipulate information in order to carry out complex tasks; impaired in schizophrenia patients

Rats were evaluated using a maze model—“delayed alternation”
Rats were trained to “criterion performance” in the maze prior to infusions.
2. Set-Shifting

“the ability to display flexibility in the face of changing schedules of reinforcement”

Also impaired in schizophrenia
Wisconsin Card Sort test

• Widely used assessment of set-shifting in humans
• Subject matches a stack of cards to “stimulus” cards

The matching rule changes during the test; subject is never told what the rule is, only whether a match is right or wrong. Score is based on mistakes made during the learning process.
Figure S1B

Day 1:
Rats trained using visual cue system

Day 2:
20 trials using previous visual cue system (to measure retention)

21st trial onward: rats must select the lever “opposite their bias,” and IGNORE the visual cue.
Scoring of set-shift errors

Trials were divided into consecutive blocks of 8

• *Perseverative errors*—rat followed visual cue, pressing the lever opposite the “correct” one. Scored when 6/8 or more trials were incorrect

• Rat judged to have adopted new strategy when 5/8 errors or less were performed

• At this point (and after), new errors are scored as *regressive*—suggesting an inability to retain the new pattern.

• *Never-reinforced errors*—rat pressed lever opposite both visual cue and required side.
Drug schedule for Set Shift-tested rats

1) Saline on both days (controls)
2) 25 ng BC on Day 1, saline on Day 2
3) 50 ng BC on Day 1, saline on Day 2
4) Saline on Day 1, 25 ng BC on Day 2
5) Saline on Day 1, 50 ng BC on Day 2
3. Response reversal

• A variation on the set shift experiment, conducted with a separate group of rats. On Day 1 they were trained to press only one lever, ignoring the visual cue. On Day 2, they were immediately trained to select the opposite lever, ignoring the cue once again. Drug schedules were 50 ng BC or saline, administered on Day 1 or Day 2.
4. Locomotor activity

- Rats were habituated to a particular chamber
- Then, each rat received infusions of saline or bicuculline (25 or 50 ng), followed 10 minutes later by saline or amphetamine injections.

*Studies indicate a heightened sensitivity to amphetamines in schizophrenic patients.*
5. Latent Inhibition

In classical conditioning, refers to the fact that stimuli that have been meaningless in the past take longer to acquire meaning than those that are unfamiliar. Latent inhibition is the basis of our ability to “filter” irrelevant information from the environment. Schizophrenia patients tend to exhibit low latent inhibition.
Latent inhibition (con’t)

- **Principle of latent inhibition test**—

  *If latent inhibition is normal*: rats that are pre-exposed to a conditioned stimulus (a tone plus a cue light) will take longer to associate that stimulus with an electric shock, than rats that first encounter the stimulus in combination with the shock.

  Fear response to the CS was measured as reduced pressing of a food lever.
Figure S1C

Latent Inhibition

9 days

Lever press training
(to VI60 schedule)

Bicuculline/Saline infusions

Preexposure:
30 CS’s over 30 min

No preexposure:
30 min in chambers

1 day

6 min break

Conditioning:
3 CS+shocks over 15 min

1 day

VI60 lever pressing baseline

1 day

Test:
3 CS’s
6. Dopamine Neuron Activity

- A recording electrode was used to measure spontaneously active neurons in the ventral tegmental area (VTA) of bicuculline and saline-treated rats.
- Dopaminergic neurons were identified by characteristic spike width.
- Parameters were (1) population, (2) firing rate, (3) proportion of bursts, and (4) number of spikes per burst.
Ventral Tegmental Area

- The major origin of dopaminergic cell bodies in the mesolimbic dopamine system.
Figure 2. The effects of reducing prefrontal cortex gamma-aminobutyric acid activity on working memory. (A) Infusions of three doses of bicuculline did not affect working memory accuracy, indexed by the number of errors committed during the test phase of the task. However, the 50-ng dose did increase response latencies to make the first choice (B) and the average time per subsequent choice (C). Star denotes *p < .05 vs. saline.
Day 1:
(A) No increase in errors was found in drugged rats during initial training
(B) No increase in response latency was observed during initial training.

Day 2:
(C) Recollection of the previously learned pattern was unaffected by the drug.
(D) Set-shifting errors were increased by the higher bicuculline dose (given on either Day 1 or Day 2)
(E) More preservative errors in Day 1-infused rats, but more never-reinforced errors in Day 2-infused rats
(F) Second-day response latencies were increased, but only in the rats drugged on Day 2.
Figure 4. Reducing prefrontal cortex gamma-aminobutyric acid activity does not affect acquisition or reversal of a response discrimination. Intraprefrontal cortex infusions of bicuculline (Bicc) on Day 1 did not alter (A) errors to criterion or (B) response latencies during the initial learning of a response rule. (C) Similarly, treatment with bicuculline either on Day 1 or Day 2 did not impair reversal learning. (D) Infusions of bicuculline before the reversal did not increase response latencies when compared with controls.
Figure 5. Reducing prefrontal cortex gamma-aminobutyric acid activity does not affect latent inhibition. Graph displays suppression of lever pressing (suppression ratios) averaged over three presentations of the shock-associated conditioned stimulus (CS) delivered 48 hours after aversive conditioning. Rats that received 30 nonreinforced preexposures of a CS displayed significantly less suppression of lever pressing during the test, when compared with rats that were not preexposed. This effect was not altered by intra-prefrontal cortex infusions of bicuculline. Note that rats in the 50 ng/nonpreexposed group (hatched bar) display suppression comparable to saline-treated/nonpreexposed rats (white bar), indicating that these treatments also did not impair acquisition of conditioned fear. Star denotes \( p < .05 \) main effect of CS preexposure.
(B) The higher bicuculline dose (50 ng) increased locomotion, as well as amphetamine susceptibility.
Percentage of spikes in bursts (C), number of spikes per burst (D) and firing rate (E) for **dopaminergic** neurons were all increased in bicuculline-treated rats.
What does this tell us?

- Working memory accuracy is unaffected; this does not agree with some other animal models. May be an effect of experimental design.

- Response latency was affected in delayed alternation (maze) and set-shifting, but not in initial pattern acquisition. GABA activity appears to be only involved in PFC-mediated cognitive tasks. Reduced processing speed is also a core feature of schizophrenia.
What does this tell us?

Set-shifting impairment

- Impairment was observed in shifting to new pattern, but not with simple response reversal. *This agrees with findings in schizophrenic patients.*

Drug infusions on the first day impaired later set shifting (more perseverative errors, implying that the old pattern was “fixed”)

Infusions on the second day increased never-reinforced errors (disorganization in shifting to new pattern).
What does this tell us?

• Bicuculline infusions had no effect on latent inhibition.

• It appears that GABA activity in the PFC does not contribute to this aspect of schizophrenia.
What does this tell us?

Bicuculline-treated rats (50 ng) were more strongly affected by a low systemic dose of amphetamine than controls.

Schizophrenics (as well as those suffering from “amphetamine psychosis”) show increased effects from low amphetamine doses. This is thought to be due to the mesolimbic dopamine system. The hyperactive dopaminergic neurons appear to be more sensitive to the action these drugs.
What does this tell us?
Mesolimbic dopaminergic activity (measured directly through the VTA):
An increased number of spike bursts, and an elevated firing rate were observed in putative dopaminergic neurons in drug-treated rats.
This may be an indication of aberrant activity, suggesting an explanation for the observed amphetamine susceptibility.
The effects of neurotransmitter imbalance are probably synergistic—midbrain dopamine neurons receive inputs from glutaminergic projections of the PFC, which is in turn regulated by the effects of GABA.