Schizophrenia & the Antipsychotics

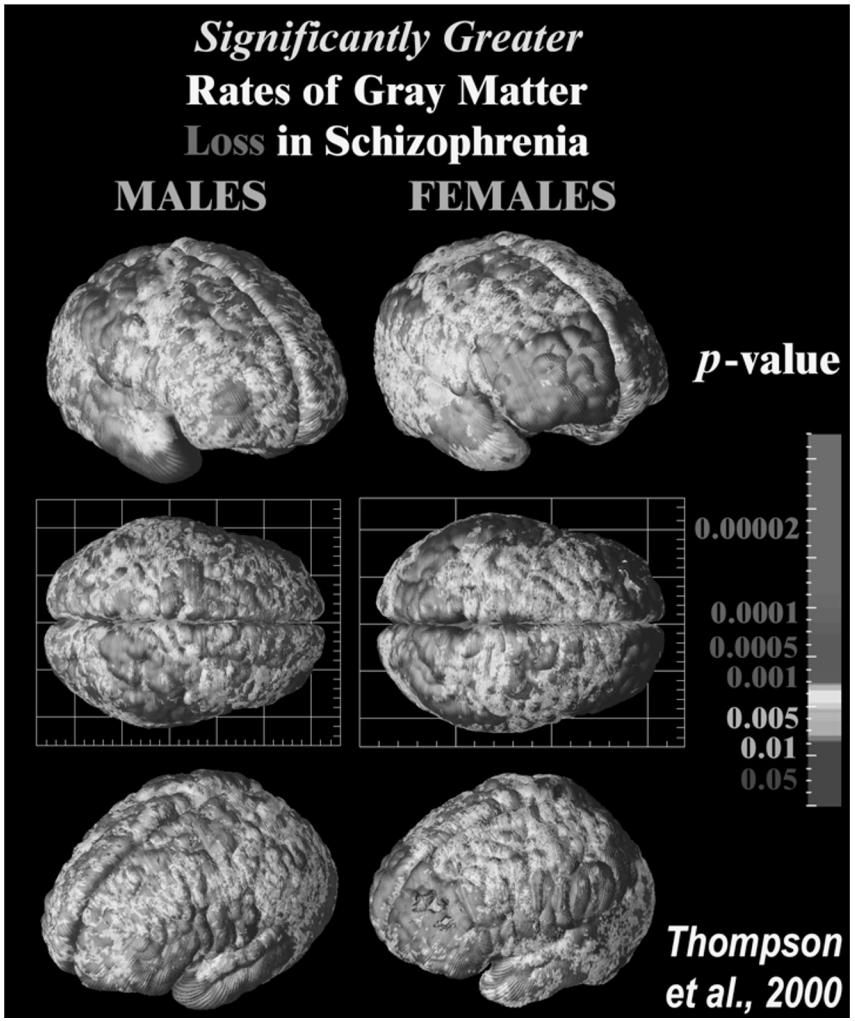
- "splitting" of mind (cognition/emotion) from reality
  - 1% of population globally
    - shamans or mentally ill

- Several subtypes: paranoid / catatonic / disorganized / undifferentiated / residual

- positive ("exaggerated) / negative ("absence") symptoms
  - perception (hallucinations)
  - delusions (false beliefs)
  - language (disorganized speech)
  - odd social behavior
  - motor (stereotyped and/or lack of movements)
  - avolition (lack of motivation / goal directed behaviors)
  - flattened affect / blunted emotional expression
  - anhedonia (lack of pleasure)
  - decreased memory, attention, executive function

Schizophrenia & the Antipsychotics

- Morphological / structural changes
  - disorganized neurons / larger ventricles
  - neurodevelopmental problems induce susceptibility
  - treatment is of the symptoms, not the underlying problem



This image is of 28-year-old identical twins, one with schizophrenia and the other well. It therefore clearly illustrates two points: (1) schizophrenia is a brain disease with measurable structural and functional abnormalities in the brain; and (2) it is not a purely genetic disease, and other biological factors play a role in its etiology.

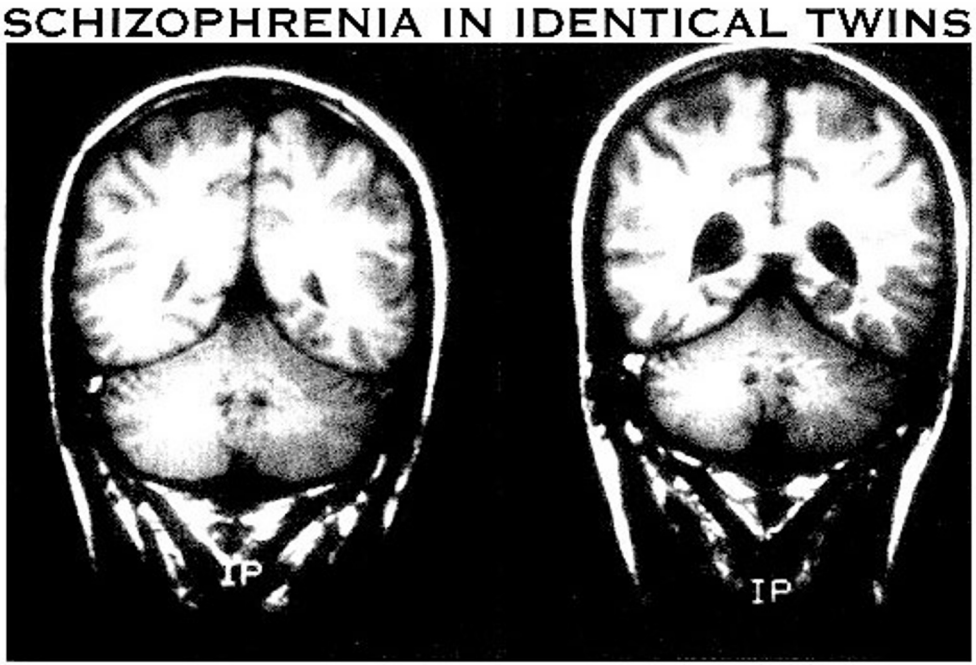
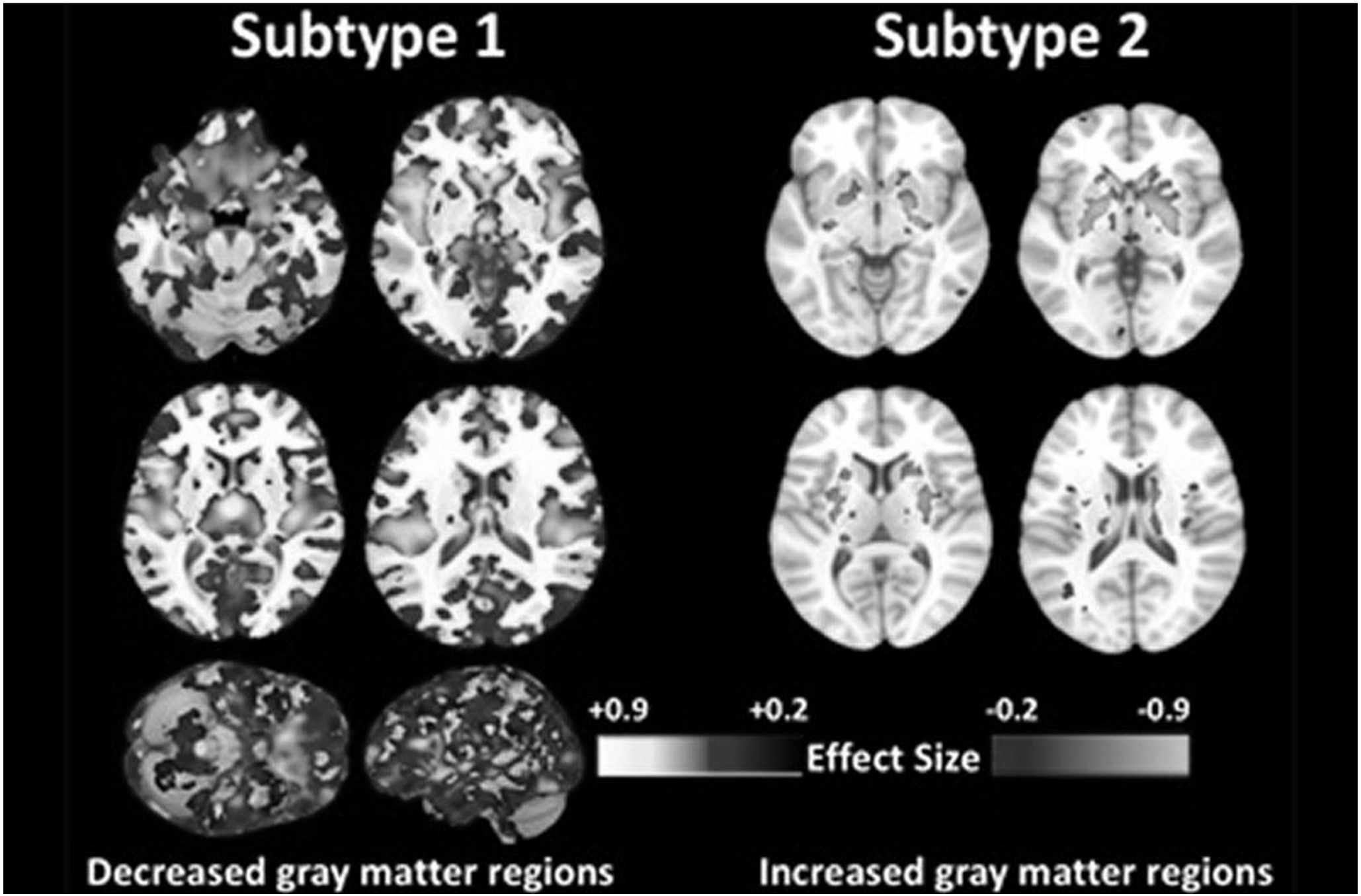


Photo courtesy of Drs. E. Fuller Torrey and Daniel Weinberger.

MRI scans of 28-year-old male identical twins showing the enlarged brain ventricles in the twin with schizophrenia (right) compared to his well brother (left).


Subtype 1
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+0.9
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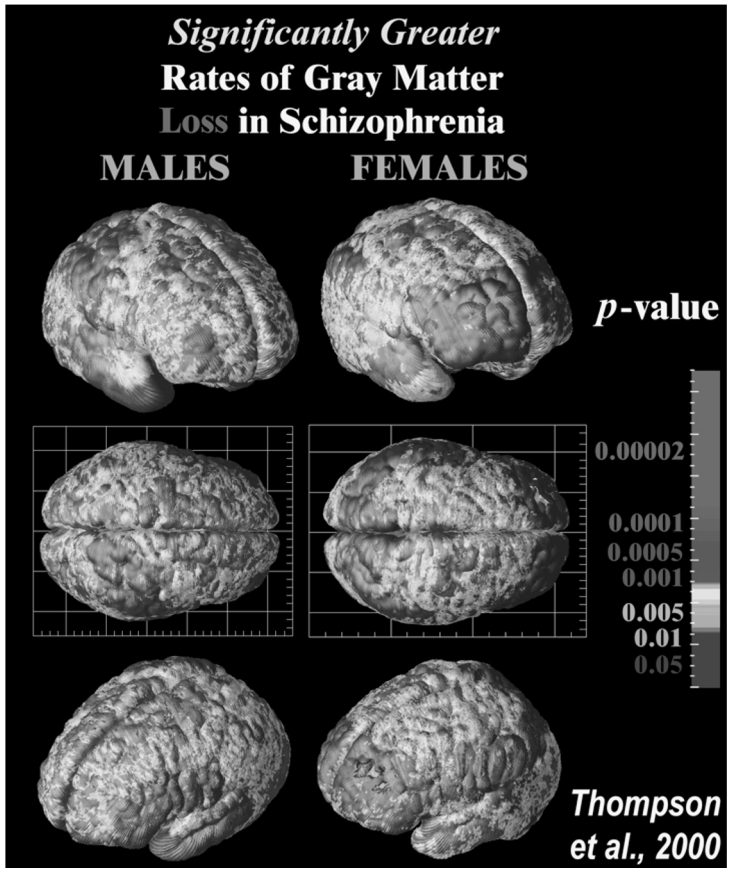
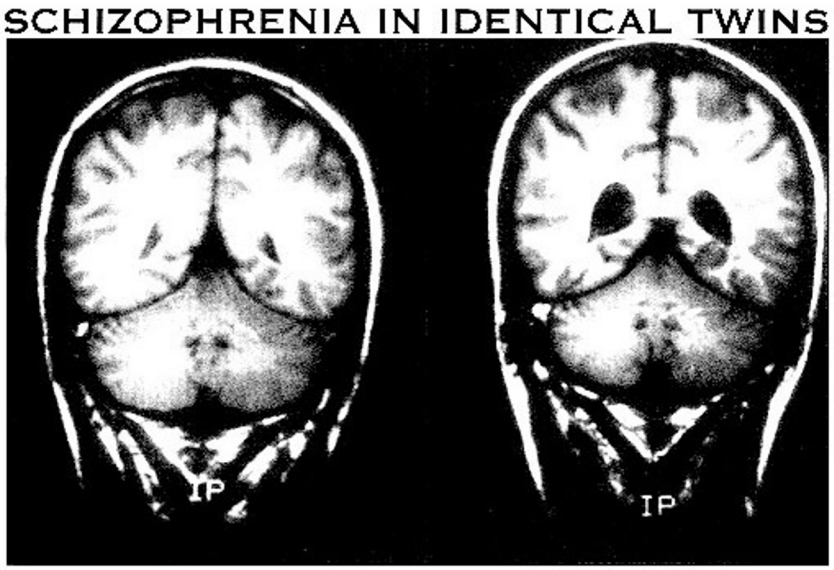
Effect Size
Decreased gray matter regions
Increased gray matter regions

Schizophrenia & the Antipsychotics

- Factors (nature and nurture)
  - genes that make one “susceptible”
  - dysfunctional reward system
  - environment - stress, infections (?)
    - *in utero* - toxoplasmosis, flu (birth month effect)





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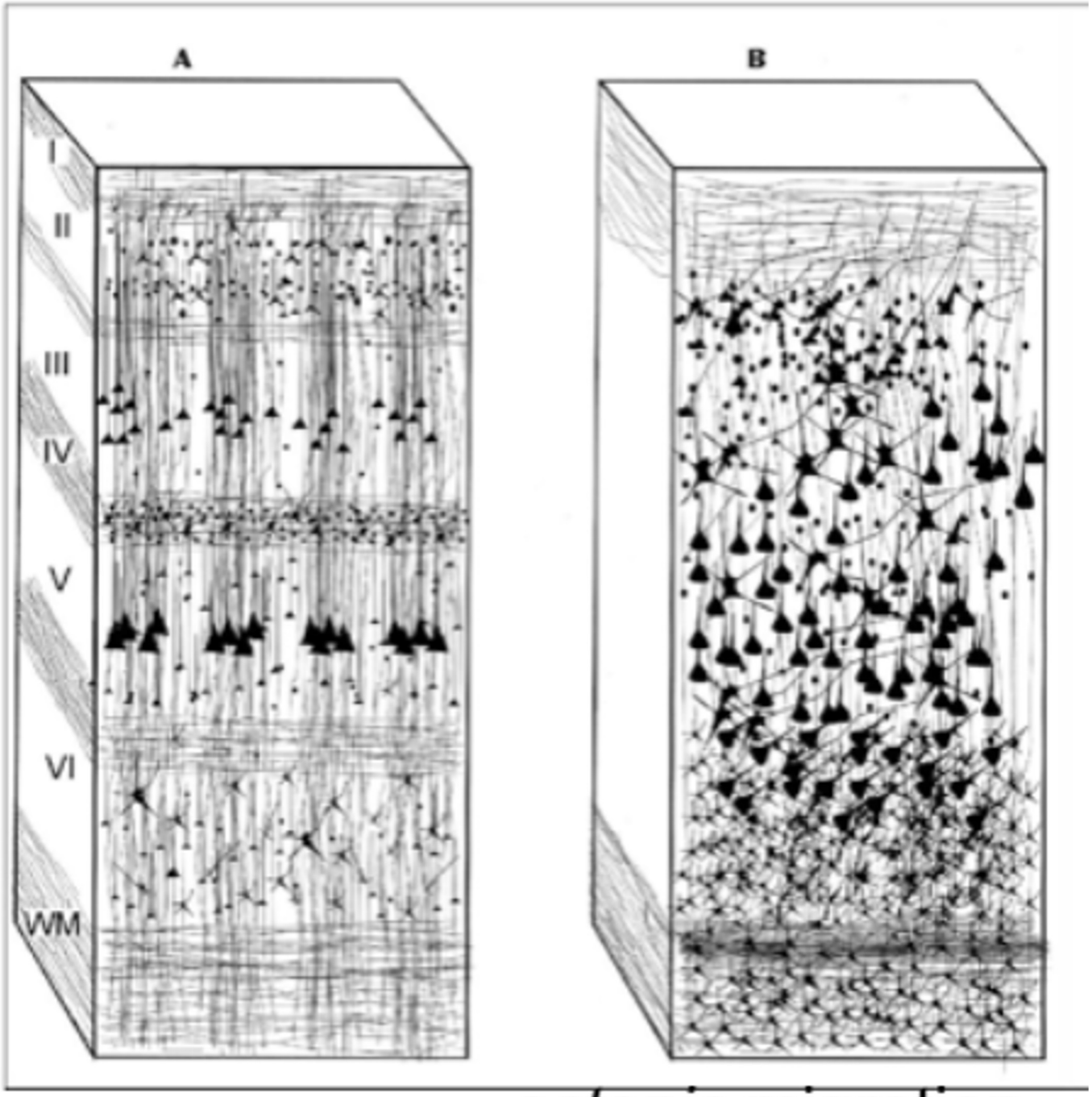


ectopic migration

Schizophrenia & the Antipsychotics

- "pre-morbid" signs sometimes seen in early childhood

- 1st overt signs generally appear after puberty / early 20's in men, mid 20's to early 30's in women
  - Age-related response to ketamine / PCP
  - Estrogen may be protective

- clinical deterioration tends to plateau after 5-10 years
  - early treatment (pharmacological + talk therapy) provides pretty good prognosis

Schizophrenia & the Antipsychotics

- 10 years after 1st diagnosis:
  - ~25% are almost totally improved
  - ~25% “much” improved
  - ~25% improved but still need support
  - ~15% unimproved or worse
  - ~10% dead (often due to suicide)

- Among those with schizophrenia:
  - ~30% live independently
  - ~25% live with family
  - ~20% live in supervised housing
  - ~10% are institutionalized
  - ~8% are incarcerated
  - ~7% are homeless

Schizophrenia & the Antipsychotics

- Neurotransmitter abnormalities – broad overview:
  - DA, 5-HT, glu

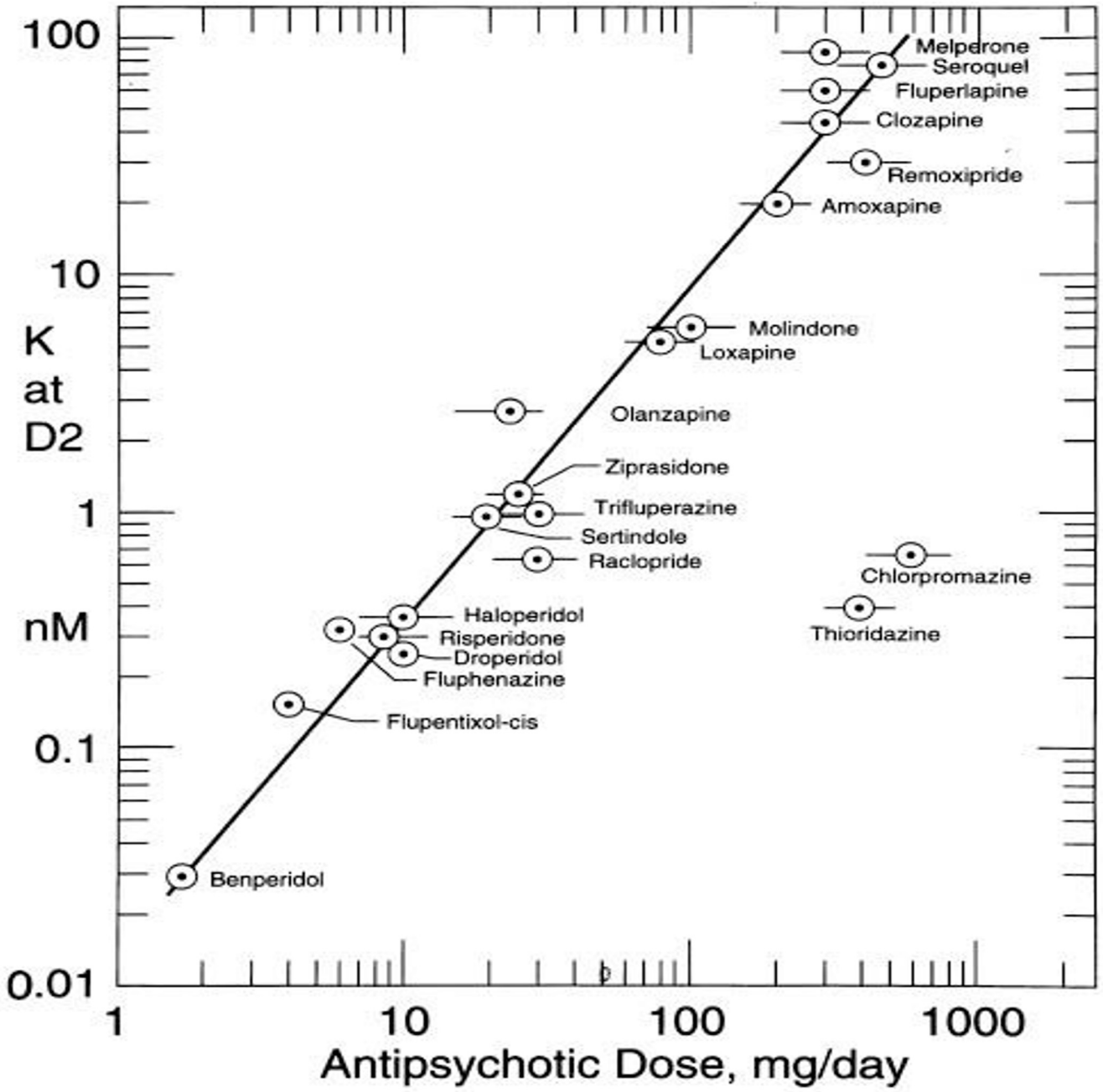
    - Originally – "pure DA" hypothesis
      - too much
      - indistinguishable from an amphetamine / cocaine OD

    - "Typical" antipsychotics are **DA antagonists**

    - 2 major receptor types
      - D_1 (subtypes: D_1, D_5)
      - D_2 (subtypes: D_2, D_3, D_4)

      - antipsychotics primarily **block D_2 receptors**
        - clinical efficacy highly correlated with degree of D_2 binding

Schizophrenia & the Antipsychotics



Schizophrenia & the Antipsychotics

- Glutamate receptors:
  - NMDA receptor *hypo*function
    - ketamine / PCP
    - NMDA receptor knockout ($NMDA^{-/-}$) mice:
      - behavioral symptoms similar to schizophrenia
        - no DA dysfunction
        - responded to antipsychotics ("dopaminergic")

- **so.....**
  - **increased DA = "positive" symptoms?**
    - **particularly in the "limbic" areas**
  - **decreased glu = "negative" symptoms?**

Schizophrenia & the Antipsychotics

- Also 5-HT:
  - 5-HT_2 activity induces cognitive / motor abnormalities
  - lots of neurons with 5-HT receptors release glu.....

  - Psychedelics are generally $5HT_2$ agonists
    - possible treatment with $5HT_2$ *antagonists*

Schizophrenia & the Antipsychotics

- **Antipsychotics** (aka the “major tranquilizers”)
  - not pleasant / euphoric like the “minor tranquilizers” (benzodiazepines)

- **Typical / classical / traditional / neuroleptic**
  - generally, control “positive” symptoms
  - have some bad motor “extrapyramidal” effects
    - *tardive dyskinesia* (Parkinson’s-like)
      - Parkinson’s medicine (”dopamine”) causes schizophrenia-like psychosis
    - inseparable from antipsychotic effects

Schizophrenia & the Antipsychotics

- **<u>Typical antipsychotics</u> - the Phenothiazines:**
  - chlorpromazine (“Thorazine”) – calming, detached effect
    - antidote for psychedelics (serotonergic ones like LSD)
- Thorazine developed in early 1950’s
  - in rats, induced indifference to aversive stimuli
    - quickly moved to use in humans
    - “woke” some individuals w/ schizophrenia (“lifted a blanket”)
      - at higher doses (“institutionalization”) can become a “chemical straight jacket”
- Medical model - started at Wash U (use of scientific method to study mental disorders)
  - 1st drug used to treat a mental disorder - started “Golden Age of Psychotropic Drugs”
    - thorazine, lithium, imipramine, & prozac
      - almost everything else is based on these

Schizophrenia & the Antipsychotics

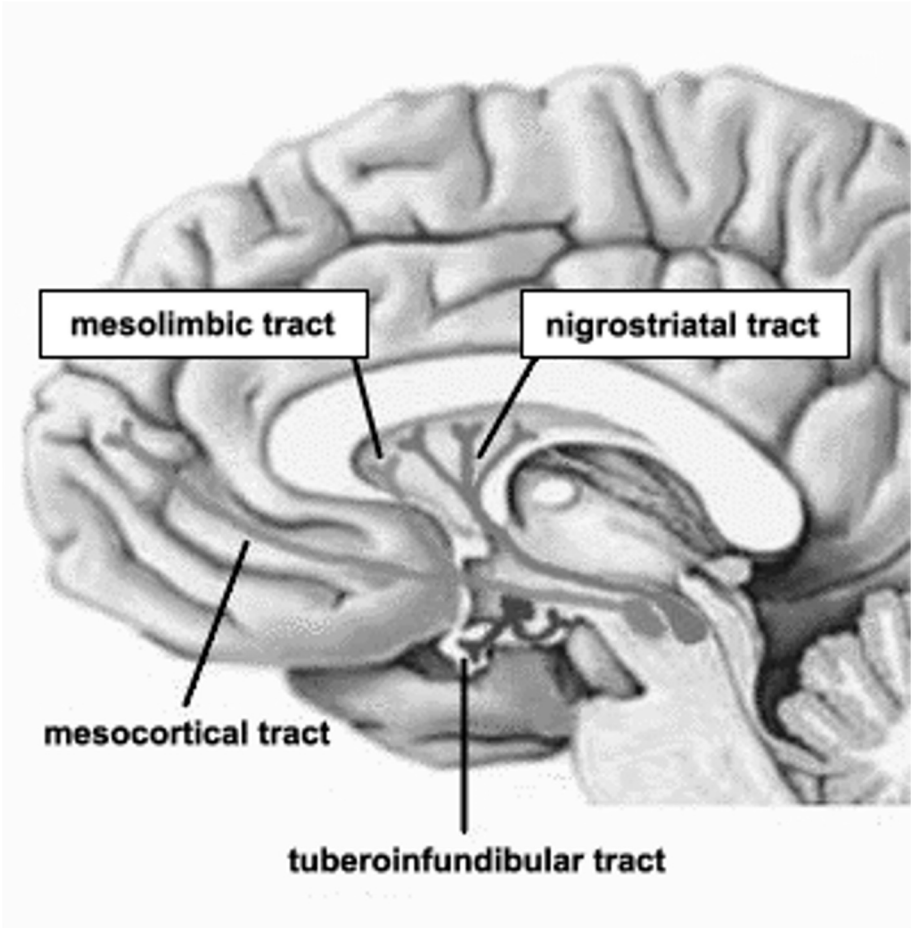
- **Pharmacokinetics:**
  - erratically absorbed orally, better by intramuscular injection
  - only a small % gets to brain
  - long half-lives (1-2 days)

- **Pharmacodynamics:**
  - **block D_2 receptors** - antipsychotic effects
    - about 60-80% of D_2 receptors must be blocked for clinical effects
    - higher blockage % leads to “extrapyramidal” motor effects

  - Also block:
    - ACh -> dry mouth, blurred vision, etc (scopolamine)
    - Histamine -> sedation
    - NE -> hypotension, sedation

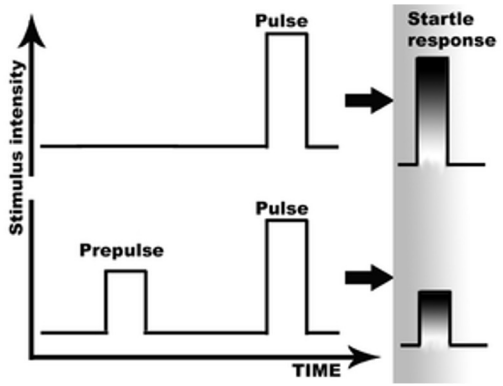
Schizophrenia & the Antipsychotics

- IF increased sensitivity to DA is responsible for the "positive" symptoms...
  - block receptors > reduce symptoms
- Blocking D_2 receptors in <u>limbic system</u> **(target):**
  - get DA from the axons of neurons originating in the midbrain brainstem
    - involved with emotional expression



Schizophrenia & the Antipsychotics

- blocking D_2 receptors in the <u>brainstem reticular formation</u>:
  - reduces sensory inflow
    - induces indifference to external stimuli



- BUT….
- blocking D_2 receptors in the <u>basal ganglia</u>:
  - causes motor deficits:
    - extrapyramidal (early Parkinson's-like) tardive dyskinesia
      - side effects may be "prophylactically" treated with anti-Parkinson's drugs

- blocking D_2 receptors in the <u>hypothalamus</u>:
  - causes deficits in eating, sleeping, sexual function

Schizophrenia & the Antipsychotics

- other effects – permanently impaired vision, cognitive deficits
- no tolerance or dependence issues

- Another class of **typical** antipsychotics:
  Butyrophenones
  - haloperidol (Haldol)
  - droperidol (Inapsine)
    - **work similarly**, and generally, no better than chlorpromazine

- **Typical antipsychotics** characterized by:
  - inseparable motor problems
  - working primarily on “positive” symptoms

Schizophrenia & the Antipsychotics

- **Newer ("atypical") drugs** – also block multiple receptors, but primarily 5-HT
  - control both positive and negative symptoms
  - have *fewer* side effects:
    - weight gain, increased risk of diabetes, cardiac arrhythmia
      - "metabolic syndrome"

Schizophrenia & the Antipsychotics

- **Atypicals** generally defined as a drug that block more than 80% of 5-HT_2 receptors and less than 80% of D_2 receptors
- may improve, rather than impair, cognition
  - by inducing release of ACh in cortex (positive memory effects)

Schizophrenia & the Antipsychotics

- **Clozapine** – 1st atypical (90s)
  - **weak D_2 antagonist**
  - **strong 5-HT_2 antagonist**
  - also blocks D_4, 5-HT_{1C}, adrenergic apha-1, plus others
  - Effective for both + / - symptoms
    - very few extrapyramidal effects
    - fewer cognitive deficits than typicals
      - sedation, extreme weight gain, white blood cell toxicity
      - withdrawal syndrome - psychotic episodes

Schizophrenia & the Antipsychotics

- **3rd generation antipsychotics**
- **Aripiprazole ("Abilify") 2003**
  - partial **AGONIST** of D_2 receptors
  - **5-HT_2 antagonist**
    - "antipsychotic"
  - **5-HT_{1A} agonist**
    - "antidepressant"
  - stabilizes neuronal activity
    - increases activity at low dose, blocks activity at higher doses
    - "compressor" - reduces dynamic range of neural activity
  - Few major side effects
  - also used for bipolar disorder
- **CBD**

Bipolar Disorder & Mood Stabilizers

- “manic depression” - recurring episodes of depression / mania
  - usually more depression
  - ~1-5% of population (2 episodes = long-term treatment)
    - high incidence of substance abuse
    - 10x more likely to commit suicide

Bipolar Disorder & Mood Stabilizers

- other causes must be ruled out:
  - thyroid hyperactivity
  - antidepressants, anti-Parkinson's
  - corticosteroids, anabolic steroids
  - caffeine, (pseudo)ephedrine, other stimulants

- progressive neurodegenerative disease:
  - loss of neurons in the hippocampus and prefrontal cortex
  - altered function / plasticity

- medication used when it becomes disruptive to life
- Certain antidepressants can induce mania

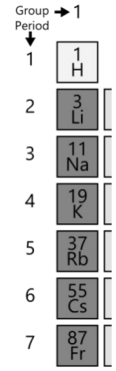
Bipolar Disorder & Mood Stabilizers

- **Mood stabilizers -** "compress" emotional dynamic range
  - major focus of treatment is reduction of mania
    - reduce / prevent "flipping" from depression to mania

- lithium (Li^+) – the classic
- current 1st treatment - atypical antipsychotics
  - lithium + antipsychotic
  - lithium + antipsychotic + anticonvulsant (GABAergic)
- omega-3s

  - like the antidepressants, most newer drugs generally don't work any *better*, but have fewer side effects

Bipolar Disorder & Mood Stabilizers



- **Lithium** (Li^+) – the classic
- chemically very similar to sodium
  - fluctuations in dietary sodium can mess with dosage
  - sodium used to treat lithium OD
- very effective (~60-70%) at controlling mania / prevents relapse
- at normal dosages, no effect in normal individuals
- bad side effects with narrow dosage range:
  - GI distress, tremor, lethargy, dizziness, slurred speech, ataxia, muscle weakness, muscle / eye twitches, massive weight gain, thyroid enlargement / goiter, cardiac arrhythmia, impaired concentration, memory, psychosis, stupor, death
  - teratogenic (harmful to developing fetus heart – especially 1st trimester)
  - relapse often result of non-compliance (almost 50%)

- also, patients can miss the “high” of manic phase
- when halted, increased risk of suicide
- relatively high % of patients resistant

Bipolar Disorder & Mood Stabilizers

- **Pharmacokinetics:**
  - rapidly absorbed orally, but crosses BBB slowly and erratically
  - long ½ life (~1 day)
    - stored in cells: ~2 weeks for “steady state” blood levels
  - excreted unchanged by the kidneys

- **Pharmacodynamics:**
  - not well-understood (2nd messengers / intracellular enzymes)
  - upregulates expression of neurotrophic / neuroprotective proteins (CREB, bdnf, bcl-2)
    - suggests early pharmacological treatment may reduce neuropathology
  - very narrow dosage range limits use (requires blood level checks)
    - nausea, tremors / neurological deficits, kidney problems, cardiotoxicity
  - More often used in combination with other drugs