Schizophrenia

DSM 5 Criteria A

- Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
  - Delusions.
  - Hallucinations.
  - Disorganized speech (e.g., frequent derailment or incoherence).
  - Grossly disorganized or catatonic behavior.
  - Negative symptoms (i.e., diminished emotional expression or avolition).

DSM 5 Criteria B

- For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

DSM 5 Criteria C

- Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

DSM 5 Criteria D

- Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

DSM 5 Criteria E

- The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

DSM 5 Criteria F

- If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

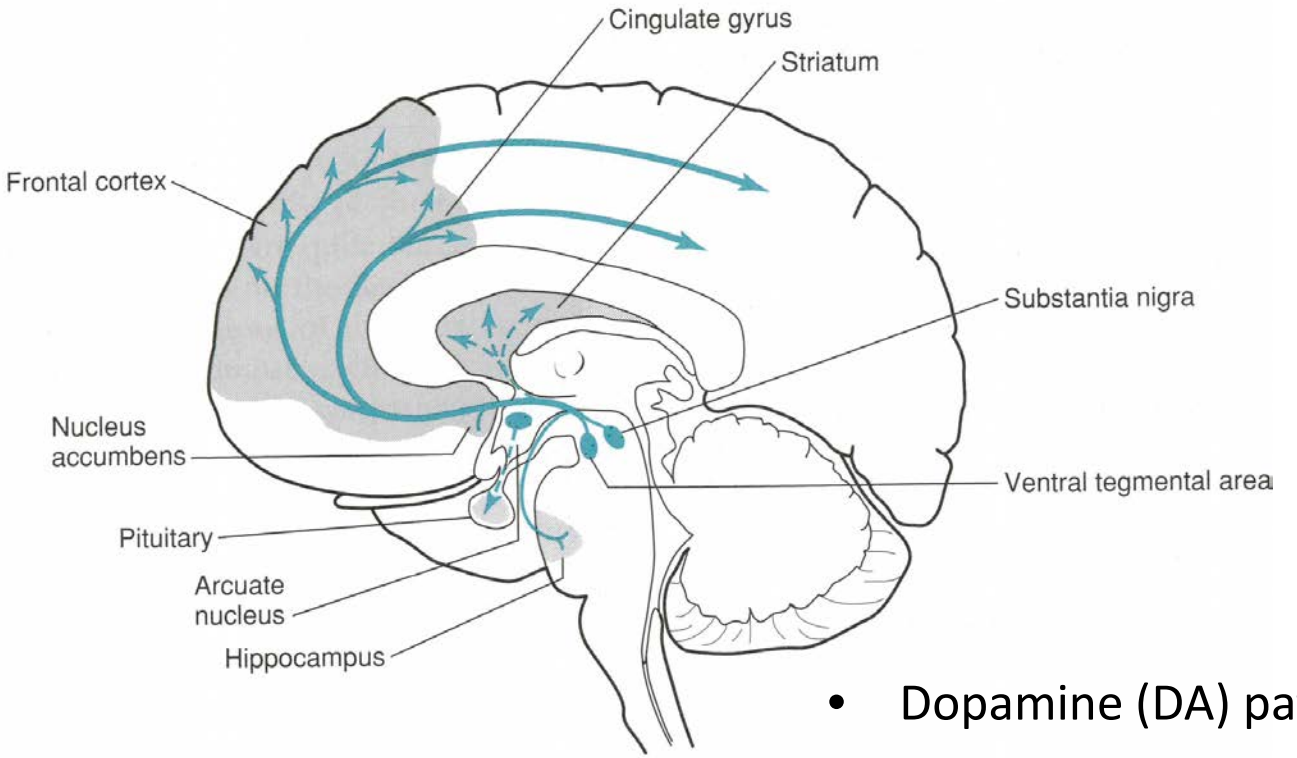
Specifiers

- The following course specifiers are only to be used after a 1-year duration of the disorder and if they are not in contradiction to the diagnostic course criteria.
- **First episode, currently in acute episode:** First manifestation of the disorder meeting the defining diagnostic symptom and time criteria. An *acute episode* is a time period in which the symptom criteria are fulfilled.
- **First episode, currently in partial remission:** *Partial remission* is a period of time during which an improvement after a previous episode is maintained and in which the defining criteria of the disorder are only partially fulfilled.
- **First episode, currently in full remission:** *Full remission* is a period of time after a previous episode during which no disorder-specific symptoms are present.
- **Multiple episodes, currently in acute episode:** Multiple episodes may be determined after a minimum of two episodes (i.e., after a first episode, a remission and a minimum of one relapse).
- **Multiple episodes, currently in partial remission**
- **Multiple episodes, currently in full remission**
- **Continuous:** Symptoms fulfilling the diagnostic symptom criteria of the disorder are remaining for the majority of the illness course, with subthreshold symptom periods being very brief relative to the overall course.
- **Unspecified**
- *Specify* if:**With catatonia** (refer to the criteria for catatonia associated with another mental disorder for definition).
  - **Coding note:** Use additional code 293.89 (F06.1) catatonia associated with schizophrenia to indicate the presence of the comorbid catatonia.
- *Specify* current severity:Severity is rated by a quantitative assessment of the primary symptoms of psychosis, including delusions, hallucinations, disorganized speech, abnormal psychomotor behavior, and negative symptoms. Each of these symptoms may be rated for its current severity (most severe in the last 7 days) on a 5-point scale ranging from 0 (not present) to 4 (present and severe). (See Clinician-Rated Dimensions of Psychosis Symptom Severity in the chapter “Assessment Measures.”)
- **Note:** Diagnosis of schizophrenia can be made without using this severity specifier.

Outline

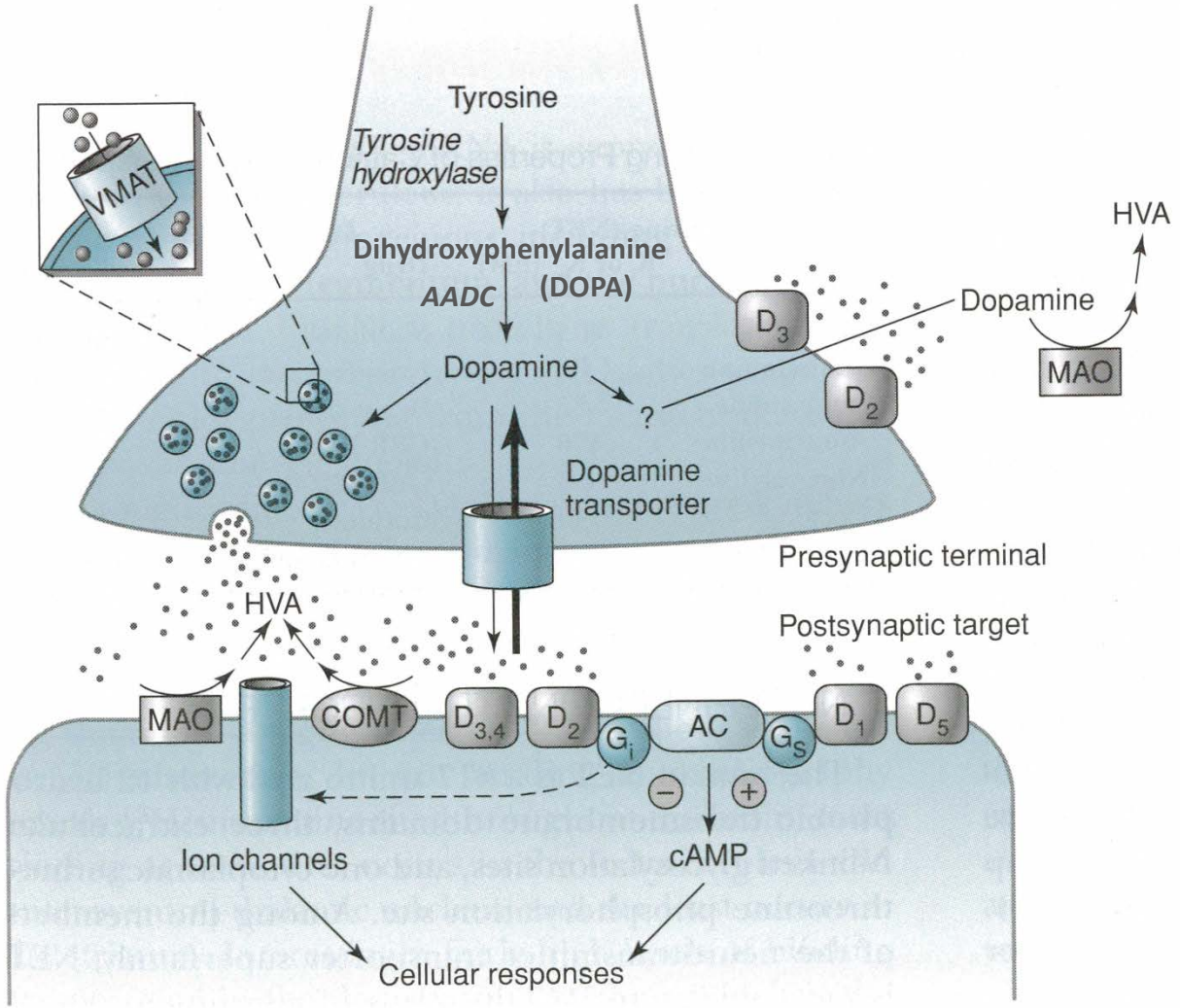
- Mechanisms of psychosis and pharmacological treatments
  - Dopamine (DA) hypothesis
  - Mechanism of action and neurological side effects of antipsychotics
    - Typical vs. atypicals (binding profiles, motor and cognitive side effects)

Dopamine Hypothesis of Schizophrenia



- Dopamine (DA) pathways
  - Nigrostriatal (substantia nigra – striatum)
  - Mesocortical (ventral tegmental area to cortex- esp. frontal cortex)
  - Schizophrenia hypothesized to involve excess sub-cortical DA function

In Vivo Evidence of DA Dysregulation in Psychosis



Presynaptic

↑ DOPA
(effect size=.79)

↑ DA release

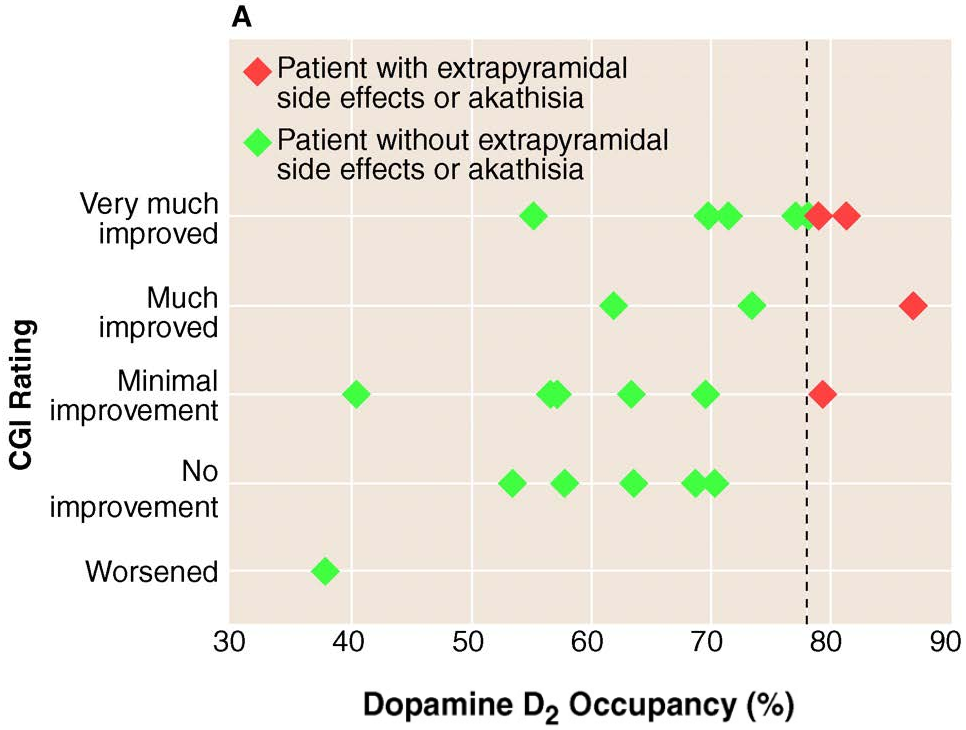
↔ DA Transporter

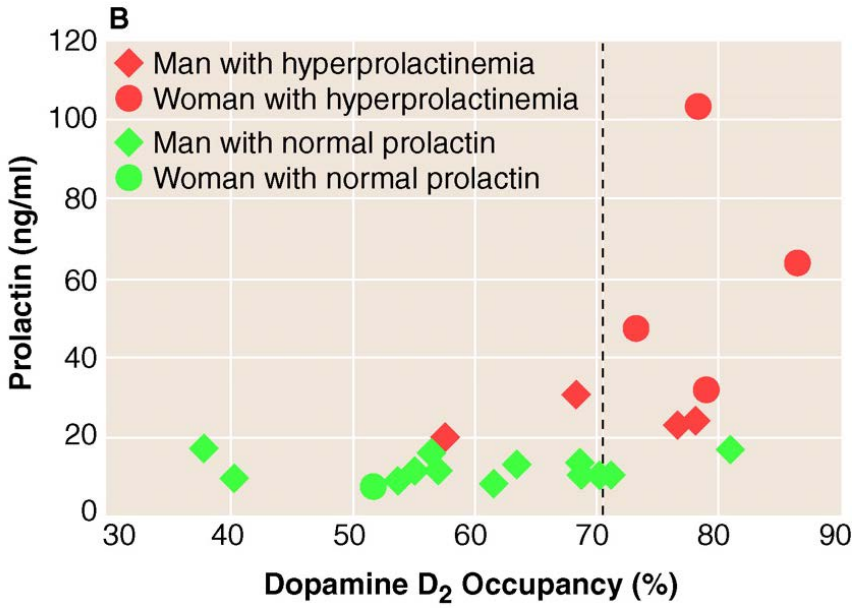
Postsynaptic

↑ D2/D3 Receptors
(effect size=.26)

Howes et al., 2012

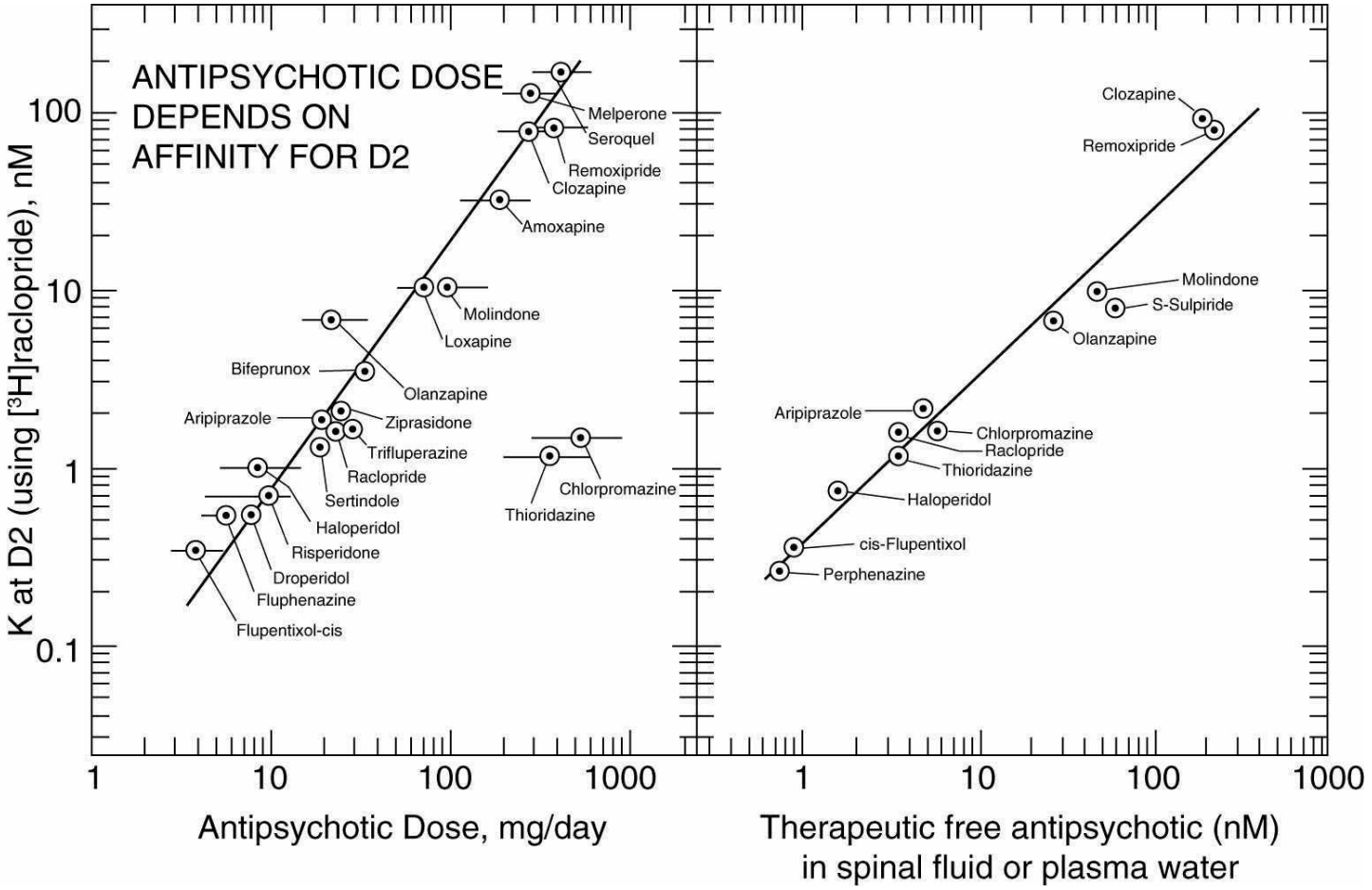
Therapeutic Window of Antipsychotics





Kapur et al., 2000

Effectiveness of Antipsychotic Drugs Related to Their Affinity for Dopamine D2 Receptors



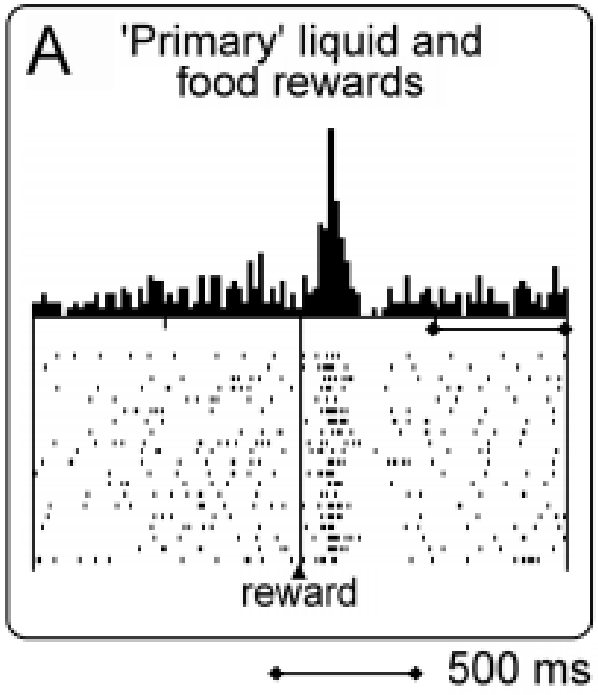
Linking Biology to Phenomenology

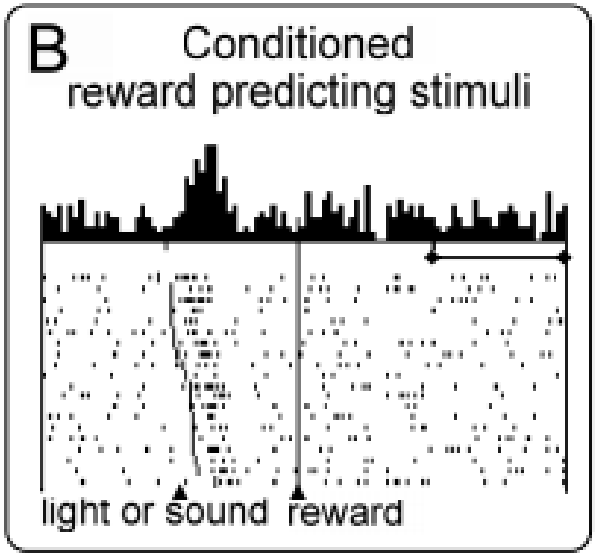
Linking Biology to Phenomenology

Hypothesis:
Abnormal dopamine regulation in schizophrenia disrupts how individuals attribute salience to their environment

Kapur et al, Schizophrenia Research 79 (2005)

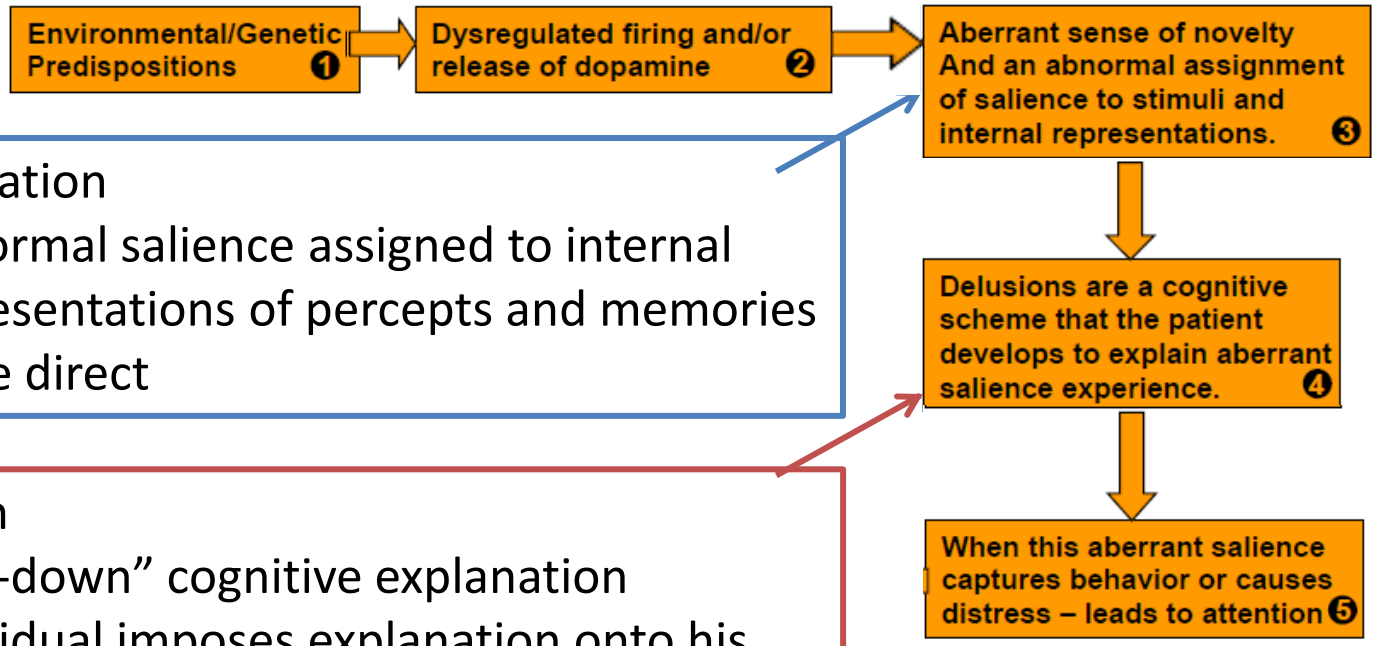
Dopamine as Salience Mediator





Schultz, Behavioral and Brain Functions 6:24 (2010)

From Dopamine Dysregulation to Psychosis



Hallucination
- Abnormal salience assigned to internal representations of percepts and memories
- More direct

Delusion
- "Top-down" cognitive explanation
- Individual imposes explanation onto his experiences of aberrant salience
- Effort to make sense of his experience

Kapur et al, Schizophrenia Research 79 (2005)

Antipsychotics Dampen Salience

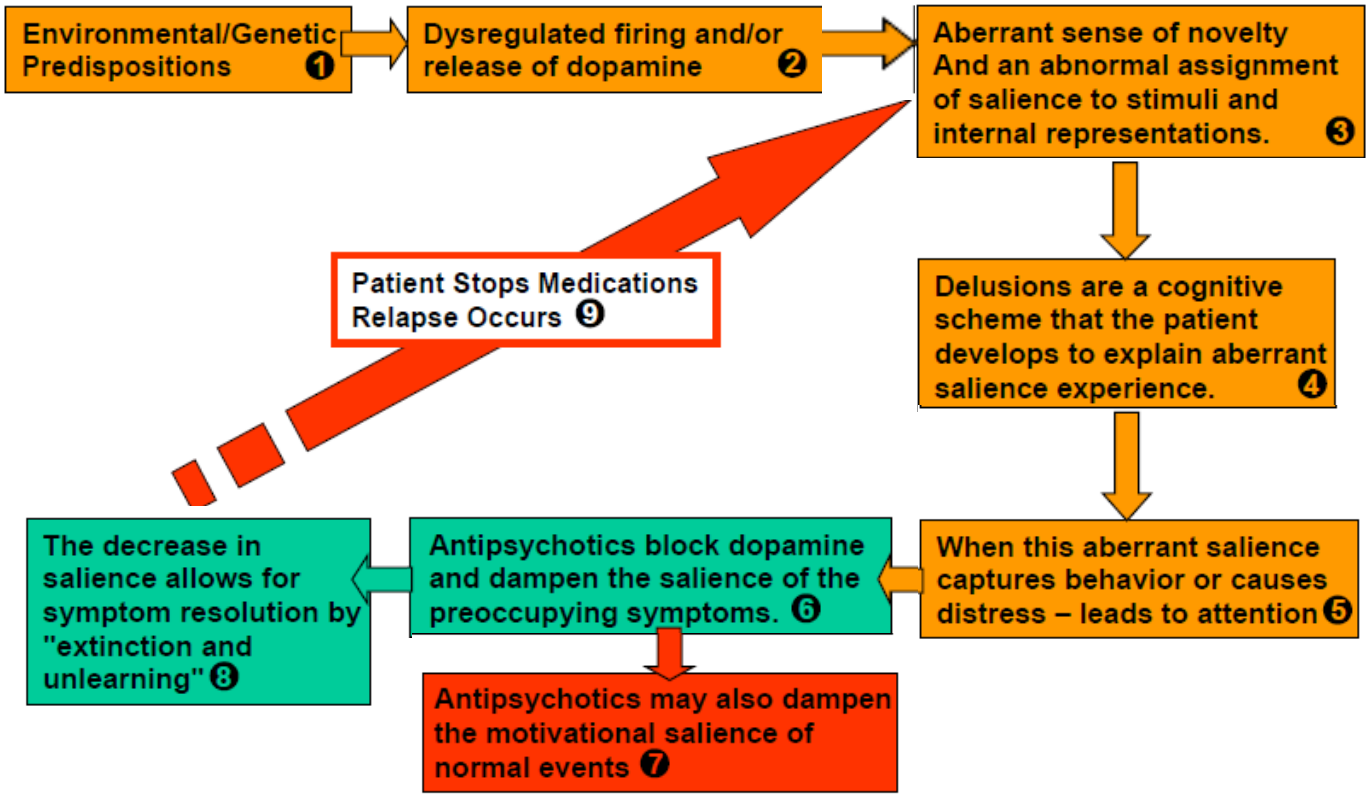
Courvoisier experiments, 1956:

- Rats conditioned to associate a ringing bell with a shock
- At baseline, rats avoided sound of bell
- When given antipsychotic,

    Rats stopped avoiding the bell

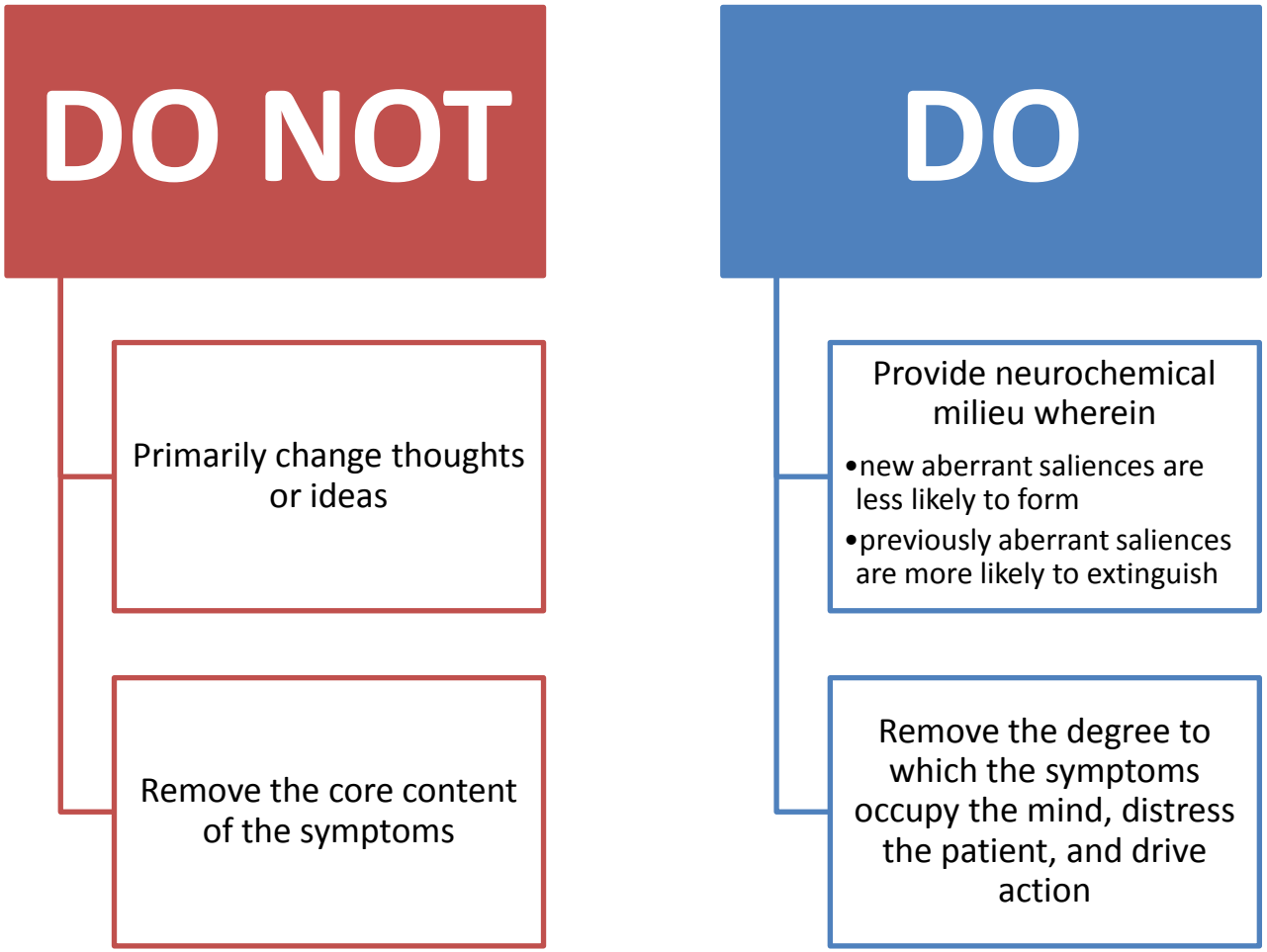
    Even though they were motoricaly capable of doing so and they still responded to the shock!

How Antipsychotics Become Anti“psychotic”



Kapur et al, Schizophrenia Research 79 (2005)

Antipsychotics' Effect on Symptoms



Delusions

- Conviction
- Extension
- Bizarreness
- Disorganization
- Pressure

Delusions

- Erotomanic
- Persecutory
- Grandiose
- Capgras
- Cotard

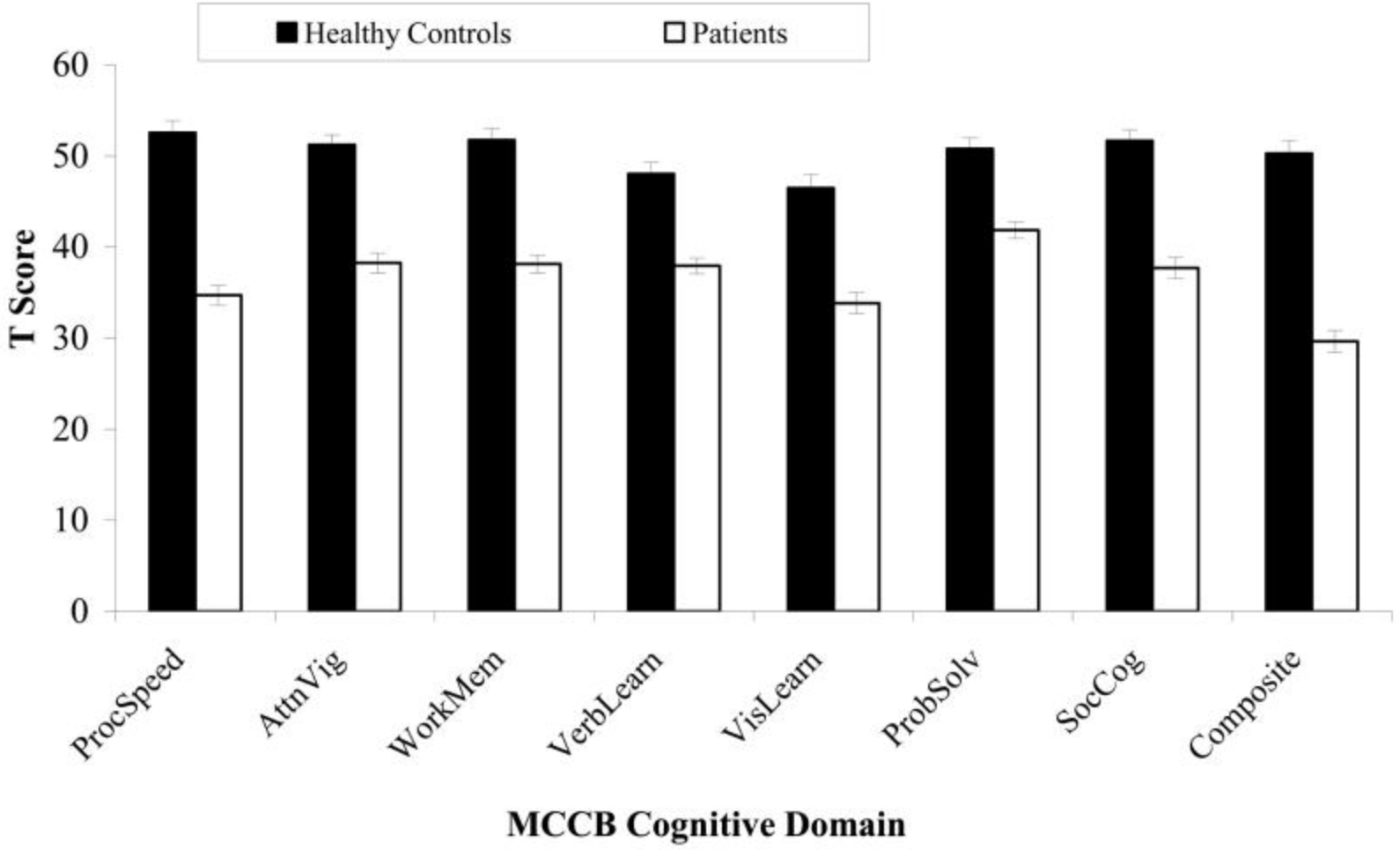
First Break Work-Up

- CBC
- CMP
- TSH
- UDS
- MRI/CT
- EEG
- UA
- RPR, HIV
- CXR
- ESR
- Magnesium
- Para-neoplastic
- Phosphate
- Albumin

Brain Dysfunction in Schizophrenia

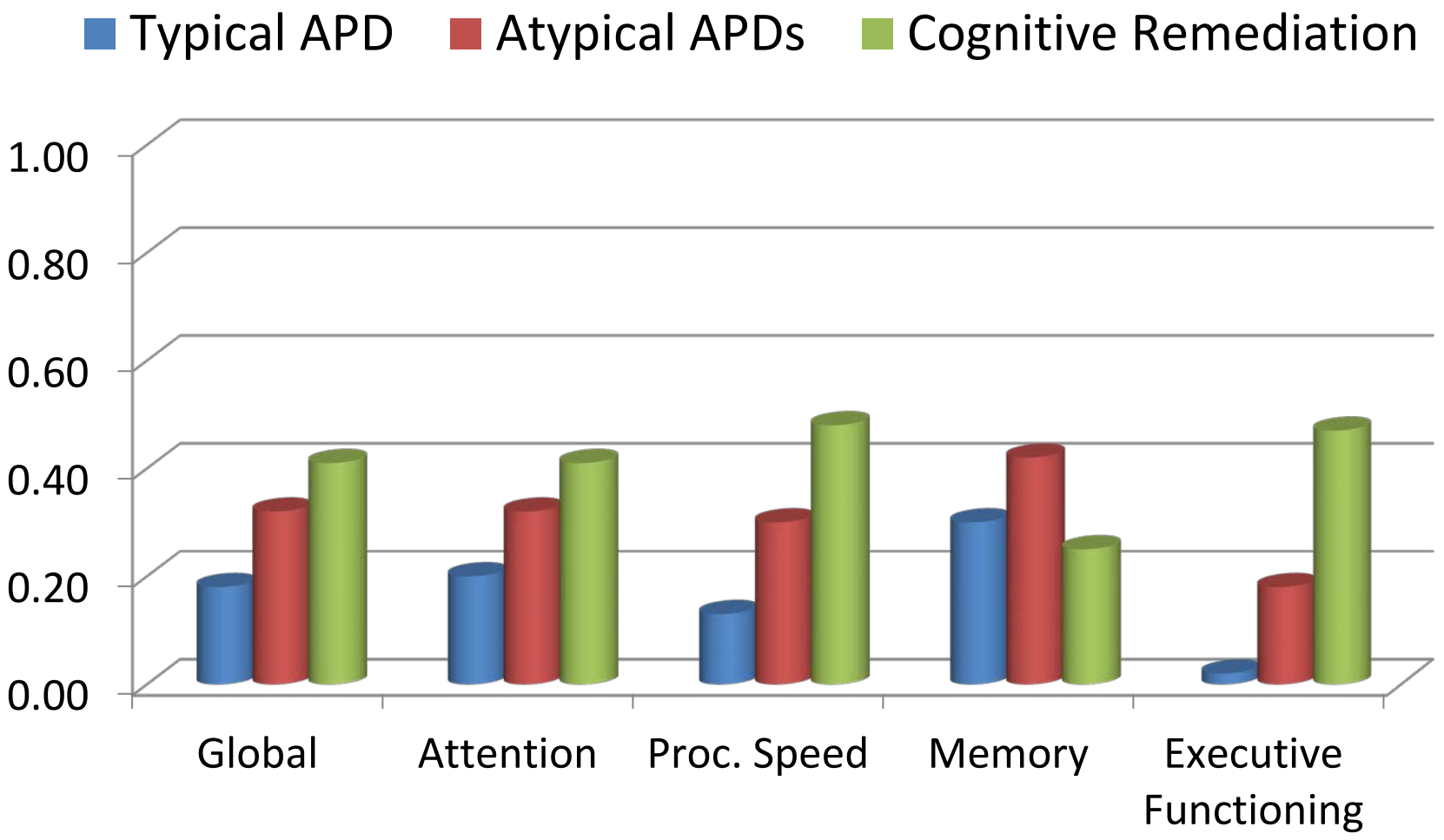
- Neuropsychological Impairment
- Neuroimaging
  - Abnormal brain structure
  - Brain function abnormalities
- Static or Progressive Brain Disorder?

Neuropsychological Impairment in Schizophrenia



August et al., 2012

Treating Cognitive Impairment

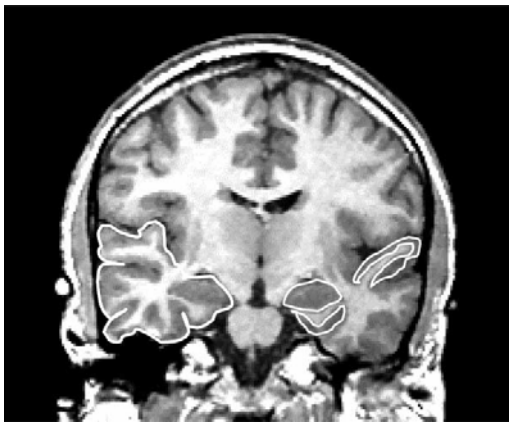


Summary of McGurk et al., 2007: Woodward et al., 2005; Woodward et al., 2007

Neuropsychological Impairment in Schizophrenia

- Moderate, widespread impairment
- Related to functional outcome (e.g. employment)
- Only mildly affected by APDs
  - Typicals: cognitive slowing
  - Atypicals: benign, possible *very* mild improvement
- Modest beneficial effect of cognitive remediation
  - More research to confirm effect
  - Outstanding issues: barriers to implementation

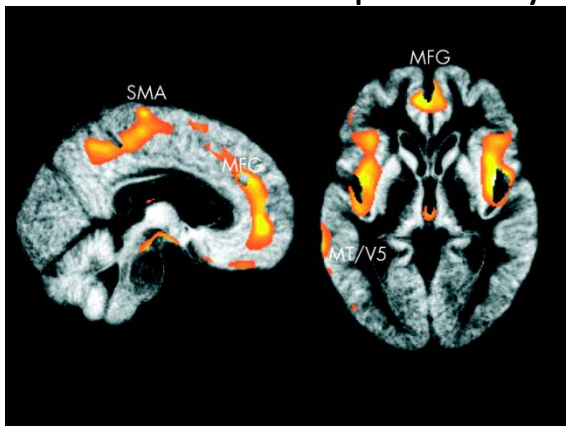
Structural Brain Changes in Schizophrenia



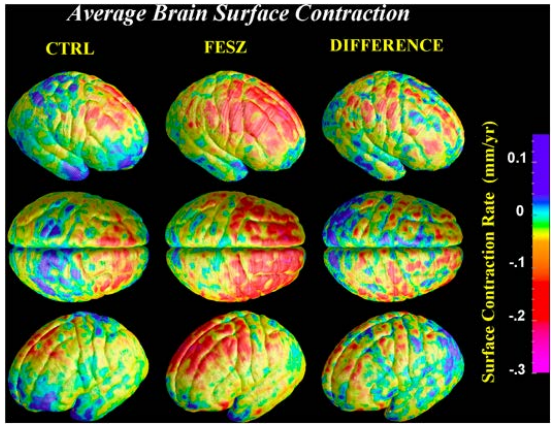
- Volumetric MRI Methods
  - Region-of-interest: specific regions of brain are traced, volume calculated, compare between groups

- Morphometric MRI Methods
  - Computational, whole-brain

Voxel-based Morphometry



Surface-based Methods

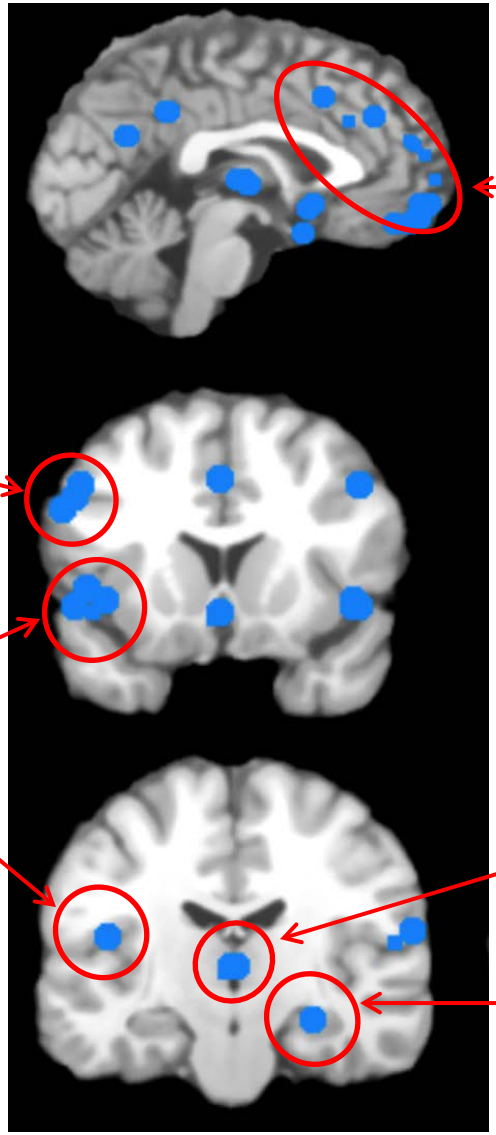


Review of MRI Structural Findings: ROI Approach

- Ventricular enlargement (80% of studies reviewed)
- Medial temporal lobe structures (74% of studies reviewed), which include the amygdala, hippocampus, and parahippocampal gyrus,
- Neocortical temporal lobe regions (superior temporal gyrus) (100% of studies reviewed)
- Frontal lobe abnormalities (59% of studies reviewed)
- Parietal lobe abnormalities (60% of studies reviewed)
- Subcortical abnormalities (i.e. cavum septi pellucidi—92% of studies reviewed, basal ganglia—68% of studies reviewed, corpus callosum—63% of studies reviewed, and thalamus—42% of studies reviewed)
- Cerebellar abnormalities (31% of studies reviewed).

Shenton et al., 2001

Grey Matter Volume Loss in Schizophrenia: Voxel-Based Approaches



Cingulate/Medial PFC

Frontal Cortex

Insula & Superior Temporal Gyrus

Thalamus

Hippocampus

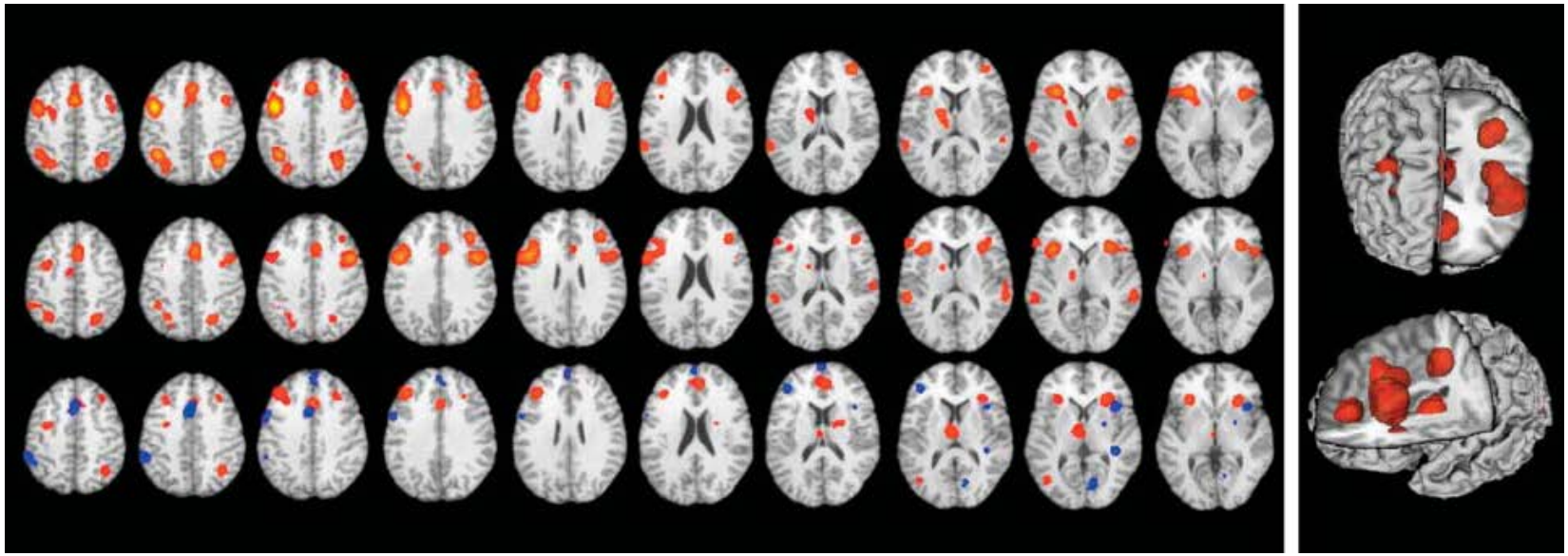
Shepherd et al, 2012

Functional Brain Changes in Schizophrenia: Executive Cognitive Functions

Controls

Scz

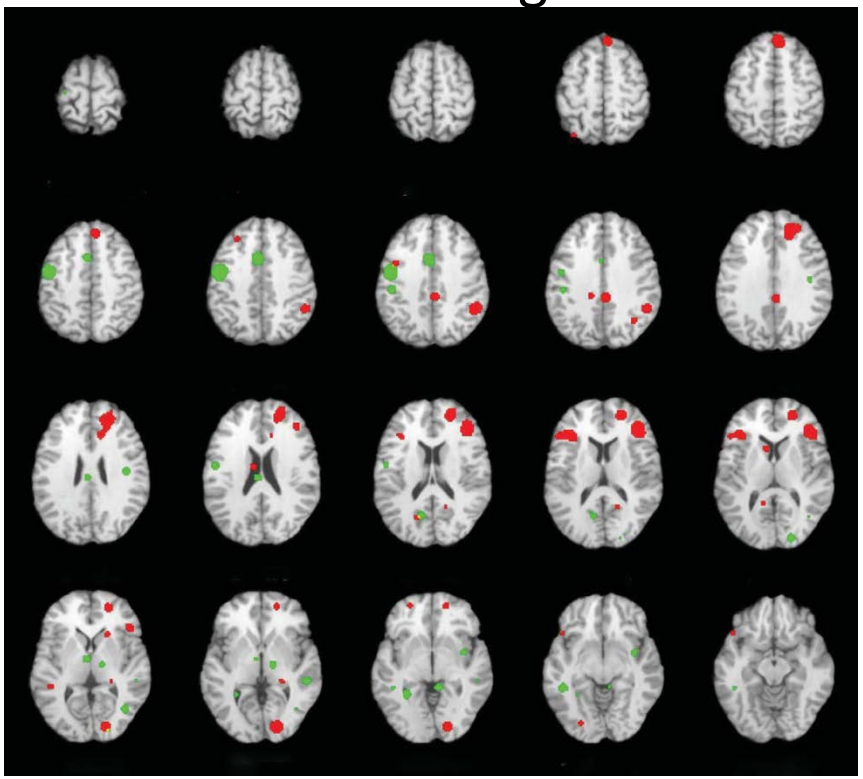
Difference



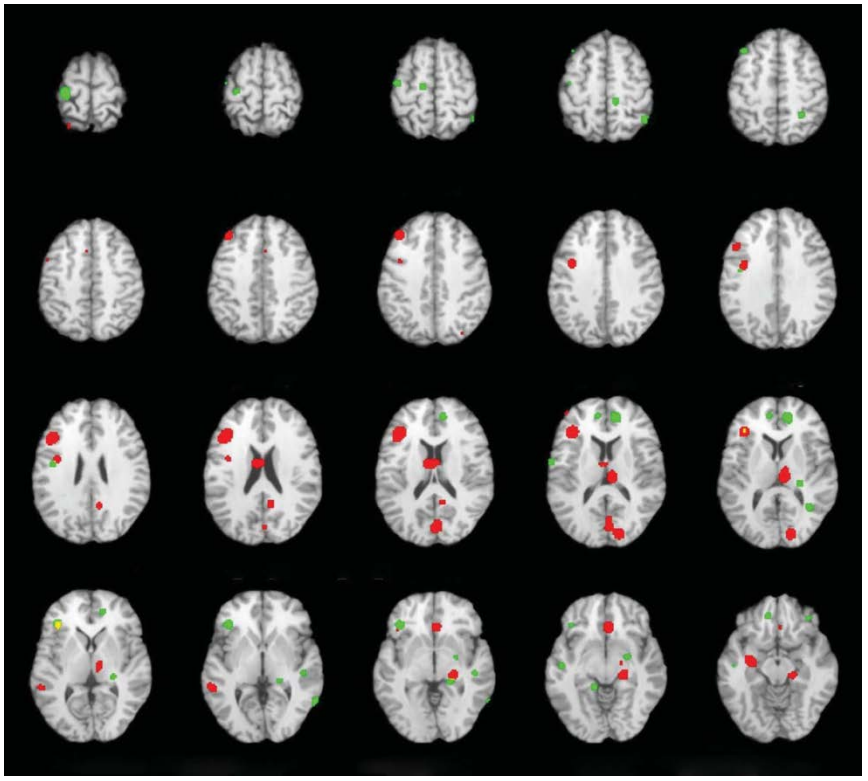
Minzenberg et al., 2011

Functional Brain Changes in Schizophrenia: Memory

Encoding



Retrieval



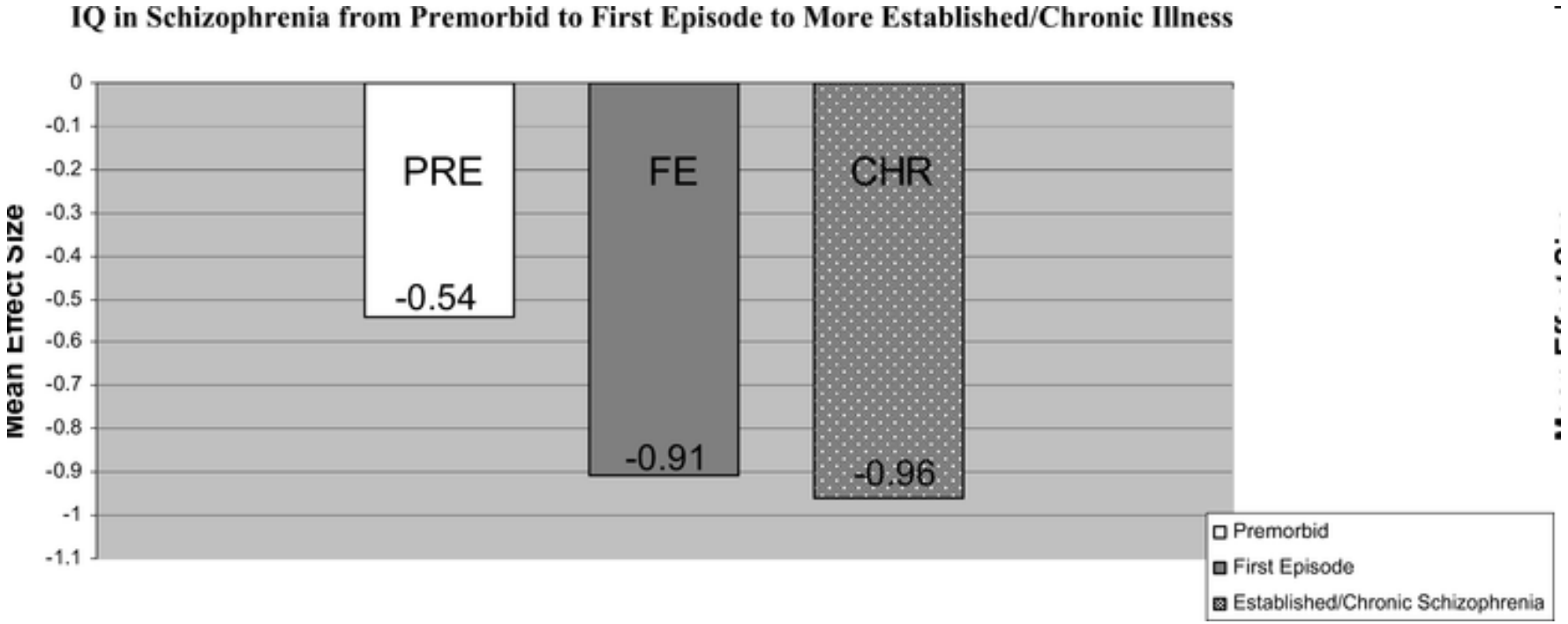
Red= Controls>Patients

Green= Patients>Controls

Ragland et al., 2009

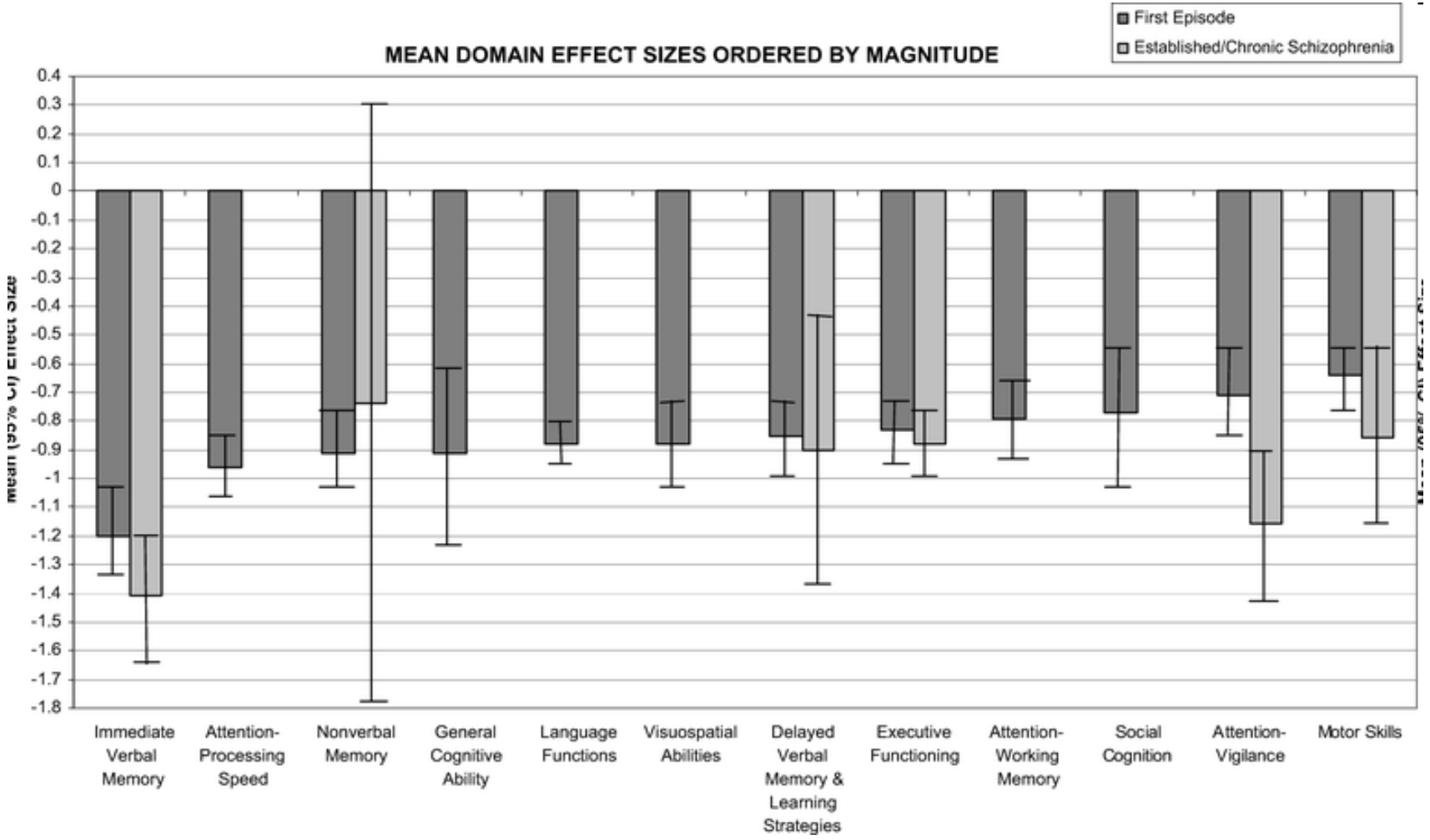
Is Schizophrenia a Progressive Illness?

Evolution of Neuropsychological Impairment in Psychosis



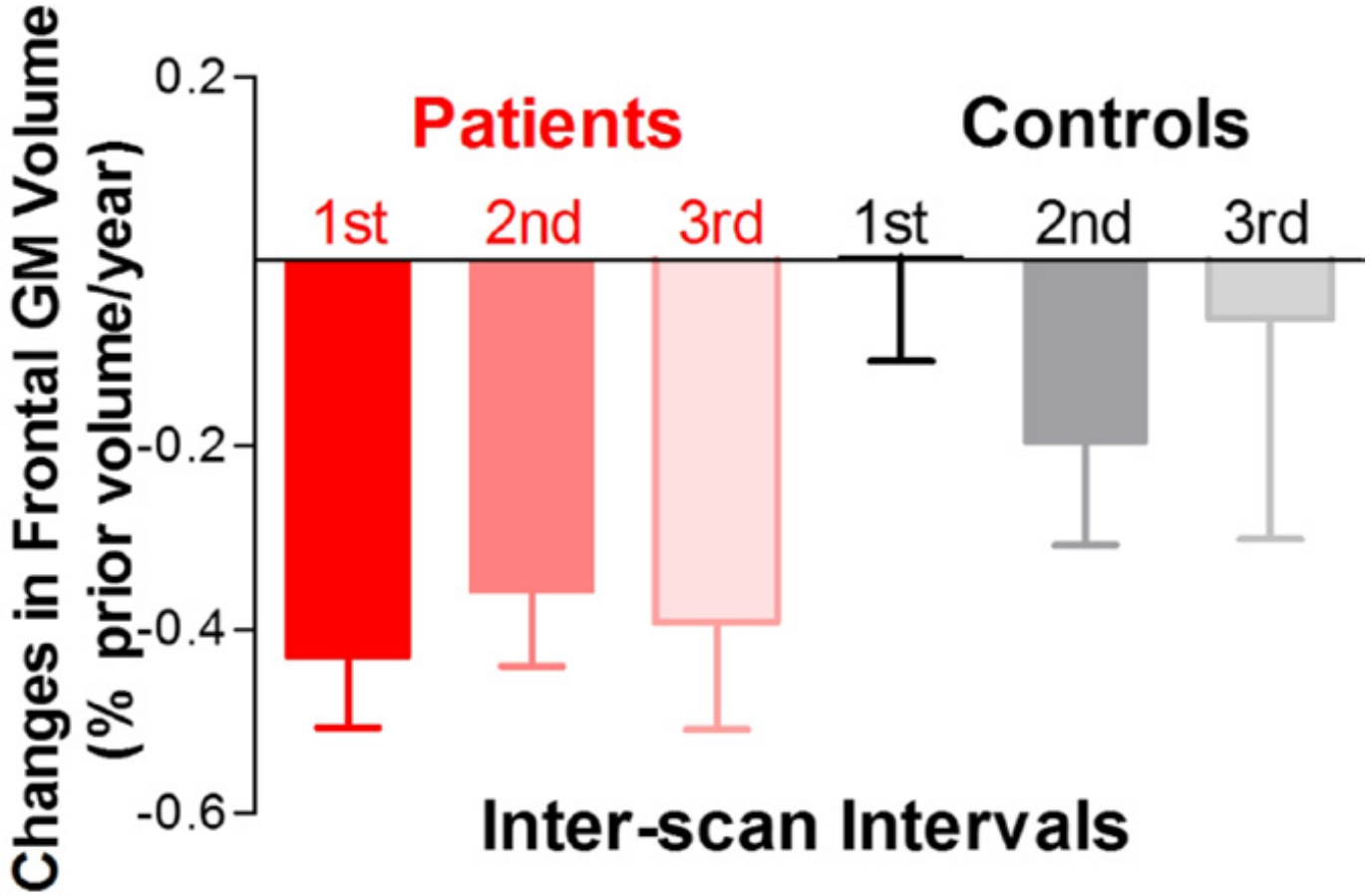
Mesholam-Gately et al., 2009

Evolution of Neuropsychological Impairment in Psychosis



Mesholam-Gately et al., 2009

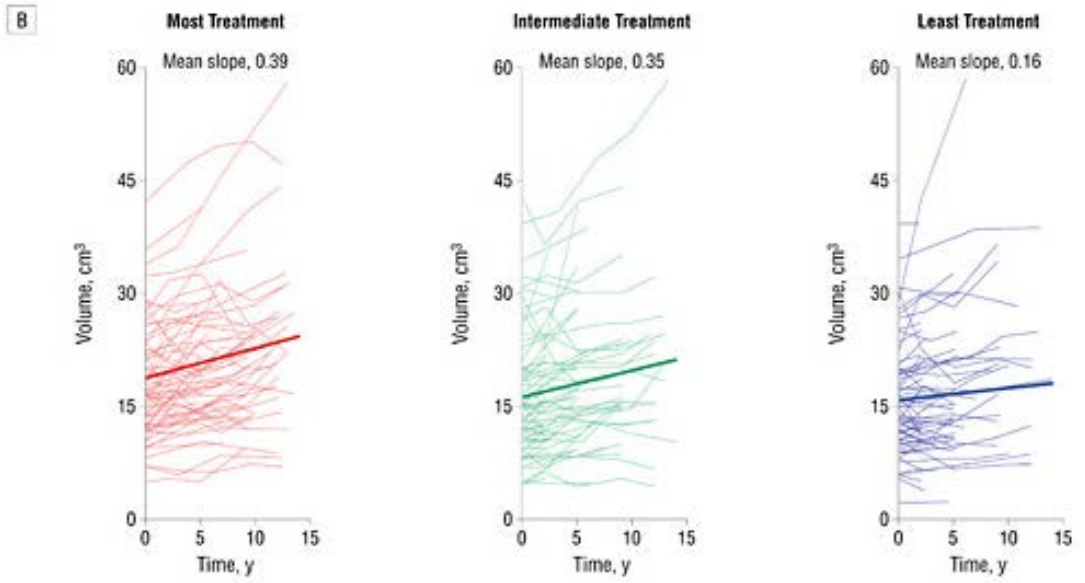
Progressive Brain Changes in First Episode Patients over 18 Years



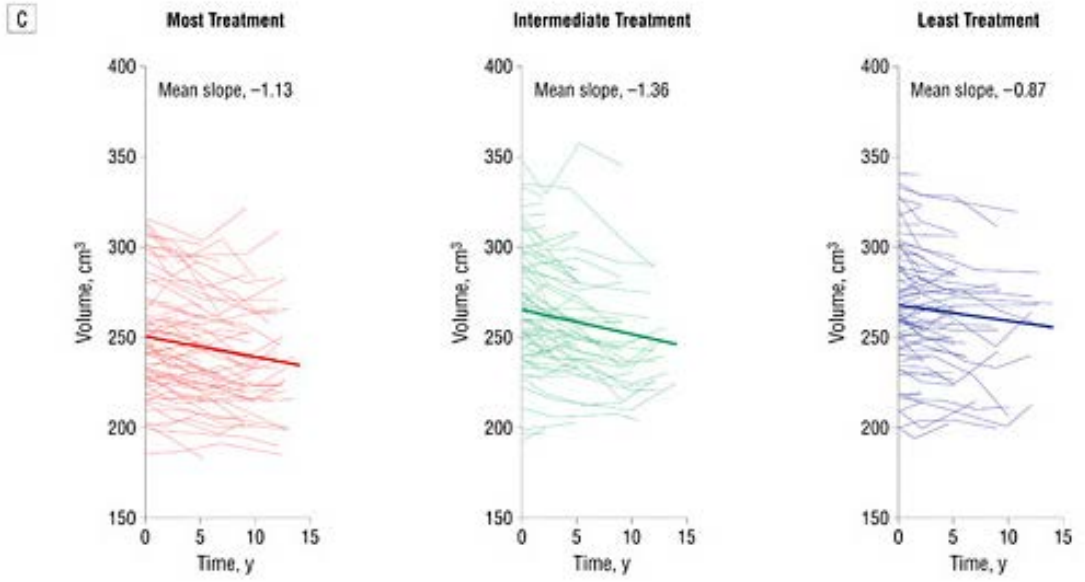
Andreasen et al., 2011

Antipsychotic Effects on Brain Structure

Ventricular Volume



Grey Matter Volume



Ho et al., 2011

OUTPATIENT TREAMENT GOALS: REMISSION

-a clinical concept implying absence of disease

-minimal symptoms

-no rehospitalization

-behavioral stability not influenced by symptoms

-lasting at least 6 months

OUTPATIENT TREATMENT GOALS: RECOVERY

-a broader concept embraced by consumers and families: a sustainable and durable recovery

-minimal symptoms

-satisfying peer relationships

-productive recreational and occupational activity

-degree of independence

-lasting at least two years

COMPARISON OF A PERSON WITH SCHIZOPHRENIA AND RECOVERY

- DEPENDENCE-professionals make decisions
- SUPPORT-from the mental health system
- SOCIAL IDENTITY-a mental patient
- MEDICATION-a requirement
- SENSE OF SELF-weak with little future

- DEPENDENCE-self determining, making one's own decisions
- SUPPORT-from friends, family
- SOCIAL IDENTITY-a worker, a parent, a friend
- MEDICATION-one tool among many
- SENSE OF SELF-strong sense of purpose

OBSTACLES TO RECOVERY
CHALLENGES TO ENGAGEMENT

1. Mistrust
2. Demoralization
3. Amotivation
4. Ambivalence
5. Stigma
6. Poor insight
7. Relationships with multiple providers
8. High rates of substance use

RECOVERY
ESTABLISHING AN ALLIANCE

1. Consistency
2. Non-judgmental attitude
3. Open door
4. Not linked to medications
5. Provide alternative explanations
6. Normalize experiences
7. Acceptance
8. Clarity of relationship: collaboration
9. Agreement upon goal (s)

WHAT HAVE WE LEARNED ABOUT OUTCOME: ZURICH

OVER 200 PATIENTS IDENTIFIED 1940'S AND 1950'S AND FOLLOWED FOR 20 YEARS

- IDENTIFIED DIFFERENT PATTERNS BASED ON ONSET, COURSE AND OUTCOME
- 50 % UNDULATING COURSE
- 25% SEVERE DECLINE
- 25 % RECOVERY

Modestin, AJP, 2003

WHAT HAVE WE LEARNED ABOUT OUTCOME: VERMONT

269 PATIENTS IDENTIFIED IN VERMONT STATE HOSPITAL IN THE LATE 1950'S AND FOLLOWED FOR UP TO 30 YEARS

- 50% STATE OF RECOVERY
- LEVEL OF FUNCTIONING LOWER THAN PREMORBID BASED ON INCOME, SOCIAL CONTACTS

- Harding, AJP, 1987

WHAT HAVE WE LEARNED ABOUT OUTCOME: IOWA

200 PATIENTS IDENTIFIED DURING THE 1930'S AND 1940'S AND FOLLOWED FOR 30-40 YEARS.

OUTCOME WAS BASED ON MARITAL, RESIDENTIAL, OCCUPATIONAL, AND PSYCHIATRIC STATUS, AND COMPARED TO SURGICAL PATIENTS

- 20-35% WITH "GOOD" OUTCOMES

Tsuang, AGP, 1979

WHAT HAVE WE LEARNED ABOUT OUTCOME: ISRAEL

2290 PATIENTS IDENTIFIED THROUGHOUT THE 1980'S AND 1990'S AND FOLLOWED FOR 10 YEARS

- 75% EXPERIENCED "PROGRESSIVE AMELIORATION" WITH VARYING PERIODS OF INITIAL DETERIORATION
- 10% PROGRESSIVE DECLINE

Rabinowitz, Schizophr Res 2007

WHAT HAVE WE LEARNED ABOUT OUTCOME

- A SIGNIFICANT NUMBER OF PATIENTS WITH SCHIZOPHRENIA (25-33%) HAVE A GOOD OUTCOME
- THE MAJORITY (50%) HAVE A RELAPSING AND REMITTING COURSE
- ONLY ABOUT 25% HAVE A CHRONIC OR PERSISTENTLY DECLINING COURSE
- PEOPLE WITH SCHIZOPHRENIA DIE YOUNGER
- WHILE THE OUTCOME IS OFTEN SUBOPTIMAL IT IS LIKELY BETTER THAN IS COMMONLY BELIEVED

WHAT FACTORS INFLUENCE OUTCOME

Absence of deficit syndrome (negative symptoms)

Later age of onset

Absence of addiction

Presence of social support

Adherence to treatment

Female gender

Access to care

Shorter duration of untreated psychosis